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Характеристика допоміжних морфотип-специфічних морфологічних індикаторів геометрії колінного суглоба при остеоартриті

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Анотація: *Остеоартрит колінного суглоба є глобальною медико-соціальною проблемою. Мета охарактеризувати допоміжні морфологічні індикатори геометрії колінного суглоба при остеоартриті з урахуванням морфотипу, визначеного за власною кластерною системою. Проаналізовано результати рентгенографічного обстеження 100 випадків дегенеративно-дистрофічного захворювання колінного суглоба з переважним ураженням медіального відділу суглоба 70 пацієнтів (26 (37,14 %) чоловіків та 44 (62,86 %) жінок). Середній вік – 63,56±8,10 років. Оцінку дегенеративних змін виконували, використовуючи стандартні рентгенограми колінних суглобів, виконані в прямій проекції при опорному навантаженні нижніх кінцівок. Серед рентгенографічних критеріїв оцінювали: MLSR (Medial-Lateral Joint Space Ratio), fICN (Femoral Intercondylar Notch Index), tICN (Tibial Intercondylar Notch Index), TIA (Tibial Intercondylar Angle), FIA (Femoral Intercondylar Angle) та FTA (Femorotibial Angle). Відповідно до власної кластерної системи серед обстежених сформовано 4 групи. Морфотип I встановлено у 21 (21,00 %) пацієнта, морфотип II – у 38 (38,00 %), морфотип III – у 29 (29,00 %), морфотип IV – у 12 (12,00 %). Статистичний аналіз цифрових даних виконували з використанням програмного засобу Statistica 13. Вірогідність безпомилкового прогнозу визначали при p≤0,05. Середній показник індексу MLSR у обстежених з морфотипом I колінного суглоба становив 0,19±0,12, з морфотипом II – 0,34±0,24, з морфотипом III – 0,44±0,32, з морфотипом IV – 0,67±1,06 (p=0,0008). Середнє значення показника fICN у осіб з морфотипом I становило 0,10±0,02, з морфотипом II – 0,11±0,03, з морфотипами III – 0,13±0,04, IV – 0,13±0,03 (p=0,007). Середнє значення індексу tICN у пацієнтів з морфотипом I становило 0,07±0,04, з морфотипом II – 0,06±0,02, з морфотипом III – 0,07±0,03, з морфотипом IV – 0,07±0,02 (p=0,17). Середнє значення кута TIA у осіб з морфотипом I – 163,90±5,00°, з морфотипом II – 160,21±4,19°, з морфотипом III – 161,33±4,33°, з морфотипом IV – 163,50±2,28° (p=0,04). Середній показник кута FIA у осіб з морфотипом I – 201,57±2,27°, з морфотипом II – 204,37±4,13°, з морфотипом III – 203,79±5,05°, з морфотипом IV – 204,75±5,26° (p=0,03). Збільшення варусної деформації у обстежених асоційовано з більш вираженими внутрішньосуглобовими порушеннями внаслідок перевантаження медіального відділу суглоба (τ=+0,28, p=0,00004), а також звуженням міжвиросткової вирізки стегнової*

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кістки та вищим ризиком пошкодженням передньої схрещеної зв'язки (τ=+0,21, p=0,002). Зміни кутів TIA та FTA у обстежених з морфотипами II, III та IV зумовлені переважно варусним відхиленням осі нижньої кінцівки, натомість у осіб з морфотипом I – руйнуванням хрящової та кісткової тканини медіальних виростків великогомілкової та стегнової кісток відповідно. Отримані дані підкреслюють доцільність врахування індивідуальних анатомо-морфологічних характеристик для більш точної оцінки ризиків та прогнозування перебігу остеоартриту колінного суглоба.

Ключові слова: анатомія, великогомілкова кістка, деформації нижніх кінцівок, морфометрія, стегнова кістка, суглоби.

Вступ

Остеоартрит колінного суглоба є однією з найактуальніших проблем медико-соціального характеру та найбільш поширеною причиною інвалідності у глобальному масштабі.

В умовах сучасності 500-595 млн людей у світі страждають на остеоартрит, що становить 7,0-7,6 % населення планети [1, 2, 3]. Предметом підвищеного інтересу є остеоартрит колінного суглоба, який становить приблизно 83 % загального тягаря дегенеративно-дистрофічних захворювань суглобів [1, 4]. До 2040 року прогнозують зростання захворюваності на 50 %, що підкреслює необхідність подальших досліджень проблеми [1].

Патогенез дегенеративно-дистрофічних захворювань суглобів залишається до кінця невідомим. Основні фактори ризику остеоартриту включають старіння, ожиріння, травми, генетику та біомеханічні зміни [4, 5, 6]. Все частіше захворювання розглядають не як однорідний патологічний стан, а як синдром із різними фенотиповими варіантами такими, як механічний, запальний, метаболічний та інші [4, 7]. Оскільки остеоартрит колінного суглоба характеризується багатовимірними структурними, біомеханічними і функціональними змінами, що погіршують якість життя пацієнтів, зростає необхідність розробки більш точних діагностичних і лікувальних підходів. Більшість сучасних стратегій лікування спрямовані на корекцію симптомів, без урахування індивідуальних відмінностей морфології суглоба та біомеханічних особливостей. Проте концепт фенотипізації остеоартриту з ідентифікацією підгруп пацієнтів з різною прогнозованою прогресією захворювання, відмінностями втрати хряща, висоти щілини та клінічних результатів набуває все більшої актуальності.

Роль анатомо-морфологічних факторів у прогнозуванні перебігу гонартрозу, а також клінічного результату лікування підтверджена результатами ряду досліджень [1, 8]. У дослідженні Van Oevelen et al. [1] продемонстровано зв'язок геометрії анатомічних сегментів нижньої кінцівки з варіабельністю моделей руйнування хряща у пацієнтів із раннім остеоартритом колінного суглоба. Доведено, що рівень задоволеності пацієнтів ортопедичним реконструктивним втручанням, зокрема ендопротезуванням колінного суглоба, значною мірою залежить від коректного балансування кісткових поверхонь, зв'язкового апарату та положення осі нижньої кінцівки [1, 8].

Таким чином, дослідження анатомо-морфологічних характеристик колінного суглоба з урахуванням особливостей перебігу остеоартриту є вкрай актуальним та необхідним для оптимізації ортопедичних технік та підвищення якості життя пацієнтів у віддаленому післяопераційному періоді.

Мета

Охарактеризувати допоміжні морфологічні індикатори геометрії колінного суглоба при остеоартриті з урахуванням морфотипу, визначеного за власною кластерною системою.

Матеріали і Методи

Проаналізовано результати рентгенографічного обстеження 100 випадків дегенеративно-дистрофічного захворювання колінного суглоба з переважним ураженням медіального відділу суглоба 70 пацієнтів, які перебували на стаціонарному лікуванні

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в травматологічному відділенні КНП «Вінницька міська клінічна лікарня швидкої медичної допомоги» за період 2017-2025 років. Середній вік – 63,56±8,10 років. До групи включено 26 (37,14 %) чоловіків та 44 (62,86 %) жінки. Ознаки одностороннього дегенеративно-дистрофічного ураження колінного суглоба встановлено у 40 (57,14 %) пацієнтів, у 30 (42,86 %) обстежених зафіксовано двосторонній характер захворювання.

Для оцінки дегенеративних змін використовували стандартні рентгенограми колінних суглобів, виконані в прямій проекції при опорному навантаженні нижніх кінцівок.

Серед рентгенографічних критеріїв оцінювали:

MLSR (*Medial-Lateral Joint Space Ratio*) – співвідношення висот медіальної суглобової щілини колінного суглоба до латеральної, виміряних в центральних точках між міжвиростковим підвищенням та краєм відповідного виростка великогомілкової кістки.

fICN (*Femoral Intercondylar Notch Index*) – співвідношення ширини міжвиросткової вирізки, виміряної у її найширшій частині, до загальної міжвиросткової ширини, визначеної як відстань між внутрішнім краєм медіального та зовнішнім краєм латерального виростків стегнової кістки.

tICN (*Tibial Intercondylar Notch Index*) – співвідношення ширини міжгорбикової ямки, виміряної у її найширшій частині, до загальної міжвиросткової ширини, визначеної як відстань між внутрішнім краєм медіального та зовнішнім краєм латерального виростків великогомілкової кістки.

TIA (*Tibial Intercondylar Angle*) – кут, утворений між лініями, дотичними до медіального та латерального плато великогомілкової кістки, які перетинаються в центральній точці міжгорбикової ямки.

FIA (*Femoral Intercondylar Angle*) – кут, утворений між лініями, дотичними до медіального та латерального виростків стегнової кістки, які перетинаються в центральній точці міжвиросткової вирізки.

FTA (*Femorotibial Angle*) – кут між анатомічними осями стегнової та великогомілкової кісток [9].

Відповідно до власної кластерної системи [10] серед обстежених сформовано 4 групи, які відповідали 4 морфологічним варіантам колінного суглоба при дегенеративно-дистрофічних захворюваннях. Морфотип I встановлено у 21 (21,00 %) пацієнта групи, морфотип II – у 38 (38,00 %) хворих, у 29 (29,00 %) обстежених зафіксовано морфотип III, ще у 12 (12,00 %) осіб – морфотип IV.

Статистичний аналіз даних виконували з використанням програмного засобу Statistica 13. Кількісні показники наведено у вигляді середнього значення ± стандартне відхилення (M ± SD), категоріальні – у форматі абсолютної кількості спостережень (n) та відповідного відсоткового співвідношення (%). При порівнянні змінних незалежних груп використовували непараметричний статистичний критерій Краскела-Уолліса, функціональний зв'язок між ознаками оцінювали за допомогою коефіцієнта рангової кореляції τ-Кендала. Вірогідність безпомилкового прогнозу визначали при $p \leq 0,05$.

Результати

У обстежених хворих середній показник кута FTA становив 177,09±5,57°. У пацієнтів з морфотипом I середнє значення кута FTA складало 169,76±1,48°, що відповідало варусному відхиленню осі нижньої кінцівки. Варусне відхилення осі зафіксовано й у хворих з морфотипом II, середній показник кута FTA яких становив 175,58±1,32°. У обстежених хворих з морфотипом III середній показник кута FTA складав 180,14±1,49° та відповідав нейтральному положенню осі нижньої кінцівки. У осіб з морфотипом IV середнє значення досліджуваного кута складало 187,33±3,75°, що відповідало вальгусному відхиленню осі. При порівнянні середніх значень кута FTA у сформованих групах доведено їх статистично значущу відмінність ($p<0,0001$).

Аналізуючи допоміжні морфологічні індикатори геометрії колінного суглоба при остеоартриті встановлено, що середній показник індексу MLSR у обстежених становив 0,38±0,44. Найвищі показники індексу спостерігали у осіб з морфотипом IV –

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Таблиця 1. Характеристика допоміжних критеріїв оцінки дегенеративно-дистрофічного ураження колінного суглоба

Критерій	Варіанти морфотипів колінного суглоба				p
	I (n=21)	II (n=38)	III (n=29)	IV (n=12)	
MLSR	0,19±0,12	0,34±0,24	0,44±0,32	0,67±1,06	0,0008*
fICN	0,10±0,02	0,11±0,03	0,13±0,04	0,13±0,03	0,007*
tICN	0,07±0,04	0,06±0,02	0,07±0,03	0,07±0,02	0,17
TIA	163,90±5,00°	160,21±4,19°	161,33±4,33°	163,50±2,28°	0,04*
FIA	201,57±2,27°	204,37±4,13°	203,79±5,05°	204,75±5,26°	0,03*

**Примітка.* Доведено статистично значущу відмінність показників при p≤0,05.

0,67±1,06, у осіб з морфотипом III – 0,44±0,32, 0,34±0,24 – у осіб з морфотипом II, найнижчі значення індексу зафіксовано у осіб з морфотипом колінного суглоба I – 0,19±0,12, відмінність показників статистично значуща (p=0,0008) (табл. 1). Між показниками індексу MLSR та значеннями кута FTA встановлено прямий слабкий кореляційний зв'язок (τ=+0,28, p=0,00004), що свідчить про нижчі значення індексу та відповідно більш виражені внутрішньосуглобові порушення у пацієнтів зі збільшенням варусного відхилення осі нижньої кінцівки.

Середнє значення показника fICN у обстежених становило 0,12±0,03. Вищі значення індексу спостерігали у пацієнтів з морфотипами III та IV – 0,13±0,04 та 0,13±0,03 відповідно. У пацієнтів з морфотипом II середній показник індексу складав 0,11±0,03, 0,10±0,02 – у осіб з морфотипом I. При порівнянні значень індексу fICN у сформованих групах доведено статистично значущу відмінність показників (p=0,007). Між показниками fICN та значеннями кута FTA доведено прямий слабкий кореляційний зв'язок (τ=+0,21, p=0,002), що свідчить про звуження міжвиросткової ямки стегнової кістки у пацієнтів зі збільшенням варусного відхилення осі нижньої кінцівки.

Оцінюючи індекс tICN, встановлено, що його середній показник у пацієнтів досліджуваної групи складав 0,07±0,03. Середнє значення індексу у обстежених з морфотипом I становило 0,07±0,04, у осіб з морфотипом II – 0,06±0,02, у пацієнтів з морфотипом III – 0,07±0,03, 0,07±0,02 – у хворих з морфотипом IV, відмінність статистично незначуща (p=0,17). Достовірний кореляційний зв'язок між показниками індексу tICN та значеннями кута FTA відсутній (τ=+0,08, p=0,27).

Середнє значення кута TIA у обстежених становило 161,71±4,45°. Найвищі значення кута зафіксовано у осіб з морфотипом I – 163,90±5,00°, найнижчі – у пацієнтів з морфотипом II – 160,21±4,19°. Середній показник TIA у осіб з морфотипом III становив 161,33±4,33°, 163,50±2,28° – у хворих з морфотипом IV, відмінність результатів статистично значуща (p=0,04) (рис. 1 а). Проте, між показниками кутів TIA та FTA достовірний кореляційний зв'язок відсутній (τ=+0,03, p=0,66).

Аналізуючи показники кута FIA, його середнє значення у хворих досліджуваної групи складало 203,66±4,36°. У пацієнтів з морфотипом II середній показник кута FIA становив 204,37±4,13°, у хворих з морфотипом III – 203,79±5,05°, у обстежених з морфотипом IV – 204,75±5,26°, найнижчі значення досліджуваного кута зафіксовано у осіб з морфотипом I – 201,57±2,27°, відмінність показників статистично значуща (p=0,03) (рис. 1 б).

Обговорення

З метою комплексної оцінки дегенеративно-дистрофічних змін колінного суглоба проаналізовано роль допоміжних морфологічних критеріїв у визначенні особливостей перебігу остеоартриту з урахуванням індивідуального морфотипу суглоба.

Аналізуючи показники індексу MLSR, встановлено його найнижчі значення у пацієнтів з морфотипом I (0,19±0,12), що свідчить про виражене звуження медіальної щі-

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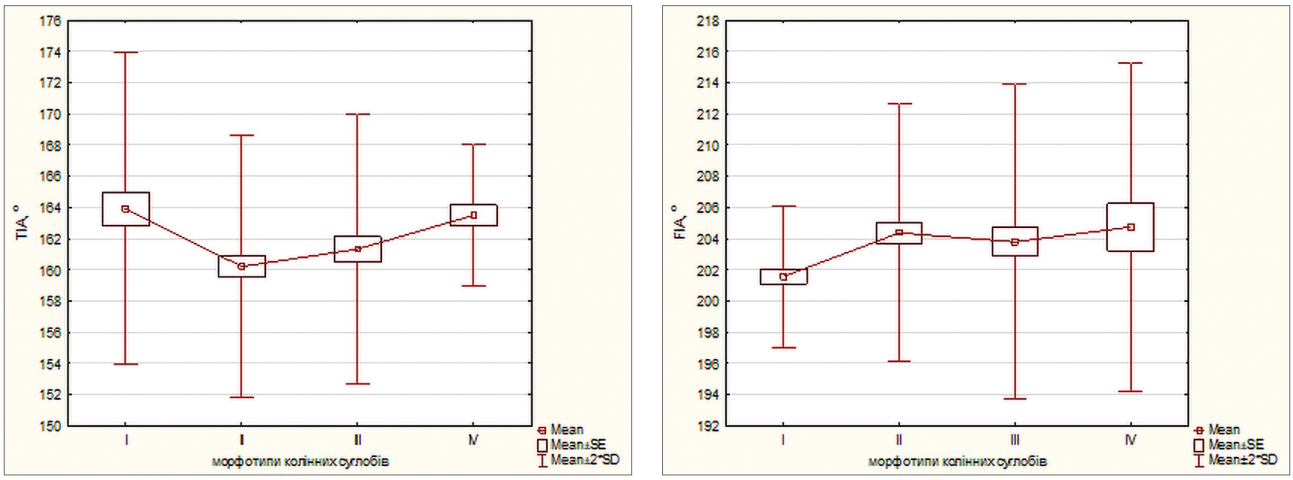

Рис. 1. Діаграма розмаху значень кутів а) TIA, б) FIA з урахуванням морфотипу колінного суглоба при дегенеративно-дистрофічних захворюваннях

лини та, відповідно, більш значуще ураження медіального відділу суглоба. Натомість, найвищі показники індексу спостерігали у пацієнтів з морфотипом IV (0,67±1,06), що обумовлено меншим ступенем навантаження на медіальний відділ суглоба. Окрім того, доведено прямий слабкий кореляційний зв'язок між значеннями індексу MLSR та кутом FTA (τ=+0,28; p=0,00004), що додатково підтверджує вищий ризик внутрішньосуглобових деформацій з переважним ураженням медіального компартменту при збільшенні варусного відхилення осі нижньої кінцівки.

Встановлені дані узгоджуються з результатами дослідження Graichen et al. [8], які аналізуючи результати обстеження 1000 пацієнтів з остеоартритом колінного суглоба, оцінювали вплив ступеня варусної деформації на зміну висоти суглобової щілини. «Стандартне» варусне коліно дослідники визначали за наявності наступних критеріїв: латеральна суглобова щілина, визначена в положенні розгинання, більша за медіальну; латеральна суглобова щілина, визначена в положенні згинання, більша за медіальну; висота суглобової щілини в положенні згинання більша за висоту, визначену при розгинанні. Згідно результатів аналізу усі 3 критерії варусного колінного суглоба встановлено у 444 із 680 (65 %) пацієнтів. Дослідники відзначили, що висота латеральної суглобової щілини (4,1 мм) була значущо більшою, ніж медіальної (0,6 мм) у 657 (97 %) пацієнтів, а також довели статистично значущий сильний кореляційний зв'язок між показником відношення суглобових висот та величиною варусної деформації (r^2=0,62). Автори праці встановили високу міжіндивідуальну варіабельність параметрів суглобових щілин при остеоартриті колінного суглоба з варусною деформацією.

У дослідженні Nelson et al. [4], шляхом бікластеризації даних великої когорти пацієнтів з остеоартритом колінного суглоба ідентифіковано шість фенотипів, відмінних за симптоматикою та структурним прогресуванням, зокрема ступенем звуження медіальної суглобової щілини. Дослідниками представлено дані 3330 осіб (середній вік – 61 рік) та 6461 випадків остеоартриту. Авторами праці визначено бікластери з кращим (№ 1), подібним (№ 2, 3, 6) і гіршим (№ 4, 5) прогнозом, порівняно із загальною когортою. У бікластерах № 4 і 5 встановлено інтенсивне прогресування захворювання з вираженим зменшенням висоти медіальної суглобової щілини, приблизно на 20 %. На відміну від цього, в бікластері № 1 доведено зменшення висоти медіальної щілини до 10 %, а також меншу частку випадків прогресування захворювання та меншу інтенсивність больового синдрому. Як відмітили дослідники, подібний підхід до стратифікації пацієнтів є перспективним для більш точного прогнозування перебігу захворювання та визначення показань до ортопедичного втручання.

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Оцінюючи значення індексу fICN, у визначених морфотипах доведено його значущі відмінності: вищі значення спостерігали у пацієнтів з морфотипами III та IV (0,13±0,04 та 0,13±0,03 відповідно), найнижчі – у пацієнтів з морфотипом I (0,10±0,02). Окрім того, збільшення варусного відхилення осі нижньої кінцівки асоційовано зі зниженням ширини міжвиросткової вирізки стегнової кістки (τ=+0,21; p=0,002), що вказує зменшення простору для передньої схрещеної зв'язки та вищий ризик її ушкодження.

Отримані результати узгоджуються з відомими літературними даними щодо зв'язку між звуженням міжвиросткової щілини та вищим ризиком розвитку нестабільності в колінному суглобі та пошкодження передньої схрещеної зв'язки. Зокрема у дослідженні Barnum et al. [11] встановлено, що збільшення кута α та наявність вузької міжвиросткової вирізки стегнової кістки типу A є незалежними факторами ризику безконтактного ушкодження передньої схрещеної зв'язки. Кут α вимірювали як кут, утворений між повздовжньою віссю стегнової кістки і лінією, дотичною до лінії Блюменталя. Тип вирізки стегнової кістки оцінювали на аксіальних зображеннях та характеризували як A, U або W-профіль. Дослідники встановили, що у жінок травма передньої схрещеної зв'язки достовірно пов'язана зі збільшенням показників кута α (відношення шансів (OR)=1,82; p=0,001), нахилу плато великогомілкової кістки (OR=1,25; p=0,022) та товщини передньо-медіального виступу міжвиросткової вирізки стегнової кістки (OR=3,36; p=0,027). Окрім того, збільшення кута α було найбільш значущим предиктором пошкодження передньої схрещеної зв'язки і у чоловіків (OR=2,19; p=0,010). Автори праці відзначили простоту вимірювання кута α та доцільність його застосування як скринінгового інструменту у клінічній практиці.

Значущої відмінності індексу tICN між морфотипами не доведено (p=0,17), що свідчить про відносну стабільність досліджуваних параметрів великогомілкової кістки незалежно від ступеня деформації або перебігу дегенеративного процесу. Відсутність значущого кореляційного зв'язку між значеннями tICN та FTA (τ=+0,08; p=0,27) додатково підтверджує його меншу клінічну чутливість.

Аналізуючи зміни кута TIA у сформованих групах, варто відмітити тенденцію до поступового зниження значень кута зі збільшенням варусного відхилення осі нижньої кінцівки у обстежених з морфотипами IV, III та II (163,50±2,28°, 161,33±4,33° та 160,21±4,19° відповідно) та збільшення показника у осіб з морфотипом I (163,90±5,00°). Збільшення значень кута TIA у пацієнтів з морфотипом I, очевидно, обумовлено руйнуванням хрящової та кісткової тканини опорного виростка великогомілкової кістки на додачу до варусного відхилення осі нижньої кінцівки.

Зміни показника кута FIA у обстежених подібні до тих, які спостерігали у великогомілковій кістці. Суттєве зниження показника кута FIA у обстежених з морфотипом I вказує на руйнування хрящової та кісткової тканини опорного виростка стегнової кістки. Таким чином, у пацієнтів з морфотипом I структурні зміни опорного виростка стегнової кістки аналогічні до тих, які виникають у великогомілковій, що свідчить про системне залучення обох компонентів медіального компартменту суглоба в патологічний процес.

Отримані результати узгоджуються з даними відомих досліджень, підтверджуючи значення індивідуального підходу в оцінці морфології колінного суглоба. Особливості геометрії колінного суглоба суттєво варіюють між індивідуумами та мають потенційний вплив як на розподіл навантаження, так і на стан зв'язкового апарату. Морфотип-специфічна оцінка індексів є перспективним напрямом для уточнення клінічної діагностики, прогнозування ризику прогресування остеоартриту колінного суглоба та формування індивідуалізованих стратегій лікування.

Висновки

Таким чином, доведено значущу варіативність допоміжних морфологічних індикаторів геометрії колінного суглоба при остеоартриті з урахуванням морфотипу, визначеного за власною кластерною системою. Дегенеративно-дистрофічні зміни колінного суглоба у обстежених з морфотипами II, III та IV зумов-

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лені переважно варусним відхиленням осі нижньої кінцівки, натомість у осіб з морфотипом I – переважно руйнуванням хрящової та кісткової тканини опорних виростків стегнової та великогомілкової кістки. Збільшення варусної деформації у обстежених асоційовано з більш вираженими внутрішньосуглобовими порушеннями внаслідок перевантаження медіального відділу суглоба, а також звуженням міжвиросткової вирізки стегнової кістки та вищим ризиком пошкодження передньої схрещеної зв'язки.

Отримані дані свідчать про доцільність використання морфологічних індикаторів геометрії колінного суглоба для оцінки ризику прогресування остеоартриту та планування індивідуалізованих підходів до лікування. Включення морфотипування у комплексну оцінку пацієнтів з остеоартритом сприятиме більш точній стратифікації ризиків і вдосконаленню ортопедичних втручання з дотриманням принципів персоналізації.

Фінансування

Дане дослідження не отримало зовнішнього фінансування.

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Авторка декларує відсутність конфлікту інтересів.

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Під час підготовки цього рукопису ШІ-інструменти не використовувалися.

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13. Project Administration: Liubov Kylymniuk;
14. Funding Acquisition: Liubov Kylymniuk.

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Characteristics of Auxiliary Morphotype-Specific Morphological Indicators of Knee Joint Geometry in Osteoarthritis

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Abstract: *Knee osteoarthritis represents a significant global medical and social challenge. Objective: To characterize auxiliary morphological indicators of knee joint geometry in osteoarthritis, with consideration of morphotypes identified using a proprietary clustering system. Radiographic data from 100 cases of medial knee degenerative-dystrophic disease were analyzed. The study included 70 patients (26 (37.14 %) men and 44 (62.86 %) women) with a mean age of 63.56±8.10 years. Degenerative changes were assessed on standard weight-bearing anteroposterior radiographs of the knees. The following radiographic parameters were evaluated: MLSR (Medial-Lateral Joint Space Ratio), fICN (Femoral Intercondylar Notch Index), tICN (Tibial Intercondylar Notch Index), TIA (Tibial Intercondylar Angle), FIA (Femoral Intercondylar Angle), and FTA (Femorotibial Angle). According to the clustering system, four morphotype groups were identified: morphotype I in 21 patients (21.00 %), morphotype II – 38 (38.00 %), morphotype III – 29 (29.00 %), and morphotype IV – 12 (12.00 %). Statistical analysis was conducted using Statistica 13, with significance set at $p \leq 0.05$. The average MLSR index for morphotype I was 0.19±0.12, for morphotype II – 0.34±0.24, for morphotype III – 0.44±0.32, and for morphotype IV – 0.67±1.06 ($p=0.0008$). The mean fICN value was 0.10±0.02 in morphotype I, 0.11±0.03 in morphotype II, 0.13±0.04 in morphotype III, and 0.13±0.03 in morphotype IV ($p=0.007$). The mean tICN was 0.07±0.04 in morphotype I, 0.06±0.02 in morphotype II, 0.07±0.03 in morphotype III, and 0.07±0.02 in morphotype IV ($p=0.17$). TIA values were 163.90±5.00° for morphotype I, 160.21±4.19° for morphotype II, 161.33±4.33° for morphotype III, and 163.50±2.28° for morphotype IV ($p=0.04$). FIA values were 201.57±2.27° in morphotype I, 204.37±4.13° in morphotype II, 203.79±5.05° in morphotype III, and 204.75±5.26° in morphotype IV ($p=0.03$). An increase in varus deformity was associated with more pronounced intra-articular alterations due to medial compartment overload ($\tau=+0.28$, $p=0.00004$), as well as narrowing of the femoral intercondylar notch and a higher risk of anterior cruciate ligament injury ($\tau=+0.21$, $p=0.002$).*

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Changes in TIA and FTA observed in morphotypes II, III, and IV were primarily due to varus alignment of the limb axis, while in morphotype I, they were mainly attributed to degradation of the cartilage and subchondral bone of the femoral and tibial condyles. These findings emphasize the importance of considering individual anatomic and morphologic characteristics for a more accurate assessment of risks and prediction of knee osteoarthritis progression.

Keywords: Anatomy, Tibia, Osteoarthritis, Femurv, Joints, Lower Extremity Deformities, Morphometrics.

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Comparative effects of liraglutide and dapagliflozin on lipid profile and cardiovascular risk in patients with metabolic dysfunction-associated steatotic liver disease and type 2 diabetes: a 6-month randomized study

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Abstract: *Metabolic dysfunction-associated steatotic liver disease frequently coexists with type 2 diabetes mellitus, resulting in increased cardiometabolic risk. Pharmacologic agents such as glucagon-like peptide-1 receptor agonists and sodium-glucose cotransporter-2 inhibitors may improve lipid metabolism and cardiovascular outcomes, but comparative data remain limited. To evaluate and compare the magnitude of change (delta values) in lipid profile parameters and cardiovascular risk scores, assessed using five validated stratification tools, in patients with ьetabolic dysfunction-associated steatotic liver disease and type 2 diabetes mellitus following 6-month treatment with liraglutide or dapagliflozin. Materials and This 6-month prospective, randomized study included 72 patients with metabolic dysfunction-associated steatotic liver disease and type 2 diabetes mellitus allocated to three groups: control (lifestyle intervention; n=23), dapagliflozin (10 mg daily; n=26), or liraglutide (up to 1.8 mg daily; n=23). Lipid profiles and cardiovascular risk were assessed at baseline and after treatment using five validated tools (Globorisk, Framingham Risk Score, ASCVD Risk Calculator, PROCAM, WHO CVD chart). Intergroup comparisons were based on changes from baseline. All groups showed significant within-group improvements in lipid parameters, with reductions in total cholesterol, low-density lipoproteins, and triglycerides and increases in high-density lipoproteins ($p<0.001$). The liraglutide group demonstrated greater improvements in total cholesterol, low-density lipoproteins, and high-density lipoproteins compared to control and dapagliflozin ($p<0.01$). Cardiovascular risk scores declined significantly within each group. Between-group comparisons revealed significant differences for the Framingham score (favoring liraglutide over control) and the PROCAM score (favoring both pharmacologic treatments over control). No consistent differences were observed between liraglutide and dapagliflozin across other risk models. Both liraglutide and dapagliflozin improved lipid profiles and reduced cardiovascular risk in patients with metabolic dysfunction-associated steatotic liver disease and type 2 diabetes mellitus. Although no statistically significant superiority of liraglutide over dapagliflozin was confirmed for cardiovascular risk scores, a consistent trend toward greater lipid improvement was noted. Further studies with larger samples and longer follow-up are needed to clarify these findings.*

Keywords: Liver Diseases, Cardiovascular Risk, Liraglutide, Dapagliflozin, Type 2 Diabetes Mellitus, Metabolic Dysfunction-Associated Steatotic Liver Disease.

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Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD) is increasingly recognized as a major hepatic manifestation of systemic metabolic dysfunction [1]. Among its strongest associations is with type 2 diabetes mellitus (T2DM), a condition present in more than 55% of patients with MASLD and known to accelerate both hepatic and cardiovascular complications [2-3]. The coexistence of MASLD and T2DM has been associated with greater severity of steatosis, higher fibrosis progression rates, and increased risk of cardiovascular events [4].

Dyslipidemia plays a central role in the pathophysiology of MASLD, especially in patients with T2DM, in whom characteristic alterations include elevated triglycerides, decreased high-density lipoprotein cholesterol (HDL-C), and increased levels of small dense low-density lipoproteins (LDL-C) [5]. These changes not only promote hepatic fat accumulation but also represent key drivers of atherosclerotic cardiovascular disease (ASCVD) [6].

Recent guidelines underscore that cardiovascular disease, not liver-related complications, remains the leading cause of mortality in patients with MASLD, especially when accompanied by T2DM. This dual metabolic burden requires an integrated approach to risk reduction, including aggressive management of lipid abnormalities and careful assessment of individual cardiovascular risk [7].

Multiple validated tools are available to estimate 10-year cardiovascular risk, such as the ASCVD Risk Calculator (ACC/AHA), Framingham Risk Score, Prospective Cardiovascular Münster (PROCAM) Score, WHO cardiovascular risk charts, and Globorisk [8–12]. While these instruments are widely used, they typically do not account for hepatic steatosis or fibrosis, which may influence cardiovascular outcomes [5]. Consequently, dynamic assessment of changes (delta values) in these scores during therapy may offer additional insight into treatment effectiveness.

In recent years, several antidiabetic agents have gained attention for their hepatometabolic effects beyond glucose control. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and sodium-glucose cotransporter-2 (SGLT2) inhibitors are widely used in the management of T2DM and have demonstrated benefits in reducing liver fat content, improving liver enzymes, lipid parameters and potentially lowering cardiovascular risk [13–14].

Liraglutide, a GLP-1 RA, reduces hepatic steatosis primarily through weight loss, improvement in insulin sensitivity, and anti-inflammatory effects. Additionally, it has been shown to enhance reverse cholesterol transport and increase HDL-C levels, contributing to improved lipid homeostasis [13].

Dapagliflozin, an SGLT2 inhibitor, exerts its effect by promoting glucosuria, improving glycemic control, and inducing mild caloric loss. In MASLD, its mechanisms include reduction of hepatic fat infiltration, improvement of mitochondrial function, and downregulation of lipogenesis via suppression of liver X receptor alpha (LXRα)-mediated pathways [15]. These complementary mechanisms suggest both agents may be effective in ameliorating the hepatic and cardiovascular burden in this high-risk population.

However, head-to-head comparisons of these agents in MASLD patients with T2DM are limited, particularly in terms of direct evaluation of the magnitude of change in lipid profile components and cardiovascular risk scores during treatment [16].

Aim

To evaluate and compare the magnitude of change (delta values) in lipid profile parameters and cardiovascular risk scores, assessed using five validated stratification tools, in patients with MASLD and type 2 diabetes mellitus following 6-month treatment with liraglutide or dapagliflozin.

Materials and Methods

This study was conducted as part of a dissertation project at the clinical base of the Department of Internal Medicine №1, Bogomolets National Medical University (Kyiv, Ukraine).

All procedures adhered to ethical standards set forth in the Declaration of Helsinki, the Council of Europe Convention on Human Rights and Biomedicine, and national legislation

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of Ukraine. All participants provided written informed consent prior to enrollment.

Patients. Eligible participants were adults aged 26 to 67 years with previously confirmed diagnoses of both metabolic dysfunction-associated steatotic liver disease (MASLD) and type 2 diabetes mellitus, as defined by the 2023 MASLD criteria [17].

Key exclusion criteria included any history of cardiovascular events, liver cirrhosis, alcoholic liver disease, viral hepatitis, malignancies, hematologic disorders, pregnancy, or lactation.

Study Design. This was a prospective, randomized, parallel-group study employing a two-stage stratification approach. A total of 72 patients met the inclusion criteria were enrolled and randomly assigned into two main groups. The control group (n = 23) received standard lifestyle modification therapy, which included adherence to a Mediterranean diet and at least 150 minutes of moderate-intensity aerobic activity per week.

The remaining 49 patients were allocated to the pharmacologic intervention group, which combined the same lifestyle recommendations with antidiabetic drug therapy. In the second phase of stratification, this group was subdivided into two treatment arms:

– Group IA (n = 26) received dapagliflozin at a fixed daily dose of 10 mg for 6 months.
– Group IB (n = 23) received liraglutide, initiated at 0.6 mg once daily and titrated weekly up to 1.8 mg, maintained throughout the 6-month period.

Randomization was performed using a computer-generated sequence and stratified by age to ensure balance across study arms and subgroups.

Study Visits. At baseline, each patient underwent a comprehensive clinical evaluation, including history-taking, physical examination, liver steatometry (Soneus P7, UltraSign, Ukraine), and laboratory testing (lipid profile, alanine aminotransferase [ALT], aspartate aminotransferase [AST]). All assessments were repeated after the 6-month intervention period to evaluate treatment effects.

Cardiovascular Risk Assessment. Cardiovascular risk was evaluated at baseline and after 6 months using five validated scoring tools: the ASCVD Risk Calculator (ACC/AHA), Framingham Risk Score, Prospective Cardiovascular Münster (PROCAM) Score, WHO CVD Risk Charts, and Globorisk [8-12]. These models were selected for their relevance to populations with metabolic dysfunction, as they incorporate type 2 diabetes mellitus and/or lipid profile indicators.

Statistical Analysis. Statistical analyses were performed using IBM SPSS Statistics software (version 29.0). Data distribution was assessed using the Shapiro–Wilk test. Normally distributed variables were expressed as mean ± standard deviation (SD), while non-normally distributed data were reported as median and interquartile range [Median (Q1–Q3)].

Comparisons between two groups were made using the independent samples t-test (for normal distribution) or the Wilcoxon rank-sum test (for non-normal distribution). Differences among three groups were analyzed using one-way ANOVA or the Kruskal–Wallis test, as appropriate. Post hoc pairwise comparisons were adjusted using the Bonferroni correction. Categorical variables were compared using the chi-squared (χ^2) test. Statistical significance was set at $p < 0.05$.

Results

Table 1 summarizes the baseline demographic, clinical, and biochemical characteristics of the study population. Participants were divided into three groups: control (n = 23), dapagliflozin group (Group IA, n = 26), and liraglutide group (Group IB, n = 23). Baseline comparability across groups supports the validity of subsequent intergroup comparisons.

Significant improvements in lipid profile parameters were observed in all three groups after 6 months of treatment. Total cholesterol, LDL cholesterol, and triglyceride levels decreased significantly, while HDL cholesterol levels increased ($p < 0.001$ for all within-group comparisons). Summary data are presented in Table 2.

Similarly, all five cardiovascular risk assessment tools demonstrated statistically significant reductions in each group following the intervention ($p < 0.05$ for all within-group comparisons).

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Table 1. Baseline characteristics of study participants. X±SD or Me [25%;75%]

Indicators		Control group (n = 23)	Group IA (n = 26)	Group IB (n = 23)	Significance of difference, p
Age, years		46.9 ± 9.5	46.9 ± 9.3	46.5 ± 9.5	p = 0.99
Sex	Men	15 (65 %)	19 (73 %)	17 (74 %)	p = 0.31
	Women	8 (35 %)	7 (27 %)	6 (26 %)	
Severity of steatosis distribution	S1	5 (21.7 %)	5 (19.2 %)	3 (13 %)	p = 0.70
	S2	10 (43.5 %)	8 (30.8 %)	11 (47.8 %)	
	S3	8 (34.8 %)	13 (50 %)	9 (39.2 %)	
Smoking (yes, %)		7 (30.4 %)	7 (26.9 %)	6 (26 %)	p = 0.94
Medication use (yes, %) *		3 (13 %)	4 (15.4 %)	2 (8.7 %)	p = 0.78
Arterial hypertension (yes, %)		5 (21.7 %)	7 (26.9 %)	4 (17.4 %)	p = 0.72
Other comorbidities (yes, %) **		2 (8.7 %)	5 (19.2 %)	2 (8.7%)	p = 0.43
Systolic blood pressure (mmHg)		131.8 ± 14.3	133.9 ± 16.5	135.2 ± 15.2	p = 0.78
Body mass index (kg/m2)		31.9 ± 3.0	32.5 ± 2.9	34.1 ± 3.9	p = 0.08
ALT (IU/L)		31 [18; 38]	32.5 [25; 43]	33 [25; 40]	p = 0.52
AST (IU/L)		27 [23; 41]	28 [24; 35]	27 [21; 38]	p = 0.85
Total cholesterol (mmol/L)		5.7 ± 1.0	5.9 ± 0.9	5.7 ± 0.9	p = 0.77
LDL-C (mmol/L)		3.4 ± 0.8	3.3 ± 0.8	3.5 ± 0.7	p = 0.84
HDL-C (mmol/L)		1.1 [1.1; 1.4]	1.3 [1.1; 1.4]	1.1 [1.0; 1.3]	p = 0.42
Triglycerides (mmol/L)		2.1 [1.9; 2.8]	2.3 [1.9; 2.8]	2.2 [1.9; 2.9]	p = 0.93
Globorisk (10-year risk, %)		27.9 [16.7; 33.9]	30.5 [21.4; 44.6]	20.8 [15.7; 40.2]	p = 0.22
Framingham (10-year risk, %)		15.1 [9.2; 21.5]	17.7 [13.5; 32.5]	15.2 [10.1; 30.3]	p = 0.62
ACC/AHA ASCVD (10-year risk, %)		8.9 [4.2; 11.7]	11.2 [7.8; 20.2]	7.9 [3.8; 17.7]	p = 0.30
PROCAM (10-year risk, points)		39.4 ± 9.4	44.3 ± 9.9	41.2 ± 11.2	p = 0.30
WHO CVD (10-year risk, %)		16 [13; 17]	19 [14; 27.5]	16 [10; 26]	p = 0.34

Note: * – medication use includes levothyroxine, sertraline or antihypertensive therapy (perindopril, enalapril + hydrochlorothiazide or valsartan); ** – other comorbidities include autoimmune thyroiditis, hypothyroidism, depressive disorder.

Changes in lipid profile parameters and cardiovascular risk scores across the three study groups over the 6-month treatment period are presented in Table 3. All groups demonstrated reductions in total cholesterol, LDL-C, and triglycerides, along with an increase in HDL-C. The liraglutide group showed significantly greater changes in total cholesterol ($p < 0.01$ vs. control), LDL-C ($p < 0.01$ vs. both groups), and HDL-C ($p < 0.01$ vs. both groups). Triglyceride reductions were also more substantial in both intervention groups compared to the control group ($p < 0.01$), with no significant difference between Group IA and Group IB ($p > 0.05$).

Regarding cardiovascular risk scores, all five tools demonstrated numerical reductions in each group. Statistically significant intergroup differences were observed for the Framingham and PROCAM scores. For the Framingham score, a greater reduction was observed in the liraglutide group compared to the control group ($p = 0.04$). In the PROCAM score, both the

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Table 2. Intra-group changes in lipid profile and cardiovascular risk (five scales) before and after 6-month therapy in MASLD patients. X±SD or Me [25%;75%].

Indicators	Control group (n = 23)		Group IA (n = 26)		Group IB (n = 23)		Significance of difference, p
	Before	After	Before	After	Before	After	
Total cholesterol (mmol/L)	5.7 ± 1.0	5.1 ± 0.8	5.9 ± 0.9	5.1 ± 0.8	5.7 ± 0.9	4.7 ± 0.8	p1 < 0.001 p2 < 0.001 p3 < 0.001
LDL-C (mmol/L)	3.4 ± 0.8	3.0 ± 0.7	3.3 ± 0.8	2.9 ± 0.7	3.5 ± 0.7	2.7 ± 0.6	p1 < 0.001 p2 < 0.001 p3 < 0.001
HDL-C (mmol/L)	1.1 [1.1; 1.4]	1.2 [1.1; 1.4]	1.3 [1.1; 1.4]	1.4 [1.2; 1.5]	1.1 [1.0; 1.3]	1.4 [1.2; 1.5]	p1 < 0.001 p2 < 0.001 p3 < 0.001
Triglycerides (mmol/L)	2.1 [1.9; 2.8]	1.87 [1.72; 2.38]	2.3 [1.9; 2.8]	1.8 [1.5; 2.2]	2.2 [1.9; 2.9]	1.6 [1.3; 2.1]	p1 < 0.001 p2 < 0.001 p3 < 0.001
Globorisk (10-year risk, %)	27.9 [16.7; 33.9]	22.1 [13.2; 27.6]	30.5 [21.4; 44.6]	21.9 [18.4; 37.2]	20.8 [15.7; 40.2]	14.8 [10.5; 28.6]	p1 < 0.001 p2 < 0.001 p3 < 0.001
Framingham (10-year risk, %)	15.1 [9.2; 21.5]	11.9 [7.3; 16.6]	17.7 [13.5; 32.5]	14.9 [9.7; 25.4]	15.2 [10.1; 30.3]	12.7 [5.9; 20.4]	p1 < 0.001 p2 < 0.001 p3 < 0.001
ACC/AHA ASCVD (10-year risk, %)	8.9 [4.2; 11.7]	6.5 [3.1; 9.1]	11.2 [7.8; 20.2]	6.4 [5.5; 15.2]	7.9 [3.8; 17.7]	4.1 [2.2; 11.1]	p1 < 0.001 p2 < 0.001 p3 < 0.001
PROCAM (10-year risk, points)	39.4 ± 9.4	34.8 ± 9.7	44.3 ± 9.9	36.4 ± 9.0	41.2 ± 11.2	34.9 ± 9.6	p1 < 0.001 p2 < 0.001 p3 < 0.001
WHO CVD (10-year risk, %)	16 [13; 17]	15 [11; 16]	19 [14; 27.5]	16 [13; 24]	16 [10; 26]	13 [8; 18]	p1 < 0.001 p2 = 0.002 p3 < 0.001

Note: p1 - statistical significance of the difference between the control group and Group IA, p2 - statistical significance of the difference between the control group and Group IB, p3 - statistical significance of the difference between Group IA and Group IB.

dapagliflozin group (p = 0.02) and the liraglutide group (p = 0.04) showed significantly greater reductions versus control. No statistically significant differences were found between the intervention groups for any of the cardiovascular risk tools (p > 0.05).

Discussion

In this 6-month prospective study, patients with MASLD and type 2 diabetes mellitus were evaluated for changes in lipid profile parameters and cardiovascular risk using five validated stratification tools (Globorisk, Framingham Risk Score, ASCVD Risk Calculator, PROCAM, and WHO CVD risk chart) [8-12]. The analysis focused on the magnitude of change (delta values) to assess the comparative effectiveness of liraglutide and dapagliflozin, alongside standardized lifestyle intervention.

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Table 3. Intergroup comparison of changes (Δ) in lipid profile and cardiovascular risk scores after 6 months of treatment (X ± SD or Me [25%; 75%]).

Indicators	Control group (n = 23)	Group IA (n = 26)	Group IB (n = 23)	Significance of difference, p
Total cholesterol (mmol/L)	-0.54 [-0.65; -0.44]	-0.74 [-0.88; -0.65]	-0.97 [-1.21; -0.85]	p1 < 0.05 p2 < 0.01 p3 < 0.01
LDL-C (mmol/L)	-0.42 [-0.48; -0.32]	-0.44 [-0.48; -0.35]	-0.77 [-0.83; -0.66]	p1 > 0.05 p2 < 0.01 p3 < 0.01
HDL-C (mmol/L)	0.05 [0.03; 0.05]	0.13 [0.1; 0.14]	0.23 [0.2; 0.26]	p1 < 0.01 p2 < 0.01 p3 < 0.01
Triglycerides (mmol/L)	-0.28 [-0.31; -0.22]	-0.53 [-0.61; -0.44]	-0.65 [-0.89; -0.59]	p1 < 0.01 p2 < 0.01 p3 > 0.05
Globorisk (10-year risk, %)	-0.52 ± 1.46	-0.64 ± 2.87	-0.67 ± 4.56	p = 0.35
Framingham (10-year risk, %)	-3.59 ± 1.78	-4.76 ± 3.43	-6.28 ± 4.58	p1 = 0.52 p2 = 0.04 p3 = 0.34
ACC/AHA ASCVD (10-year risk, %)	-2.34 [-2.93; -1.17]	-3.76 [-5.42; -1.82]	-2.66 [-5.68; -1.41]	p = 0.27
PROCAM (10-year risk, points)	-4.67 ± 2.83	-7.87 ± 4.4	-7.62 ± 3.58	p1 = 0.02 p2 = 0.04 p3 = 0.97
WHO CVD (10-year risk, %)	-2 [-3; -1]	-3 [-4; -1]	-3 [-7.5; -2]	p = 0.06

Note: p – statistical significance of the overall difference between the three groups; p1 – significance between control and Group IA; p2 – between control and Group IB; p3 – between Group IA and Group IB.

Within-group analysis demonstrated significant improvements in all lipid profile components across the three study groups, confirming the metabolic benefit of both pharmacological and non-pharmacological approaches [18]. Notably, the liraglutide group showed the most pronounced improvements in total cholesterol, LDL-C, and HDL-C levels compared to the control and dapagliflozin groups [19]. These findings are consistent with previously reported data on the lipid-modulating effects of GLP-1 receptor agonists, which are thought to enhance reverse cholesterol transport, reduce hepatic lipogenesis, and improve insulin sensitivity [14].

Triglyceride levels also decreased significantly in all groups, with both pharmacologic interventions outperforming lifestyle modification alone. Although liraglutide demonstrated numerically greater triglyceride reduction compared to dapagliflozin, the difference did not reach statistical significance [20].

Cardiovascular risk, as assessed by all five tools, declined significantly within each group. Intergroup comparisons revealed that the liraglutide group achieved a greater reduction in Framingham risk score compared to the control group, while both active treatment groups demonstrated significantly greater reductions in PROCAM scores. No statistically significant differences were observed between the two pharmacologic agents across the other risk models, which may reflect the overall effectiveness of both drugs in addressing cardiometabolic risk,

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as well as the inherent limitations of standard cardiovascular risk calculators in detecting subtle therapeutic differences, particularly in populations with existing metabolic disease [21].

Although liraglutide did not demonstrate statistically significant superiority over dapagliflozin in the change of lipid parameters and cardiovascular risk scores, a numerical trend toward a greater effect was observed. This trend can be explained by the limited duration of treatment and the small sample size. This observation warrants further investigation in larger, longer-term studies.

Conclusions

This 6-month prospective study demonstrated that both liraglutide and dapagliflozin significantly improved lipid profiles and reduced cardiovascular risk in patients with MASLD and type 2 diabetes mellitus. Total cholesterol, LDL cholesterol, and triglyceride levels decreased, while HDL cholesterol increased in all study groups.

Intergroup comparisons based on changes from baseline (delta values) revealed more pronounced improvements in total cholesterol, LDL-C, and HDL-C levels in the liraglutide group compared to both the control and dapagliflozin groups, suggesting a potential advantage of GLP-1 receptor agonists in modulating lipid metabolism.

Cardiovascular risk, assessed using five validated stratification tools, decreased significantly within each group. Statistically significant intergroup differences were observed for the Framingham score, favoring liraglutide over control, and for the PROCAM score, favoring both pharmacological treatments over lifestyle modification alone, with no consistent difference between liraglutide and dapagliflozin.

The observation that only the PROCAM score demonstrated statistically significant intergroup differences for both pharmacological treatments, while the Framingham score detected a significant difference only for liraglutide versus control, suggests that these models may be more sensitive to capturing between-group treatment effects in this specific patient population. However, this hypothesis requires confirmation in larger studies.

Informed Consent of Patients

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

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Conflict of Interest

The authors declare that they have no financial, academic, or personal conflicts of interest related to the publication of this article.

Consent to publication

The author has read and approved the final version of the manuscript. All authors consented to the publication of this manuscript.

AI Disclosure

No AI tools were used in the preparation of this manuscript.

Ethical approval

Approved by the Bioethics Committee, protocol №187, dated 23.09.2024.

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Порівняльний вплив ліраглутиду та дапагліфлозину на ліпідний профіль і серцево-судинний ризик у пацієнтів з стеатотичною хворобою печінки, асоційованою з метаболічною дисфункцією, та цукровим діабетом 2 типу: рандомізоване 6-місячне дослідження

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Анотація: *Стеатотична хвороба печінки, асоційована з метаболічною дисфункцією, часто поєднується з цукровим діабетом 2 типу, що призводить до підвищення кардіометаболічного ризику. Фармакологічні засоби, такі як агоністи рецепторів глюкагоноподібного пептиду-1 та інгібітори натрійзалежного котранспортера глюкози-2, можуть покращувати ліпідний обмін і серцево-судинні наслідки, однак порівняльні дані залишаються обмеженими. Оцінити та порівняти величину змін (дельти) показників ліпідного профілю та серцево-судинного ризику, розрахованого за п'ятьма валідованими шкалами, у пацієнтів із стеатотичною хворобою печінки, асоційованою з метаболічною дисфункцією, і цукровим діабетом 2 типу після 6-місячного лікування ліраглутидом або дапагліфлозином. Це 6-місячне проспективне рандомізоване дослідження включало 72 пацієнтів із стеатотичною хворобою печінки, асоційованою з метаболічною дисфункцією, і цукровим діабетом 2 типу, розподілених на три групи: контроль (модифікація способу життя; n=23), дапагліфлозин (10 мг/добу; n=26) або ліраглутид (до 1,8 мг/добу; n=23). Ліпідний профіль та серцево-судинний ризик оцінювали на початку та після лікування за п'ятьма валідованими шкалами (Globorisk, Framingham Risk Score, ASCVD Risk Calculator, PROCAM, WHO CVD chart). Міжгрупові порівняння проводили за змінами від вихідного рівня. У всіх групах відмічено достовірні внутрішньогрупові покращення ліпідних показників: зниження рівнів загального холестерину, ліпопротеїнів низької щільності та тригліцеридів і підвищення ліпопротеїнів високої щільності (p<0.001). Група ліраглутиду продемонструвала більш виражені покращення загального холестерину, ліпопротеїнів низької щільності та ліпопротеїнів високої щільності порівняно з контрольною групою та групою дапагліфлозину (p<0.01). Показники серцево-судинного ризику достовірно знизилися в кожній групі. Міжгрупові порівняння показали значущі відмінності для шкали Framingham (на користь ліраглутиду порівняно з контролем) та шкали PROCAM (на користь обох фармакологічних втручань порівняно з контролем). Узгоджених відмінностей між ліраглутидом і дапагліфлозином за іншими моделями ризику не виявлено. Ліраглутид і дапагліфлозин покращують ліпідний профіль та знижують серцево-судинний ризик у пацієнтів із стеатотичною хворобою печінки, асоційованою з метаболічною дисфункцією, і цукровим діабетом 2 типу. Хоча статистично значущої переваги ліраглутиду над дапагліфлозином*

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щодо показників серцево-судинного ризику не встановлено, спостерігалася стійка тенденція до більш вираженого покращення ліпідного профілю. Необхідні подальші дослідження з більшою вибіркою та тривалішим спостереженням для уточнення цих результатів.

Ключові слова: стеатотична хвороба печінки, асоційована з метаболічною дисфункцією, серцево-судинний ризик, ліраглутид, дапагліфлозин, цукровий діабет 2 типу.

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Diagnostic and Prognostic Potential of Circulating HSP70 and GRIN2B in Primary Open-Angle Glaucoma

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Abstract: *Primary open-angle glaucoma is increasingly recognized as a multifactorial neurodegenerative disease in which the progression of optic nerve damage is driven not only by elevated intraocular pressure but also by disturbances in vascular regulation, metabolic imbalance, oxidative stress, and glutamate-mediated excitotoxicity. These mechanisms create the need to identify circulating biomarkers capable of reflecting early and ongoing injury of retinal ganglion cells. The HSP70 is considered an indicator of cellular stress and a potential mediator of endogenous neuroprotection, while the NR2B subunit of the glutamate receptor, encoded by the GRIN2B gene, is involved in excitotoxic neuronal damage. The present study investigated the plasma concentrations of these two markers in individuals with primary open-angle glaucoma and healthy participants, as well as their dynamics after a short course of neuroprotective therapy consisting of reduced glutathione and citicoline. The findings demonstrated a significantly higher level of HSP70 in patients compared with healthy individuals, supporting its role as a marker of oxidative and stress-related neuronal injury. In contrast, the GRIN2B marker did not differ significantly between groups before treatment, although a tendency toward higher values in patients was observed. After ten days of combined therapy, neither marker showed a statistically significant group-level change, which may reflect substantial inter-individual variability, insufficient treatment duration, or the need for larger sample sizes to detect subtle neurobiological effects. Despite the lack of a significant difference in baseline values, the GRIN2B marker exhibited a strong prognostic ability in identifying individuals who demonstrated a favorable biochemical response to treatment, suggesting potential utility in patient stratification and monitoring early therapeutic effects. HSP70 demonstrated limited predictive value over the short therapeutic interval, which may reflect the complexity of its regulation and the need for longer observation windows. Overall, the results indicate that these circulating proteins may complement existing clinical tools for assessing disease mechanisms in primary open-angle glaucoma. HSP70 may serve as an indicator of oxidative stress and retinal ganglion cell injury, while the GRIN2B marker may hold promise as an early indicator of treatment response. Further research is required to determine their stability over time, relevance in different disease stages, and suitability for integration into clinical decision-making.*

Key words: Apoptosis, Glaucoma, Glutamate Receptor, HSP70 Heat-Shock Proteins, Oxidative Stress, Nerve Neuroprotection, Degeneration.

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Introduction

Glaucoma is one of the leading causes of irreversible blindness, with primary open-angle glaucoma (POAG) being its most common form in older adults. Although elevated intraocular pressure remains a key factor, current evidence indicates that the progression of glaucomatous neuropathy is also driven by vascular, metabolic, oxidative, and excitotoxic mechanisms [1, 2]. This has increased interest in systemic biomarkers of neurodegeneration for assessing the condition of retinal ganglion cells and the effectiveness of neuroprotection.

In recent years, compelling evidence has accumulated regarding the role of oxidative stress in the pathogenesis of glaucoma. Meta-analyses and systematic reviews have demonstrated an imbalance between pro-oxidant and antioxidant systems in glaucoma patients—characterized by elevated oxidative markers and reduced activity of antioxidant enzymes and reduced glutathione [3, 4].

Heat shock proteins, particularly HSP70, are considered universal molecular chaperones that are induced in response to various forms of cellular stress (ischemia, oxidative injury, inflammation). They may reflect both the degree of tissue damage and the activation of endogenous neuroprotective mechanisms. A recent literature review demonstrated that HSP70 expression increases in ocular tissues across a broad spectrum of pathologies, including glaucoma, and that most experimental studies show protective effects of HSP70 on the retina and optic nerve [5]. In experimental ischemia–reperfusion models, pharmacological induction of HSP70 is accompanied by reduced apoptosis of retinal ganglion cells and decreased glial activation, confirming its key role in neuroprotection [6]. Several reports have shown that alterations in HSP70 expression in blood and aqueous humor are associated with the risk of POAG development and progression, although these findings remain fragmented and require confirmation in larger cohort studies [7]. Therefore, HSP70 may serve as a circulating marker of stress-induced damage to the visual pathway in glaucoma; however, its clinical relevance in POAG remains insufficiently defined.

In parallel with oxidative stress, glutamate-mediated excitotoxicity via NMDA receptor activation plays a crucial role in retinal ganglion cell death. The NR2B subunit of this receptor is encoded by the GRIN2B gene and is critical for calcium-dependent signaling that triggers apoptosis and neurodegeneration [8]. During acute ischemic injury of neural tissues, degradation fragments of NR2 (the so-called NR2 peptide), as well as autoantibodies to NR2A/NR2B, can be detected in the blood and are considered specific biomarkers of excitotoxic neuronal injury. Contemporary reviews on biomarkers of stroke and transient ischemic attacks identify the NR2 peptide and NR2A/NR2B autoantibodies as among the most promising markers of acute ischemic brain damage, demonstrating high sensitivity and specificity [9].

Despite the clear pathophysiological parallels between glaucomatous optic neuropathy and other chronic neurodegenerative or ischemic CNS disorders, systemic markers of NMDA-receptor-related excitotoxicity (NR2/GRIN2B) remain virtually unexplored in POAG patients. Existing studies largely focus on genetic variants of GRIN2B and their role in psychiatric and cognitive disorders rather than on the measurement of circulating proteins or their fragments as indicators of glutamate-mediated neuronal damage [10]. Data on circulating GRIN2B/NR2 levels in glaucoma patients, their association with clinical characteristics of the disease, and their dynamics during treatment are currently lacking, creating a substantial gap in current knowledge.

A distinct direction in modern glaucoma research is the development of effective neuroprotective strategies aimed at preserving retinal ganglion cells, independently of intraocular pressure. Citicoline, a precursor of phosphatidylcholine and acetylcholine, is considered one of the key neuroprotective agents. Recent randomized trials have shown that oral citicoline (as part of combination regimens) improves pattern electroretinogram parameters in patients with open-angle glaucoma with well-controlled IOP [11]. Additionally, recent studies on oxidative stress in POAG highlight reduced levels of reduced glutathione, providing

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a rationale for the use of glutathione-containing agents as components of antioxidant therapy [4].

Thus, on the one hand, the search for reliable circulating biomarkers reflecting oxidative stress (HSP70) and glutamate-mediated excitotoxicity (GRIN2B/NR2) in POAG patients remains highly relevant; on the other hand, evaluating their dynamics during combined neuroprotective therapy with citicoline and glutathione represents an important research objective.

Aim

To investigate the levels of HSP70 and GRIN2B in patients with POAG and to evaluate the dynamics of changes in these biomarkers following a course of reduced glutathione and citicoline.

Materials and methods

The study included 47 individuals aged 50 to 77 years, comprising 22 women and 25 men. The control group (group 1) consisted of 9 healthy participants with no ophthalmic or systemic pathology. The main group (group 2) included 38 patients with POAG and compensated intraocular pressure on standard hypotensive therapy, without concomitant neurological diseases or other conditions that could potentially affect metabolic or neurodegenerative biomarkers. Exclusion criteria for both groups included the use of medications capable of modulating oxidative stress or neuroprotective mechanisms (excluding ocular hypotensive therapy and the study-assigned treatment). Among the main group, 15 patients received pharmacological therapy for 10 days, including reduced glutathione at a dose of 250 mg/day and citicoline at a dose of 500 mg/day. All procedures complied with the Declaration of Helsinki, and the study received approval from the local ethics committee. All participants voluntarily signed informed consent.

Venous blood samples were collected from all participants in the morning, after an overnight fast, under standard conditions. The control group and POAG patients underwent baseline sampling at the beginning of the study. The second sampling was performed after 10 days only in the 15 patients who received pharmacological therapy. Peripheral blood was centrifuged according to standard protocols, and the resulting plasma was stored at –80 °C until analysis. Biomarker concentrations were determined using enzyme-linked immunosorbent assay (ELISA) with certified commercial kits. The markers measured included HSP70 (Heat Shock Protein 70) and Human GRIN2B (glutamate receptor, NR2B subunit). Results were expressed in ng/mL. All laboratory procedures were performed in accordance with Good Laboratory Practice (GLP).

Statistical analysis was conducted using Statistica 10.0 (Statsoft, USA). Descriptive statistics were presented as mean ± standard deviation (M ± SD). An independent samples t-test was used to compare the control group and POAG patients before treatment, while the paired t-test was used to evaluate changes after therapy. Diagnostic informativeness of HSP70 and GRIN2B was assessed through intergroup comparisons. Clinical significance of changes was evaluated using Cohen's d. Relationships between pre- and post-treatment values were analyzed using linear regression with calculation of β and R^2. The prognostic capability of the markers was assessed using ROC analysis, with calculation of AUC and optimal threshold based on Youden's index (sensitivity, specificity). A p-value < 0.05 was considered statistically significant.

Results

To assess the diagnostic informativeness of the HSP70 and GRIN2B markers, their levels were compared between the patient group before treatment and healthy individuals (Fig. 1).

The mean GRIN2B level in patients before treatment was 1.95 ng/mL, whereas in the control group it was 1.48 ng/mL. Although patients demonstrated a tendency toward higher GRIN2B values, the difference was not statistically significant ($p = 0.483$). In contrast to GRIN2B, HSP70 showed clearly pronounced differences. The mean HSP70 level in patients before treatment was 12.35 ng/mL, which significantly exceeded the control group value of 5.08 ng/mL, with a statistically significant difference ($p = 0.032$).

A total of 15 paired measurements of heat shock protein (HSP70) levels before and after treatment were analyzed. In most cases, post-

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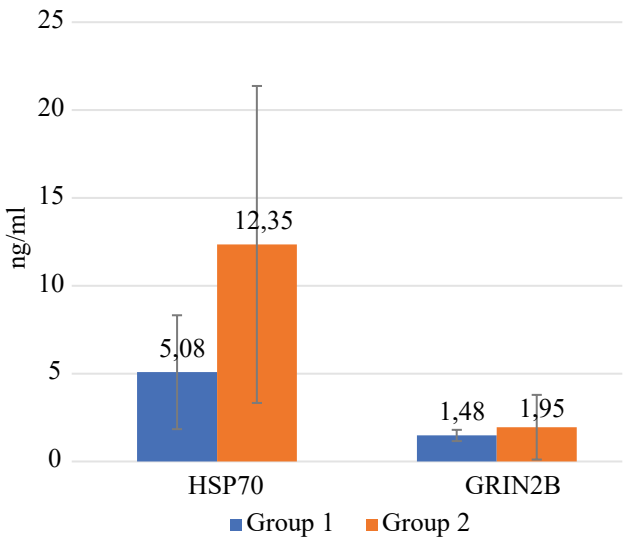

Fig. 1. Levels of HSP70 and GRIN2B in control group and patients with POAG

treatment HSP70 levels exceeded baseline values. The mean difference was 4.72 ± 16.74; however, no statistically significant changes were detected ($p = 0.29$). Cohen's d indicated a small effect size ($d = 0.28$), suggesting high inter-individual variability in treatment response. Linear regression demonstrated a weak and statistically non-significant association between baseline and post-treatment HSP70 levels ($\beta = 0.41$; $p = 0.13$; $R^2 = 0.17$), indicating limited prognostic value of this marker (Fig. 2).

The GRIN2B marker demonstrated a different pattern. In a subset of patients, GRIN2B decreased after treatment, which was interpreted as a positive therapeutic response. The mean difference was –0.02 ± 1.09, and Cohen's d was close to zero ($d = –0.02$), indicating an overall absence of a group-level effect.

Linear regression analysis for GRIN2B before and after treatment showed a weak and statistically non-significant association ($\beta = 0.05$; $R^2 = 0.01$), indicating that baseline levels did not predict post-treatment values (Fig. 2).

In the initial analysis, treatment effectiveness was evaluated based on an increase in HSP70 after therapy. The AUC was only 0.20, indicating no prognostic ability of HSP70 (Fig. 3). Even when using a ≥20% increase in HSP70 as the response criterion, diagnostic accuracy remained low.

After defining a positive response as a decrease in GRIN2B following treatment, ROC analysis demonstrated a substantial improvement in the prognostic ability of this marker. The AUC reached 0.812, indicating good diagnostic accuracy (Fig. 3).

Using Youden's index, the optimal pre-treatment GRIN2B cutoff was determined as 1.88. This threshold provided a sensitivity of 0.71 and a specificity of 1.00, making it a promising cutoff for patient stratification.

Discussion

In light of current evidence confirming the multifactorial nature of POAG — highlighting not only intraocular pressure but also vascular, metabolic, oxidative, and excitotoxic mechanisms — the search for circulating biomarkers capable of reflecting retinal ganglion cell neurodegeneration remains highly relevant. In particular, increased expression of

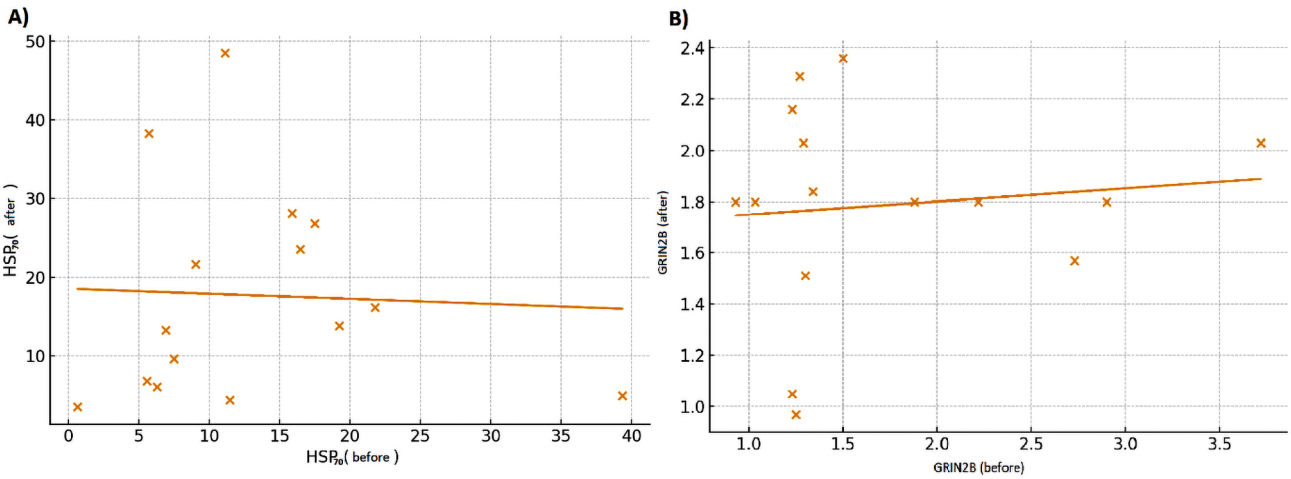

Fig. 2. Linear regression for (A) HSP70 and (B) GRIN2B before and after treatment

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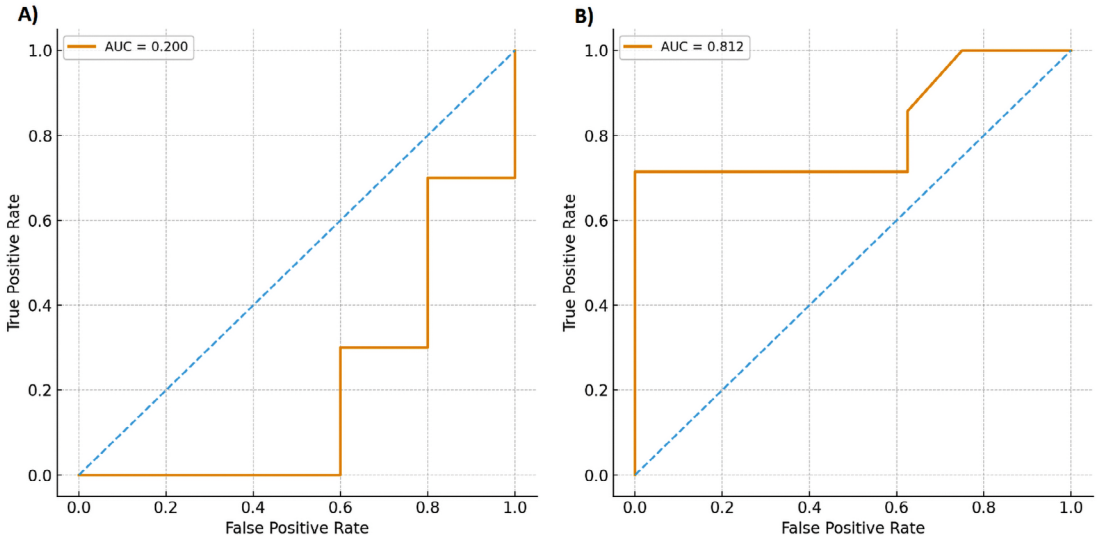

Fig 3. ROC analysis for (A) HSP70 and (B) GRIN2B.

HSP70 and the involvement of GRIN2B gene in the pathogenesis of neuronal injury provide a rational basis for our investigation. Notably, oxidative stress has been shown to play a key role in glaucomatous neuropathy through mitochondrial dysfunction and activation of reactive oxygen species [12, 13]. Additionally, NMDA-receptor activation and glutamate excess induce calcium-dependent retinal ganglion cell death [14].

In our study, we found a significant elevation of plasma HSP70 levels in POAG patients compared with healthy controls (12.35 ± 9.02 ng/mL vs. 5.08 ± 3.23 ng/mL; $p = 0.032$). This is consistent with evidence of enhanced cellular stress-response activation in glaucoma and a possible upregulation of endogenous neuroprotection via HSP70 [15]. Thus, HSP70 may serve as a potential marker of oxidative/stress-related injury within the visual pathway. However, our attempt to evaluate HSP70 dynamics after 10 days of treatment (glutathione + citicoline) revealed only a slight, statistically insignificant increase ($p = 0.29$; $d = 0.28$) and a weak prognostic association ($\beta = 0.41$; $R^2 = 0.17$). This indicates high inter-individual variability in treatment response and limited short-term prognostic value of HSP70.

Regarding the NR2/GRIN2B marker, although a tendency toward elevation before treatment was observed (1.95 ± 2.13 ng/mL in patients vs. 1.48 ± 0.35 ng/mL in controls; $p = 0.483$), the difference did not reach statistical significance. Following treatment, the mean change was minimal (–0.02 ± 1.09; $d = –0.02$), with no correlation between baseline and post-treatment levels ($\beta = 0.05$; $R^2 = 0.01$). However, a noteworthy finding emerged from the ROC analysis: AUC = 0.812, and the optimal cutoff of 1.88 ng/mL provided a sensitivity of 0.71 and a specificity of 1.00. This suggests that plasma NR2/GRIN2B may serve as a marker of therapeutic response or patient stratification, despite the absence of a statistically significant group shift. Given the limited number of studies assessing circulating NR2/GRIN2B biomarkers in glaucoma, our findings address an important knowledge gap.

When comparing our results with existing literature, it should be noted that most studies focus on oxidative stress while few investigate circulating protein biomarkers of neurodegeneration in glaucoma. For example, a recent review emphasized oxidative stress as a central mechanism of glaucomatous neuropathy and a potential therapeutic target [16]. Meanwhile, the role of NMDA-mediated excitotoxicity in glaucoma is discussed mainly in experimental models, and clinical data on NR2B protein or its autoantibodies remain fragmented. Our findings support the concept that NR2/GRIN2B may be a relevant biomarker — although larger studies with longer therapeutic interventions and inclusion of clinical endpoints are required.

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From a practical perspective, the results obtained have several implications. First, elevated HSP70 in POAG reinforces the rationale for incorporating antioxidant and neuroprotective strategies alongside intraocular pressure control. Second, NR2/GRIN2B may serve as a tool for patient stratification or monitoring treatment response to neuroprotective agents, though its clinical use requires further validation. At the same time, the short 10-day treatment period did not allow for conclusive HSP70 changes, indicating the need for longer observation and larger samples.

In summary, our study demonstrates that HSP70 and NR2/GRIN2B hold potential as circulating biomarkers in POAG: HSP70 as an indicator of stress-related neuroinjury, and NR2/GRIN2B as a possible marker of therapeutic response. However, further research involving larger cohorts and longer treatment durations is necessary before their implementation in clinical practice.

Conclusions

In patients with primary open-angle glaucoma, a significantly elevated level of HSP70 was detected compared with healthy individuals, confirming its role as a marker of oxidative stress and neuronal injury. In contrast, GRIN2B/NR2 did not demonstrate statistically significant intergroup differences but showed good prognostic capability in the ROC analysis for identifying patients who may potentially respond to neuroprotective therapy. The short 10-day course of glutathione and citicoline treatment did not produce significant changes in the levels of the studied biomarkers, which may indicate the need for a longer therapeutic intervention or larger sample sizes to detect meaningful effects. The results obtained highlight the potential of HSP70 as a diagnostic indicator and GRIN2B as a marker of therapeutic response, emphasizing the need for further studies to clarify their clinical significance in the management of glaucomatous neuropathy.

Financing

This study did not receive external funding.

Conflict of interest

The authors declare that there is no conflict of interest and no financial interest in the preparation of this article.

Consent to publication

All authors have read and approved the final version of the manuscript. All authors have agreed to publish this manuscript. AI tools were not used in preparing this manuscript.

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Діагностичний та прогностичний потенціал циркулюючих HSP70 та GRIN2B при первинній відкритокутовій глаукомі

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Анотація: *Первинна відкритокутова глаукома дедалі частіше розглядається як мультифакторне нейродегенеративне захворювання, прогресування якого зумовлене не лише підвищеним внутрішньоочним тиском, а й порушеннями судинної регуляції, метаболічним дисбалансом, оксидативним стресом та глутамат-опосередкованою ексайтотоксичністю. Ці механізми формують потребу у виявленні циркулюючих біомаркерів, здатних відображати*

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раннє та поточне ураження гангліозних клітин сітківки. HSP70 вважають індикатором клітинного стресу та потенційним медіатором ендогенного нейропротекційного захисту, тоді як субодиниця рецептора глутамату NR2B, кодована геном GRIN2B, бере участь в ексайтотоксичному ушкодженні нейронів. У цьому дослідженні було проаналізовано концентрації цих двох маркерів у плазмі крові в осіб з первинною відкритокутовою глаукомою та у здорових учасників, а також їхню динаміку після короткого курсу нейропротективної терапії, що включала відновлений глутатіон і цитиколін. Отримані результати показали значно вищий рівень HSP70 у пацієнтів порівняно зі здоровими особами, що підтверджує його роль як маркера оксидативного та стрес-асоційованого нейронального ушкодження. На відміну від цього, рівень маркера GRIN2B достовірно не відрізнявся між групами до лікування, хоча спостерігалася тенденція до вищих значень у пацієнтів. Після десятиденного комбінованого лікування жоден із маркерів не продемонстрував статистично значущої зміни на груповому рівні, що може відображати значну міжіндивідуальну варіабельність, недостатню тривалість терапії або потребу у збільшенні вибірки для виявлення тонких нейробіологічних ефектів. Незважаючи на відсутність суттєвої різниці у вихідних значеннях, маркер GRIN2B продемонстрував високу прогностичну здатність щодо ідентифікації осіб, які показали сприятливу біохімічну відповідь на лікування, що свідчить про його потенційну користь для стратифікації пацієнтів і моніторингу ранніх терапевтичних ефектів. HSP70 продемонстрував обмежену прогностичну цінність у короткий терапевтичний інтервал, що може бути зумовлено складністю його регуляції та необхідністю тривалішого періоду спостереження. Загалом результати свідчать, що ці циркулюючі білки можуть доповнювати наявні клінічні інструменти для оцінки механізмів розвитку первинної відкритокутової глаукоми. HSP70 може слугувати індикатором оксидативного стресу та ушкодження гангліозних клітин сітківки, тоді як маркер GRIN2B може мати перспективу як ранній індикатор відповіді на лікування. Подальші дослідження необхідні для визначення їх рівнів в динаміці, значення на різних стадіях захворювання та можливості інтеграції у процес клінічного прийняття рішень.

Ключові слова: Апоптоз, Глаукома, Рецептор Глутамату, Дегенерація, HSP70 Білки теплового шоку, Нейропротекція, Оксидативний стрес.

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Dynamics of endogenous intoxication in combination with insulin resistance and excretory pancreatic insufficiency under the influence of various treatment complexes

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Abstract: *In type 2 diabetes mellitus, a connection has been established between markers of inflammation, endogenous intoxication and the functional activity of pancreatic β-cells. A significant increase in endogenous intoxication due to the inflammatory process in the pancreatic tissue impairing its functions, including excretory. The aim was to assess the severity of endogenous intoxication in the presence of comorbidity of type 2 diabetes mellitus and excretory pancreatic insufficiency, to verify the feasibility of enhancing conventional treatment with the drug phenibut and acupressure techniques. 45 people with a combination of type 2 diabetes mellitus and excretory pancreatic insufficiency underwent several assessments of the severity of endogenous intoxication. Levels of medium-mass molecules with maximum absorption at wavelengths of 254 nm and 280 nm, and the sorption capacity of erythrocytes were determined. The study group was divided into subgroups according to the treatment method: standardized therapy, additional inclusion of phenibut, and strengthening the drug complex with acupressure courses. The violation of the processes of maintaining homeostasis and the increase in endogenous intoxication in the studied group is indicated by a significant excess of the control values of the indicators by 1.7-2.1 times. A decrease in endogenous intoxication indicators (on average by 9.14 %) was detected during standardized therapy. However, in the sixth month, a significant repeated increase in the above indicators was observed. Additional use of phenibut had a more significant effect on the manifestations of endogenous intoxication by an average of 27.70 %. The positive dynamics were still evident when repeating the laboratory test after six months. The combination of conventional treatment, use of phenibut and undergoing a course of acupressure during the first month caused the most pronounced correction of endogenous intoxication – on average by 42.44 %. No significant dynamics of endogenous intoxication parameters were observed during the sixth month of the study, which indicates the stability of the changes achieved during the first stage of treatment. The only exception was the sorption capacity of erythrocytes, which showed signs of normalization. A significant increase in endogenous intoxication due to the accumulation of metabolic products was found in the combination of type 2 diabetes mellitus with excretory pancreatic insufficiency. Additional use of the drug phenibut and acupressure courses led to a decrease in endogenous intoxication, which was more pronounced and persistent than in the subgroup with exclusively conventional treatment.*

Keywords: Acupressure, Diabetes Mellitus, Dyspepsia, Phenibut, Pancreatic Insufficiency, Medium-Weight Molecules, Sorption Capacity Of Erythrocytes.

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Introduction

Endogenous intoxication (EI) occurs as a result of an imbalance between the synthesis and excretion of metabolic products. In addition, deterioration of gas exchange, microcirculation, activation of the coagulation and kallikrein-kinin systems, accumulation of reactive oxygen species and stress molecules also develops [1]. The vast majority of metabolic products are medium-mass molecules (MMM) – from 300 to 5000 daltons. These include products of fibrinogen hydrolysis, globulins, hormone catabolism, phagocytosis inhibitors, etc. These protein compounds in increased concentrations have a toxic effect on the body [2]. EI can be especially pronounced in those pathological conditions whose pathogenesis is characterized by metabolic disorders. Examples of these are hyperglycemia caused by insulin resistance and excretory insufficiency of the pancreas, which worsens the trophic status [3, 4].

A relationship between inflammatory markers, EI, and functional activity of pancreatic β-cells has been established in type 2 diabetes mellitus (DM). This further reduces glycemic control in the presence of insulin resistance [2, 5]. Excretory pancreatic insufficiency (EPI) is most often a consequence of chronic fibrotic inflammation of the pancreas [6]. It causes dyspepsia due to maldigestion (impaired digestion) and malabsorption (impaired absorption due to the development of secondary enteritis), which leads to a general destabilizing effect on the body [7, 8].

The higher probability of endotoxicosis can complicate the management of patients with a combination of type 2 DM and EPI, creating the need to take into account additional laboratory indicators to understand the current state of the body in conditions of comorbidity, the selection of optimal treatment and rehabilitation regimens. The drug phenibut and the reflexotherapy technique of acupressure were chosen as auxiliary correction tools. Phenibut has antihypoxic properties, contributes to the normalization of metabolism and improvement of blood flow, primarily in brain tissue [9]. The acupressure technique was chosen of the non-drug methods. It is a stimulation of biologically active points, combines the therapeutic effects of massage and reflexotherapy [10].

Aim

The aim was to assess the severity of endogenous intoxication in the presence of comorbidity of type 2 diabetes mellitus and excretory pancreatic insufficiency, to verify the feasibility of enhancing conventional treatment with the drug phenibut and acupressure techniques.

Materials and methods

The study was carried out on the basis of the Center for Primary Health Care of Ternopil and the polyclinic of the Ternopil Municipal City Hospital No. 2 Patients were informed about the study and provided written consent in accordance with the World Medical Association Declaration of Helsinki «Ethical Principles for Medical Research Involving Human Subjects» (2013, principles No. 25-27, 31), the Council of Europe Convention on Human Rights and Biomedicine, as well as in accordance with the legislation of Ukraine (Protocol No. 82 of the Bioethics Commission of I. Horbachevsky Ternopil National Medical University of the Ministry of Health of Ukraine of September 03, 2025). Comorbidity of type 2 DM and EPI was a criterion for inclusion in the study group. Exclusion criteria: type 1 DM, previous surgical interventions on the abdominal organs, malignant neoplasms of the pancreas, the presence of other clinically significant concomitant diseases in the phase of exacerbation or unstable remission. Examination, treatment courses and rehabilitation were conducted by 45 people with a combined course of type 2 DM with EPI. The study group was randomly divided into three equal subgroups of 15 people:

- use of standardized therapy (ST) according to current protocols;
- ST enhancement by taking phenibut (STP) 1 tablet (250 mg) twice a day (morning and afternoon) for 10 days with subsequent transition to half the dose for the next 4 days;
- strengthening of drug treatment with a course of acupressure (STPA) of 14 sessions using the braking method, massage was performed at points along the

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paravertebral lines and areas related to the pancreas.

A second course of phenibut for patients in the second subgroup and a second course of phenibut and acupressure for patients in the third were carried out after 6 months. The results were compared with a control group consisting of 10 healthy individuals.

The EI characteristic was represented by medium-mass molecules with an absorption maximum at a wavelength of 254 nm (MMM1, containing aromatic amino acids, indicating the activation of catabolic processes) and 280 nm (MMM2, containing nucleotides, indicating the content of nitrogenous metabolic products), sorption capacity of erythrocytes (SCoE). MMM were determined in blood plasma according to a modification of the method of N. Gabrielyan and co-authors [2, 11]. SCoE was determined according to the method of A. Togoibayev and co-authors [12].

Statistical analysis of the research results was performed using an Intel Core i3-8100 personal computer, MicrosoftOffice 2016 and IBM SPSS Statistics 26 licensed software packages. It included calculation of the arithmetic mean and its error (M ± m), parametric (Student's t test) and nonparametric methods (if the data distribution differs from the "normal"): Mann-Whitney U test, Wilcoxon W test. The risk of error of less than 5.0 % ($p<0.05$) was considered a reliability criterion.

Results

A significant ($p<0.001$) excess of the control values of MMM1 (1.7 times), MMM2 (1.8 times), SCoE (2.1 times) indicates a violation of the processes of maintaining homeostasis and increased EI in the combination of type 2 DM and EPI (Fig. 1).

A decrease in the concentration of MMM1 (by 8.76 %), MMM2 (by 6.78 %) and SCoE (by 11.87 %) by an average of 9.14 % was detected in the ST subgroup 1 month after the start of treatment (Table 1). However, at the sixth month, a significant re-growth of the above indicators was observed, which ceased to be statistically different from their own values before the start of treatment. This indicates a short-term decrease in EI when using conventional treatment, which may subsequently worsen the controllability of hyperglycemia and exocrine insufficiency, requiring the search and inclusion of additional means of correcting the patient's condition.

The combination of ST with the use of phenibut had a more significant effect on the manifestations of EI (Table 2). The decrease in MMM1 by 23.77 %, MMM2 by 24.72 %, SCoE by 34.60 % (on average by 27.70 %) during the first month of treatment was significantly different from the results of ST subgroup. When

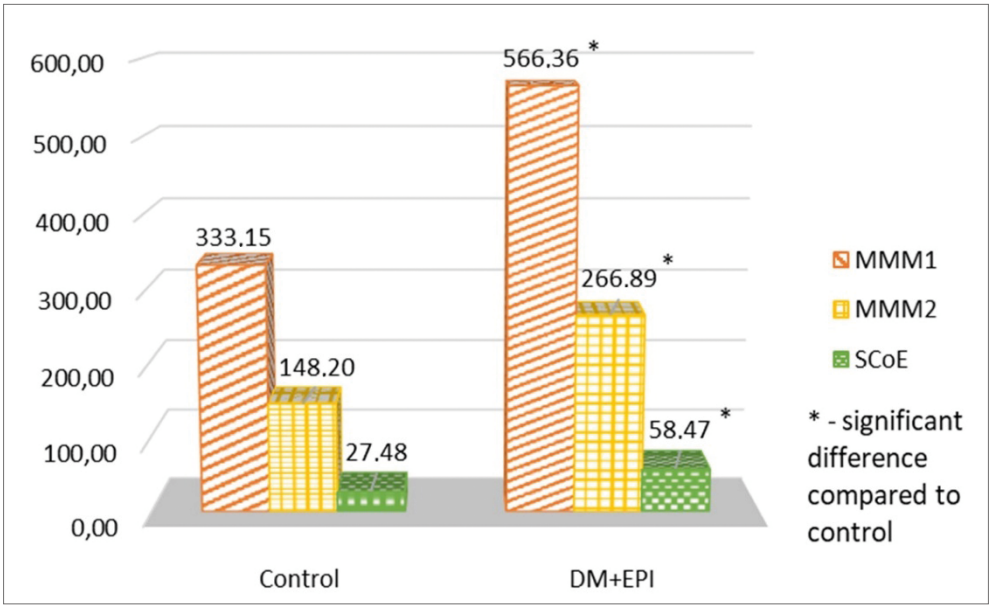

Figure 1 – EI indicators

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Table 1. Dynamics of EI parameters in patients with a combination of type 2 DM and EPI in the ST subgroup

Research group	EI parameter		
	MMM1	MMM2	SCoE
Control (n=10)	333.15±5.65	148.20±1.78	27.48±0.81
ST, pre-treatment (n=15)	574.80±12.61 *	259.60±10.88 *	60.27±1.78 *
ST, 1st month. (n=15)	524.47±15.28 *#	242.00±9.84 *#	53.12±1.62 *#
ST, 6st month. (n=15)	566.44±22.44 *##	261.53±12.56 *##	57.90±1.40 *##

Note 1. * – significant difference compared to control ($p<0.05$).
Note 2. # – significant difference compared to pre-treatment value ($p<0.05$).
Note 3. ## – significant difference compared to post first stage of treatment value ($p<0.05$).

Table 2. Dynamics of EI parameters in patients with a combination of type 2 DM and EPI in the STP subgroup

Research group	EI parameter		
	MMM1	MMM2	SCoE
Control (n=10)	333.15±5.65	148.20±1.78	27.48±0.81
STP, pre-treatment (n=15)	567.40±12.62 *	268.87±10.76 *	60.43±1.55 *
STP, 1st month. (n=15)	432.53±17.33 *#^	202.40±8.50 *#^	39.52±1.46 *#^
STP, 6st month. (n=15)	381.87±23.49 ###^	166.81±11.35 ###^	33.52±1.43 *###^

Note 1. * – significant difference compared to control ($p<0.05$).
Note 2. # – significant difference compared to pre-treatment value ($p<0.05$).
Note 3. ## – significant difference compared to post first stage of treatment value ($p<0.05$).
Note 4. ^ – significant difference compared to subgroup ST ($p<0.05$).

repeating the laboratory study after half a year, the preservation of positive dynamics was revealed, which was combined with its slowdown: MMM1 decreased by 11.71 %; MMM2 – by 17.59 %; SCoE – 15.18 %. The indicators of medium-molecular peptides ceased to differ from the control, indicating normalization.

The combination of conventional treatment, the use of phenibut and the course of acupressure during the first month caused the most pronounced correction of EI (Table 3). The decrease in MMM1 by 38.17 %, MMM2 by 45.58 % and SCoE by 43.57 % (on average by 42.44 %) significantly exceeded the corresponding values of the ST and STP subgroups. Normalization of the levels of medium-molecular peptides was also noted, which indicates the possibility of faster achievement of their target concentrations with the combined use of drug and non-drug therapeutic methods. At the 6-th month of the study, no significant dynamics of EI parameters were observed, which means the stability of the changes achieved during the first stage of treatment. The only exception was the SCoE indicator, which showed signs of normalization.

Discussion

Experiments on laboratory animals confirmed the increase in EI by the levels of MMM1 and MMM2 in experimental diabetes mellitus [13]. According to a 2022 publication, the addition of insulin resistance to the course of chronic pancreatitis in patients caused an increase in MMM1 (by 29.57 %), MMM2 (by 35.39 %), SCoE (by 19.22 %). This indicates a significant imbalance between the synthesis and excretion of metabolic products due to worsening glycemic control. Analysis of data from 112 patients

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Table 3. Dynamics of EI parameters in patients with a combination of type 2 DM and EPI in the STPA subgroup

Research group	EI parameter		
	MMM1	MMM2	SCoE
Control (n=10)	333.15±5.65	148.20±1.78	27.48±0.81
STPA,pre-treatment (n=15)	556.87±14.02 *	272.20±8.35 *	54.70±2.30 *
STPA, 1st month. (n=15)	344.33±9.38 # ^ ^^	148.13±7.13 # ^ ^^	30.87±1.09 * # ^ ^^
STPA, 6st month. (n=15)	335.20±12.46 # ^	147.41±8.01 # ^	30.28±1.57 # ^

Note 1. * – significant difference compared to control (p<0.05).
Note 2. # – significant difference compared to pre-treatment value (p<0.05).
Note 3. ## – significant difference compared to post first stage of treatment value (p<0.05).
Note 4. ^ – significant difference compared to subgroup ST (p<0.05).
Note 5. ^^ – significant difference compared to subgroup STP (p<0.05).

revealed a direct correlation between SCoE and glycated hemoglobin (r=0.552; p<0.05) and an inverse relationship between SCoE and fecal α-elastase (r=0.517; p<0.05). The above confirms the existence of mutually aggravating effects of EI, hyperglycemia, and EPI [1].

One of the potential mechanisms of influence of the means considered in our study, namely the nootropic drug phenibut and the reflexotherapy technique (acupressure), may be the relationship of EI with the autonomic nervous system and psychoemotional state. Thus, in a 2021 study, direct correlations of the Kalf-Kalif leukocyte intoxication index with autonomic dysfunction, personal anxiety, and neuroticism were found in patients with pancreatic lesions [14]. Phenibut affects the nervous system by interacting with γ-aminobutyric acid receptors, and acupressure creates a focus of prolonged impulses due to local treatment of biologically active points on the skin. Although the Kalf-Kalif index was not determined in our study, its direct correlation with MMM1 (r=0.533; p<0.05) and MMM2 (r=0.515; p<0.05) was found in a 2021 study [2].

Several studies have confirmed the beneficial effect of correction of EI indicators by infusion therapy, which led to an improvement in the course of DM and EPI comorbidity [11, 15]. However, the assessment of effective outpatient treatment methods, which was carried out in our work, is no less important. The prospect of our further studies is to increase the sample size in order to obtain a more complete statistical picture and eliminate possible calculation errors.

Conclusions

A significant increase in EI was found due to the accumulation of metabolic products when combining type 2 DM with EPI. Additional use of phenibut, as well as strengthening of combined drug therapy with acupressure courses, caused a decrease in medium molecular weight proteins and SCoE, which was more pronounced and stable than in the subgroup with exclusively conventional treatment. The inclusion of reflexology led to the achievement of target values of EI indicators more quickly.

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This study did not receive external funding.

Conflict of interests

There is no conflict of interest.

Consent to publication

Consent for publication was obtained from all patients involved in this manuscript.

AI Disclosure

No AI tools were used in the preparation of this manuscript.

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Динаміка ендогенної інтоксикації при поєднанні інсулінорезистентності та екскреторної панкреатичної недостатності під впливом різних комплексів лікування

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Анотація. *При цукровому діабеті 2-го типу встановлений зв'язок між маркерами запалення, ендогенної інтоксикації та функціональною активністю β-клітин підшлункової. Суттєве посилення інтоксикації внаслідок запального процесу у тканині підшлункової залози погіршує її функції, у тому ж числі – екскреторну. Метою дослідження є оцінка вираженості ендогенної інтоксикації при коморбідності цукрового діабету 2-го типу і екскреторної панкреатичної недостатності, перевірка доцільності посилення загальноприйнятого лікування за допомогою медикаментозного препарату фенібуту та методики акупресури. 45 осіб із поєднанням цукрового діабету 2-го типу та екскреторної панкреатичної недостатності кількаразово проходили оцінку вираженості ендогенної інтоксикації. Визначалися рівні молекул середньої маси з максимумом поглинання на довжині хвилі 254 нм та 280 нм, сорбційної здатності еритроцитів. Дослідна група була поділена на підгрупи згідно методики лікування: стандартизована терапія, додаткове включення у неї фенібуту й посилення медикаментозного комплексу курсами акупресури. Про порушення процесів підтримки гомеостазу та посилення ендогенної інтоксикації у досліджуваній групі говорить достовірне перевищення контрольних значень показників у 1.7-2.1 рази. При використанні стандартизованої терапії виявлено зниження параметрів інтоксикації (у середньому на 9.14 %). Однак на шостому місяці спостерігався достовірний повторний ріст наведених показників. Додаткове вживання фенібуту більш істотно вплинуло на прояви ендогенної інтоксикації у середньому на 27.70 %. При повторенні лабораторного дослідження через пів року виявлено збереження позитивної динаміки. Поєднання загальноприйнятого лікування, вживання фенібуту та проходження курсу акупресури протягом першого місяця викликало найбільш виражену корекцію ендогенної інтоксикації – у середньому на 42.44 %. На шостому місяці дослідження достовірної динаміки досліджуваних параметрів не спостерігалось, що означає стійкість досягнутих у ході першого етапу лікування змін. Виняток становив тільки показник сорбційної здатності еритроцитів, який проявляв ознаки нормалізації. Виявлено істотне посилення ендогенної інтоксикації за рахунок накопичення продуктів метаболізму при поєднанні цукрового діабету 2-го типу із екскреторною панкреатичною недостатністю. Додаткове вживання препарату фенібуту та проходження курсів акупресури призводили до зниження ендогенної інтоксикації, що було більш вираженим й стійким, ніж у підгрупі із виключно загальноприйнятим лікуванням.*

Ключові слова: акупресура, цукровий діабет, диспепсія, молекули середньої маси, фенібут, сорбційна здатність еритроцитів.

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Dynamics of non-specific quality of life in volunteers with neurotic and stress-related mental disorders before and after a corrective-therapeutic program

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Abstract: *This article presents the results of a study on the dynamics of non-specific quality of life in volunteers with neurotic and stress-related mental disorders before and after completion of a corrective-therapeutic program. The study included 288 volunteers aged 18 to 60 years (mean age 27.10 ± 8.36), who were divided into three groups: an experimental group (40 participants), a control group (42 participants), and a reference group (206 participants). The experimental group underwent a program that combined pharmacological treatment with a low-intensity psychological intervention, Problem Management Plus. The control group received standard treatment, while the reference group consisted of volunteers without signs of mental disorders. Quality of life was assessed using the Medical Outcomes Study Short Form 36-Item (SF-36). At baseline, quality of life indicators in volunteers with mental disorders were significantly lower across all scales compared to the reference group. In particular, on the Physical Functioning scale, mean values were 89.1 ± 6.6 in the experimental group and 89.3 ± 6.7 in the control group, both lower than 95.5 ± 6.5 in the reference group. Three months after the program, the score in the experimental group increased to 98.7 ± 2.7, exceeding the reference level ($p = 0.003$), while the control group reached 94.6 ± 4.5. On the Role-Physical scale, scores in the experimental group improved from 71.4 ± 13.7 to 92.3 ± 6.6, surpassing the reference group ($p < 0.001$), whereas the control group showed a less pronounced increase to 78.8 ± 12.6. Marked improvements were also observed in psychological domains. The Role-Emotional score in the experimental group increased from 39.4 ± 13.8 to 79.3 ± 8.0, exceeding the reference level (72.4 ± 17.7; $p < 0.001$), while remaining lower in the control group. Vitality increased from 33.6 ± 10.1 to 64.1 ± 5.8 in the experimental group, higher than the reference group (58.1 ± 11.6; $p < 0.001$), whereas the control group achieved only 45.8 ± 8.3. On the Mental Health scale, the experimental group improved from 40.4 ± 8.9 to 70.0 ± 7.3, reaching a level comparable to the reference group (65.6 ± 13.6; $p = 0.053$), while the control group remained significantly lower (47.5 ± 10.6; $p < 0.001$). Similar positive dynamics in the experimental group were observed on other scales: Social Functioning increased to 88.5 ± 7.2, surpassing the reference group (77.5 ± 18.1; $p < 0.001$); Bodily Pain reached 100 ± 0.0, higher than the control group (93.1 ± 9.2; $p < 0.001$); and General Health increased to 73.1 ± 8.3, comparable to the reference group (70.0 ± 15.0; $p = 0.220$). In the control group, quality of life indicators also improved, but the changes were less pronounced, and even after three months, most scales remained lower than those of the reference group. The obtained results demonstrate the effectiveness of combining pharmacological treatment with the Problem Management Plus psychological intervention in improving the non-specific quality of life of volunteers*

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exposed to stress factors during wartime. The application of the comprehensive program contributed not only to the normalization of quality of life but also to exceeding the levels of healthy respondents in several domains. Further research should focus on evaluating the long-term effects of this intervention and the potential for its broad implementation within psychosocial support systems for volunteers.

Keywords: Adjustment Disorders, Anxiety Disorders, Depressive Disorder, Mental Health, Psychiatry, Quality of Life, Trauma and Stressor Related Disorders, Volunteers, Stress, Psychological, Stress Disorders, Post-Traumatic, Psychoeducation.

Introduction

During the period of russia's full-scale invasion of Ukraine, the number of people exposed to traumatic events has increased, leading to the development of neurotic and stress-related disorders. According to estimates by the World Health Organization (WHO), one in five individuals (22%) who have experienced war or another armed conflict within the past 10 years is at risk of developing depression, anxiety disorder, post-traumatic stress disorder, or other mental disorders [1].

A sociological survey conducted within the framework of the nationwide mental health program "*How Are You?*", initiated by First Lady Olena Zelenska and carried out by the 4Service company, revealed a gradual decline in satisfaction with one's own mental health. The study, which took place from December 12, 2024, to January 4, 2025, found that only 21% of respondents reported being satisfied with their mental state, whereas 44% indicated dissatisfaction [2].

With regard to the emotional sphere, high levels of fatigue, tension, fear, and irritability continue to be observed among Ukrainians. The main sources of stress remain the full-scale war with russia (78% in the fourth wave of the survey) and financial difficulties (52%). At the same time, the proportion of individuals concerned about the socio-political situation in the country has significantly increased from 29% in the first wave to 47% in the fourth [2].

The greatest war-related concerns are associated with the safety of loved ones (74% in the fourth wave) and the risk to life or potential for injury (54%). In addition, 39% of respondents expressed worry about losing their source of income [2].

Among the most common negative psycho-emotional states reported by respondents were: anxiety and tension (58%), sleep disturbances (50%), exhaustion (49%), low mood (49%), emotional instability (45%), and irritability or anger (44%) [2].

One of the main groups affected by traumatization consists of individuals who directly provide assistance to those in need volunteers. The impact of psychotraumatic factors, physical strain, and changes in living and working conditions significantly affect the quality of life of individuals engaged in volunteer activities [3].

Despite the relevance of this issue, the problem of non-specific quality of life among volunteers in Ukraine during wartime remains insufficiently studied. Therefore, the present study aims to assess the non-specific quality of life in volunteers with neurotic and stress-related mental disorders during the russia-Ukraine war.

Aim

To investigate the dynamics of non-specific quality of life in volunteers with neurotic and stress-related mental disorders before and after participation in a corrective-therapeutic program.

Materials and methods

Group formation

The study included 288 volunteers engaged in humanitarian aid during the russia–Ukraine war. The sample comprised individuals aged 18 to 60 years with varying levels of experience in volunteer activity. The dynamics of non-specific quality of life in volunteers with neurotic and stress-related mental disorders were analyzed before and after participation in a corrective-therapeutic program.

Three study groups were formed:

- *Experimental group (EG)*: volunteers with neurotic and stress-related mental disorders

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who underwent the corrective-therapeutic program developed by the authors (n = 40).
- *Control group (CG)*: volunteers with similar mental disorders who received standard treatment (n = 42).
- *Reference group (RG)*: volunteers without signs of neurotic or stress-related mental disorders (n = 206).

Inclusion criteria:
- engagement in volunteer activities;
- ability to provide informed consent;
- age between 18 and 60 years.

Exclusion criteria:
- established diagnosis of a mental disorder or substance use disorder according to ICD-10 prior to participation in the study;
- status of active-duty or demobilized military personnel;
- organic brain lesions;
- participation in any other research studies at the time of recruitment.

Methods

For qualitative data, absolute values (n) and relative frequencies (%) were used. Quantitative data with a normal distribution were described using the mean (M) and standard deviation (SD). In cases of non-normal distribution, the median (Me) and interquartile range (IQR) were applied. Normality was assessed using the Shapiro–Wilk test. Two-tailed tests were used for statistical hypothesis testing, and results were considered statistically significant at $p < 0.05$.

To assess non-specific quality of life, the MOS SF-36 (Medical Outcomes Study Short Form 36-Item) was employed a standardized self-report instrument developed to measure different aspects of quality of life in medical research and clinical practice. The questionnaire was originally designed in the United States in the 1980s based on the large-scale Medical Outcomes Study and has since gained wide international recognition [4].

The SF-36 consists of 36 items covering the following domains:
- physical functioning;
- role limitations due to physical health;
- bodily pain;
- general health;
- vitality;
- mental health;
- social functioning;
- role limitations due to emotional problems [4].

Each scale is transformed into a score ranging from 0 to 100, where 0 indicates maximum loss of function and 100 represents full functional capacity. Lower scores reflect poorer quality of life, whereas higher values indicate better functioning [5].

Results

A total of 288 respondents were assessed, with a mean age of 27.10 ± 8.36 years.

The experimental group (EG) participated in a corrective-therapeutic program that included pharmacological treatment combined with a low-intensity psychological intervention, *Problem Management Plus*. As a result, the quality of life of respondents in the EG, control group (CG), and reference group (RG) was analyzed before and after the program. Outcomes were evaluated using the scales of the MOS SF-36 (Medical Outcomes Study Short Form 36-Item) questionnaire.

Physical Functioning (PF)

The PF scale assesses the extent to which physical health limits daily activities (e.g., walking, climbing stairs, self-care).
- *At baseline:* mean PF scores in the EG and CG (89.1 ± 6.6 and 89.3 ± 6.7, respectively) were significantly lower compared to the RG (95.5 ± 6.5).
- *Immediately after completion of the program:* the PF score in the EG increased to the level of the RG, reaching 96.3 ± 3.5.
- *Three months after the program:* the EG demonstrated further improvement in PF, which was significantly higher than in the RG (98.7 ± 2.7; $p = 0.003$).
- *In the CG:* PF scores increased gradually. Only three months after treatment did the mean value (94.6 ± 4.5) no longer differ significantly from the RG ($p = 0.426$) (Table 1).

Role-Physical (RP)

The RP scale evaluates the extent to which physical problems limit the performance of work and other daily roles.
- *At baseline:* no significant differences were observed between groups (EG –

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Table 1. Physical Functioning (PF) scale results.

	EG n=40	CG n=42	RG n=206	p EG-CG	p EG-RG	p CG-RG
Baseline	89,1±6,6	89,3±6,7	95,5±6,5	0,914	p<0,001	p<0,001
post-program	96,3±3,5	92,4±5,0		p<0,001	0,472	0,004
3 months after program	98,7±2,7	94,6±4,5		p<0,001	0,003	0,426
p-baseline–post-program	p<0,001	p<0,001				
p baseline–3 months	p<0,001	p<0,001				
p post–3 months	p<0,001	p<0,001				

71.4 ± 13.7; CG – 75.3 ± 14.4; RG – 75.5 ± 18.3).

- *In the EG:* RP scores increased significantly immediately after the program ($p < 0.001$) and continued to rise three months later ($p < 0.001$), reaching an average of 92.3 ± 6.6.
- *In the CG:* a significant improvement in RP was recorded only three months after treatment ($p < 0.001$); however, the mean score (78.8 ± 12.6) did not exceed the level observed in the RG (Table 2).

Bodily Pain (BP)

The BP scale reflects the intensity of pain and its impact on work capacity and daily activities.

- *At baseline:* mean BP scores in the EG (89.1 ± 11.5) and CG (89.0 ± 11.7) were significantly higher than in the RG (83.1 ± 17.8; $p = 0.042$ and $p = 0.040$, respectively).
- *In the EG and CG:* significant increases in BP scores were observed both immediately after the program and three months later.
- *Three months after the program:* the mean BP score in the EG reached 100.0 ± 0.0 and was significantly higher ($p < 0.001$) than in the CG (93.1 ± 9.2) (Table 3).

General Health (GH)

The GH scale reflects the subjective perception of one's own health and expectations regarding its changes.

Table 2. Role-Physical (RP) scale results.

	EG n=40	CG n=42	RG n=206	p EG-CG	p EG-RG	p CG-RG
Baseline	71,4±13,7	75,3±14,4	75,5±18,3	0,219	0,187	0,958
post-program	86,4±10,3	77,2±14,1		0,001	p<0,001	0,554
3 months after program	92,3±6,6	78,8±12,6		p<0,001	p<0,001	0,278
p-baseline–post-program	p<0,001	0,199				
p baseline–3 months	p<0,001	0,018				
p post–3 months	p<0,001	p<0,001				

Table 3. Bodily Pain (BP) scale results.

	EG n=40	CG n=42	RG n=206	p EG-CG	p EG-RG	p CG-RG
Baseline	89,1±11,5	89±11,7	83,1±17,8	0,977	0,042	0,040
post-program	97,2±5,2	91,1±9,3		p<0,001	p<0,001	0,005
3 months after program	100,0±0	93,1±9,2		p<0,001	p<0,001	p<0,001
p-baseline–post-program	p<0,001	0,278				
p baseline–3 months	p<0,001	0,056				
p post–3 months	0,003	0,049				

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- *At baseline:* mean GH scores in the EG (43.3 ± 13.4) and CG (48.1 ± 16.2) were significantly lower compared to the RG (70.0 ± 15.0; $p < 0.001$).
- *I n the EG and CG:* significant increases in GH scores were observed both immediately after the program and three months later.
- *Three months after the program:* the mean GH score in the EG reached 73.1 ± 8.3 and did not differ significantly from the RG ($p = 0.220$). In contrast, the mean score in the CG (56.1 ± 13.2) remained significantly lower than in the RG ($p < 0.001$) (Table 4).

Vitality (VT)

The VT scale reflects levels of energy, vigor, and fatigue.

- *At baseline:* mean VT scores in the EG (33.6 ± 10.1) and CG (35.1 ± 11.6) were significantly lower compared to the RG (58.1 ± 11.6; $p < 0.001$).
- *In the EG and CG:* significant increases in VT scores were observed both immediately after the program and three months later.
- *Three months after the program:* the mean VT score in the EG reached 64.1 ± 5.8 and was significantly higher than in the RG ($p < 0.001$). In contrast, the mean VT score in the CG (45.8 ± 8.3) remained significantly lower than in the RG ($p < 0.001$) (Table 5).

Social Functioning (SF)

The SF scale reflects the extent to which physical or mental problems limit social contacts and communication.

- *At baseline:* mean SF scores in the EG (55.0 ± 16.5) and CG (54.2 ± 15.3) were significantly lower than in the RG (77.5 ± 18.1; $p < 0.001$).
- *In the EG:* a significant increase in SF was observed immediately after the program ($p < 0.001$), reaching values comparable to the RG ($p = 0.589$). Three months later, the mean SF score rose to 88.5 ± 7.2 and was significantly higher than in the RG ($p < 0.001$).
- *In the CG:* mean SF values increased gradually – 58.9 ± 15.0 immediately after the program ($p = 0.031$) and 63.4 ± 14.1 three months later ($p < 0.001$). However, they did not reach the level of the RG (Table 6).

Role-Emotional (RE)

The RE scale assesses the impact of emotional problems (e.g., stress, depression) on the performance of daily roles.

Table 4. General Health (GH) scale results.

	EG n=40	CG n=42	RG n=206	p EG-CG	p EG-RG	p CG-RG
Baseline	43,3±13,4	48,1±16,2	70,0±15,0	0,150	p<0,001	p<0,001
post-program	61,1±8,4	51,9±13,8		p<0,001	p<0,001	p<0,001
3 months after program	73,1±8,3	56,1±13,2		p<0,001	0,220	p<0,001
p-baseline–post-program	p<0,001	0,031				
p baseline–3 months	p<0,001	p<0,001				
p post–3 months	p<0,001	p<0,001				

Table 5. Vitality (VT) scale results.

	EG n=40	CG n=42	RG n=206	p EG-CG	p EG-RG	p CG-RG
baseline	33,6±10,1	35,1±11,6	58,1±11,6	0,535	p<0,001	p<0,001
post-program	53,0±8,8	40,2±10,5		p<0,001	0,008	p<0,001
3 months after program	64,1±5,8	45,8±8,3		p<0,001	0,002	p<0,001
p-baseline–post-program	p<0,001	0,002				
p baseline–3 months	p<0,001	p<0,001				
p post–3 months	p<0,001	p<0,001				

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Table 6. Social Functioning (SF) scale results.

	EG n=40	CG n=42	RG n=206	p EG-CG	p EG-RG	p CG-RG
Baseline	55,0±16,5	54,2±15,3	77,5±18,1	0,816	p<0,001	p<0,001
post-program	75,9±11,3	58,9±15,0		p<0,001	0,589	p<0,001
3 months after program	88,5±7,2	63,4±14,1		p<0,001	p<0,001	p<0,001
p-baseline–post-program	p<0,001	0,031				
p baseline–3 months	p<0,001	p<0,001				
p post–3 months	p<0,001	p<0,001				

- *At baseline:* mean RE scores in the EG (39.4 ± 13.8) and CG (42.1 ± 16.7) were significantly lower than in the RG (72.4 ± 17.7; $p < 0.001$).
- *In the EG:* a significant increase in RE scores was observed immediately after the program ($p < 0.001$), reaching levels comparable to the RG ($p = 0.293$). Three months later, the mean RE score rose to 79.3 ± 8.0 and was significantly higher than in the RG ($p < 0.001$).
- *In the CG:* significant improvements in RE were recorded both immediately after the program and three months later ($p < 0.001$), but the scores did not reach the level of the RG (Table 7).

Mental Health (MH)

The MH scale reflects the level of psychological well-being, including anxiety, depressive symptoms, and emotional stability.

- *At baseline:* mean MH scores in the EG (40.4 ± 8.9) and CG (38.7 ± 10.6) were significantly lower compared to the RG (65.6 ± 13.6; $p < 0.001$).
- *In the EG and CG:* significant increases in MH scores were observed both immediately after the program and three months later.
- *Three months after the program:* the mean MH score in the EG reached 70.0 ± 7.3 and did not differ significantly from the RG ($p = 0.053$). In contrast, the mean score in

Table 7. Role-Emotional (RE) scale results.

	EG n=40	CG n=42	RG n=206	p EG-CG	p EG-RG	p CG-RG
Baseline	39,4±13,8	42,1±16,7	72,4±17,7	0,436	p<0,001	p<0,001
post-program	69,4±9,2	51,6±15,2		p<0,001	0,293	p<0,001
3 months after program	79,3±8,0	56,7±12,0		p<0,001	0,019	p<0,001
p-baseline–post-program	p<0,001	p<0,001				
p baseline–3 months	p<0,001	p<0,001				
p post–3 months	p<0,001	p<0,001				

Table 8. Mental Health (MH) scale results.

	EG n=40	CG n=42	RGn=206	p EG-CG	p EG-RG	p CG-RG
Baseline	40,4±8,9	38,7±10,6	65,6±13,6	0,444	p<0,001	p<0,001
post-program	60,9±7,1	44,2±10,9		p<0,001	0,033	p<0,001
3 months after program	70,0±7,3	47,5±10,6		p<0,001	0,053	p<0,001
p-baseline–post-program	p<0,001	p<0,001				
p baseline–3 months	p<0,001	p<0,001				
p post–3 months	p<0,001	p<0,001				

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the CG (47.5 ± 10.6) remained significantly lower than in the RG ($p < 0.001$) (Table 8).

Discussion

The obtained results indicate an increased vulnerability of volunteers to the development of stress-related mental disorders, which significantly affects their quality of life. This is largely due to the specific nature of volunteer activities, which are accompanied by intense workloads and prolonged exposure to psychotraumatic factors.

One of the key issues is the insufficient system of psychological support for volunteers, which complicates their adaptation and increases the risk of developing neurotic and stress-related disorders.

Our study demonstrated the feasibility of applying the scalable psychological intervention Problem Management Plus in combination with pharmacological treatment to improve non-specific quality of life among volunteers with neurotic and stress-related disorders during the period of full-scale invasion.

At the same time, this topic requires further comprehensive investigation to clarify the effectiveness of the proposed intervention in addressing stress-related mental disorders, as well as to develop a sustainable support system aimed at preserving the mental health of volunteers in the long term.

Conclusions

The study of the dynamics of non-specific quality of life in volunteers with neurotic and stress-related mental disorders before and after participation in a corrective-therapeutic program revealed significant improvements across all scales of the Medical Outcomes Study Short Form 36-Item (SF-36):

- Physical Functioning (PF): in the EG, scores reached the RG level immediately after the program and exceeded it three months later; in the CG, the RG level was achieved only after three months.
- Role-Physical (RP): in the EG, scores were significantly higher than those of the RG both immediately after the program and three months later; in the CG, scores remained at the RG level.
- Role-Emotional (RE): in the EG, scores reached the RG level after the program and exceeded it three months later; in the CG, scores did not reach the RG level even after three months.
- Vitality (VT): in the EG, significant improvements were observed, and scores exceeded the RG level after three months; in the CG, increases were significant but did not reach the RG level.
- Mental Health (MH): in the EG, scores increased significantly and reached the RG level after three months; in the CG, growth was insufficient, and RG levels were not achieved.
- Social Functioning (SF): in the EG, scores equaled those of the RG after the program and exceeded them after three months; in the CG, scores increased but remained below the RG.
- Bodily Pain (BP): significant increases were recorded in both groups, although scores in the EG were significantly higher than in the CG.
- General Health (GH): in the EG, scores reached the RG level after three months; in the CG, increases were noted, but values remained significantly lower than those of the RG.

Thus, the results indicate substantial improvement in quality of life among volunteers with neurotic and stress-related disorders following the implementation of the psychocorrective program. Further comprehensive studies are warranted to explore the potential of the scalable psychological intervention *Problem Management Plus*, in combination with pharmacological treatment, to enhance mental well-being and quality of life of volunteers in wartime conditions.

Financing

No external funding was received for this study.

Conflict of interest

The authors declare no conflicts of interest.

Consent to publication

All authors consent to the publication of this manuscript. All authors have read and approved the final version of the manuscript.

AI Disclosure

The authors used ChatGPT (OpenAI, San Francisco, CA, USA) for language editing of the

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English text. The authors reviewed and verified all AI-generated content to ensure accuracy and integrity.

Ethical Considerations

The study was conducted in accordance with the principles of the World Medical Association's Declaration of Helsinki (2013). The study protocol was reviewed and approved by the Local Biomedical Ethics Committee (approval No. 2, dated 16.10.2025).

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Динаміка неспецифічної якості життя у волонтерів з невротичними та стрес-асоційованими психічними розладами до і після корекційно-лікувальної програми

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Анотація: *У статті представлено результати дослідження динаміки неспецифічної якості життя у волонтерів з невротичними та стрес-асоційованими психічними розладами до та після проходження корекційно-лікувальної програми. У дослідженні взяли участь 288 волонтерів віком від 18 до 60 років (середній вік 27,10 ± 8,36), які були розподілені на три групи: експериментальну (40 осіб), контрольну (42 особи) та референтну (206 осіб).*

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Експериментальна група проходила програму, що включала медикаментозне лікування та психологічну інтервенцію низької інтенсивності «Управління проблемами +», контрольна група отримувала стандартне лікування, а референтна група складалася з волонтерів без ознак психічних розладів. Для оцінки використовувався опитувальник Medical Outcomes Study Short Form 36-Item. На початковому етапі показники якості життя у волонтерів з психічними розладами були достовірно нижчими за всіма шкалами порівняно з референтною групою. Зокрема, за шкалою Physical Functioning середні значення становили 89,1 ± 6,6 у експериментальній групі та 89,3 ± 6,7 у контрольній, що було нижче ніж 95,5 ± 6,5 у референтній групі. Через три місяці після програми у експериментальній групі показник зріс до 98,7 ± 2,7 і перевищив рівень референтної групи (p = 0,003), тоді як у контрольній групі він склав 94,6 ± 4,5. За шкалою Role-Physical у експериментальній групі показники зросли з 71,4 ± 13,7 до 92,3 ± 6,6, перевищивши рівень референтної групи (p < 0,001), у той час як у контрольній групі підвищення було менш вираженим і склало 78,8 ± 12,6. Значні зміни відбулися й у психологічних доменах. Показник Role-Emotional зріс в експериментальній групі з 39,4 ± 13,8 до 79,3 ± 8,0, перевищивши референтний рівень (72,4 ± 17,7; p < 0,001), тоді як у контрольній групі він залишався нижчим. Показники Vitality збільшилися з 33,6 ± 10,1 до 64,1 ± 5,8 у експериментальній групі, що було вище ніж 58,1 ± 11,6 у референтній групі (p < 0,001), тоді як у контрольній групі середнє значення склало лише 45,8 ± 8,3. За шкалою Mental Health у експериментальній групі середній бал зріс з 40,4 ± 8,9 до 70,0 ± 7,3 і не відрізнявся від референтної групи (65,6 ± 13,6; p = 0,053), у той час як у контрольній групі він залишався значно нижчим (47,5 ± 10,6; p < 0,001). Подібна позитивна динаміка в експериментальній групі спостерігалася й за іншими шкалами: Social Functioning зріс до 88,5 ± 7,2, перевищивши рівень референтної групи (77,5 ± 18,1; p < 0,001), Bodily Pain досяг 100,0 ± 0,0, що було вище ніж у контрольній групі (93,1 ± 9,2; p < 0,001), а General Health зріс до 73,1 ± 8,3, що відповідало рівню референтної групи (70,0 ± 15,0; p = 0,220). У контрольній групі зростання показників також відбувалося, але воно було менш вираженим, і навіть через три місяці більшість шкал залишалися нижчими за показники референтної групи. Отримані результати засвідчують ефективність поєднання медикаментозного лікування з психологічною інтервенцією «Управління проблемами +» для покращення неспецифічної якості життя волонтерів, які зазнали впливу стресових факторів у період війни. Встановлено, що застосування комплексної програми сприяло не лише нормалізації, а й перевищенню рівня якості життя здорових респондентів у низці доменів. Подальші дослідження мають бути спрямовані на оцінку довготривалих ефектів даної інтервенції та можливість її широкого застосування у системі психосоціальної допомоги волонтерам.

Ключові слова: Тривожні розлади; Депресивний розлад; Психічне здоров'я; Психіатрія; Психоосвіта; Якість життя; Психологічний стрес; Посттравматичні стресові розлади (ПТСР); Розлади, пов'язані з травмою та стресом; Волонтери.

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Features of heart and vascular remodeling in patients who have had coronavirus disease

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Abstract: *The aim is to study the impact of COVID-19 on the state of heart and vascular remodeling in patients with coronary heart disease and arterial hypertension. During 2024-2025, 50 people (30 men and 20 women aged 64,2±3,1 years) with coronary heart disease and arterial hypertension were examined one month after treatment for coronavirus disease. In the examined patients after the transferred coronavirus disease on the background of existing hypertension and ischemic heart disease, 52,0 % had left ventricular hypertrophy and changes in the circadian rhythm of blood pressure, in 46,0 % – thickening of the intima-media complex. Among all patients with LV hypertrophy, concentric remodeling (in 23,1 %) and hypertrophy (in 34,6 %), as well as eccentric hypertrophy (in 42,3 % of cases) were found. Such diurnal BP profiles among individuals with concentric remodeling and hypertrophy, as well as with eccentric hypertrophy, as non-dipper were found in 50,0, 33,3 and 36,4 %, night-peaker – in 16,7, 11,2 and 18,2 %, dipper – in 33,3, 55,5 and 45,4 % of the examined. An increase in the thickness of the intima-media complex in eccentric and concentric hypertrophy and in individuals with concentric remodeling was observed in 36,3; 22,2 and 50,0 % of cases. Ultrasound examinations of the heart and blood vessels, their ability to qualitatively and quickly assess the morpho-functional state, the nature of hemodynamics, the risk of possible complications should be used in the diagnosis and treatment of persons with a history of coronavirus disease at the stage of primary medical care.*

Keywords: Coronavirus disease, Prognosis, Pandemics, Hypertension, COVID-19, Cardiovascular disease, Echocardiography, Heart ventricles, Heart failure, Cardiovascular complications,

Introduction

The coronavirus pandemic has led to a significant increase in morbidity and mortality due to cardiovascular diseases (CVD) [1]. The manifestations of coronavirus disease, starting in 2019, have been almost constantly changing, but respiratory symptoms, pneumonia, thrombotic complications, acute cardiovascular pathology and myopericarditis are almost always present to varying degrees [2, 3]. The pathophysiological mechanisms associated with cardiovascular damage in coronavirus disease are still far from being fully understood [4, 5], but the role of dysregulation of the immune inflammatory response is undeniable [6]. Elderly patients with cardiovascular diseases are of particular concern in CVD, given the risk of decompensation, especially in cases of severe or prolonged disease [1, 7]. The prevalence of coronavirus disease in individuals with existing coronary heart disease (CHD) and arterial hypertension is significantly increasing [7], which is due to SARS-CoV-2 induction of an inflammatory response and progression of vascular dysfunction [6].

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The pathophysiological basis for the formation of myocardial ischemia is erosion of atherosclerotic plaque, thrombus formation, coronary artery spasm and decreased blood flow in them [7]. Activation of plasma homeostasis occurs against the background of increased platelet homeostasis with endothelial damage, which increases as CHD progresses. As Krasnova A. notes, signs of blood hypercoagulability appear: an increase in fibrinogen levels and blood clotting factors, a decrease in activated partial thromboplastic time, a decrease in the ability to anticoagulate and fibrinolysis [7].

Impaired quality of life, especially physical functioning, is one of the typical consequences of a previous coronavirus disease [8]. Minor structural and functional heart disorders that do not manifest as worsening heart failure always remain unnoticed in patients after COVID-19, but can lead to an exacerbation of the long-term course of this disease. According to Gonchar O, Ashcheulova T, 2023, in patients with coronary artery disease without hypertension after a previous coronavirus disease, concentric remodeling of the left ventricle is often found, with predominant diastolic dysfunction and a slight decrease in longitudinal systolic function [9]. It has been established that the comorbidity of coronary artery disease and COVID-19, ventricular dilatation and worsening hemodynamics, led to an increase in QT interval variability in patients [10]. Therefore, the question of the impact of COVID-19 on the course of chronic coronary artery disease is still far from being finally clarified.

Aim

To assess the impact of COVID-19 on the characteristics of cardiovascular remodeling in patients with chronic ischemic heart disease and arterial hypertension.

Materials and methods

During 2024-2025 years, 50 people with coronary heart disease and arterial hypertension were examined in outpatient settings one month after treatment for COVID-19. In accordance with the recommendations of the World Health Organization [11], the order of the Ministry of Health of Ukraine dated April 2, 2020 No. 762 “Protocol for providing medical care for the treatment of coronavirus disease (COVID-19)” [12], the clinical guideline “Clinical management of patients with COVID-19” [13], the order of the Ministry of Health of Ukraine dated April 20, 2021 No. 771 “On approval of the Protocol for providing rehabilitation care to patients with coronavirus disease (COVID-19) and convalescents” [14], a clinical diagnosis of COVID-19 was established and confirmed by detecting SARS-CoV-2 RNA in clinical laboratories earlier [15].

The inclusion criteria for the study were: patients with coronary artery disease and hypertension aged 45-65 years, who had laboratory-confirmed COVID-19 1 month ago and consulted a family doctor for outpatient care, who agreed to participate in the study [16]. Exclusion criteria: no confirmed COVID-19 disease, age > 65 years, disagreement with participation in the study.

The results of the study were obtained by the author during the research work of the Department of Family Medicine of Shupyk National University of Health of Ukraine on the topic «Development and Justification of Programs For the Prevention and Treatment of Patients With Comorbid Pathology of Organs and Systems» (state registration number 0122U-002416; term: 2022-2026 years). The study protocol was drawn up in accordance with the Declaration of Helsinki [17] and agreed with the Ethics Committee of Shupyk National University of Health of Ukraine (Protokol № 3/3 22.03.2024). Examination and treatment of patients were carried out in accordance with the “Protocol for providing medical care for the treatment of coronavirus disease (COVID-19)” [18].

In outpatient settings, 50 people with chronic coronary artery disease and arterial hypertension (30 men and 20 women) aged 64,24±3,16 years were examined. All patients were examined in accordance with the order of the Ministry of Health of Ukraine dated 20.04.2021 No. 771 “Protocol for providing rehabilitation care to patients with coronavirus disease (COVID-19) and convalescents [14]. Structural and functional changes in the myocardium and features of autonomic regulation of heart rate were assessed

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using Doppler echocardiography [19], daily blood pressure monitoring [20, 21]; features of vascular remodeling – using ultrasound examination of the brachiocephalic arteries [22].

To evaluate the results of the study, methods of primary statistical and correlation analysis were used [23]. The author used ChatGPT (OpenAI, San Francisco, CA, USA) for language editing of the English text. The author reviewed and verified all AI-generated content to ensure accuracy and integrity.

Results

Against the background of existing hypertension, ischemic heart disease and previous coronavirus disease, 52,0 % of the examined patients were diagnosed with left ventricular hypertrophy. Among all individuals with LV hypertrophy, eccentric hypertrophy was observed in 42,3 %, concentric hypertrophy in 34,6 %, and concentric remodeling in 23,1 % of the examined (Fig. 1a and 1b).

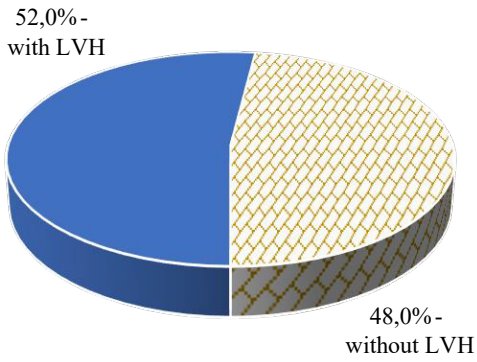

Fig. 1a. Prevalence of left ventricular hypertrophy in people who had coronavirus disease

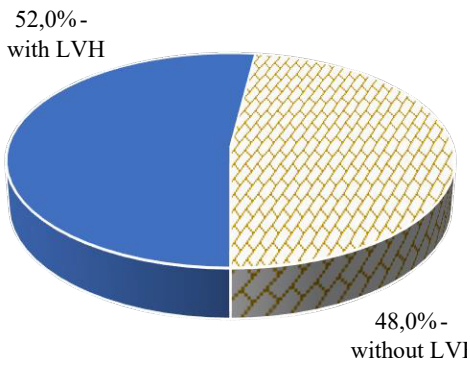

Fig. 1b. Prevalence of different types of remodeling of left ventricular in people who had coronavirus disease

Our results are comparable with the data of Gonchar O, Ashcheulova T, 2023, which showed that concentric left ventricular remodeling was detected in 59,0 % of the examined patients with CVD, including 49,0 % of patients without hypertension, diastolic dysfunction was detected in 35,0 and 25,0 % of the examined patients, respectively; a moderate increase in absolute and relative wall thickness, worsening of diastolic parameters and global longitudinal deformation were observed [9]. The diameter of the aortic root in patients tended to increase with concentric LV remodeling by 4,0 % and with eccentric hypertrophy by 1,6 %, while with concentric hypertrophy it significantly increased by 6,0 % ($p<0,05$) (Table 1).

The size of the left atrium in the examined patients increased with concentric hypertrophy by 15,0 % ($p<0,001$) and eccentric hypertrophy by 11,1 % ($p<0,001$), while with concentric remodeling it had only a tendency to increase by 2,2 %. The left atrial index in patients increased with eccentric hypertrophy by 9,2 % ($p<0,001$) and concentric hypertrophy by 13,2 % ($p<0,001$), with concentric remodeling – only by 1,1 % ($p>0.05$). The left atrial area in these individuals increased most with concentric hypertrophy by 14,5 % and eccentric hypertrophy by 14,3 % ($p<0,05$) and decreased with concentric remodeling by 9,4 % ($p>0,05$). In individuals who had undergone coronavirus disease, the left atrial area index significantly increased with eccentric hypertrophy by 19,6 % ($p<0,01$) and had a tendency to increase with concentric hypertrophy by 9,9 % and decrease with concentric remodeling by 10,0 % ($p>0,05$) (Table 1).

In the patients we examined, the LV end-diastolic size significantly increased with eccentric hypertrophy by 11,0 % and concentric hypertrophy by 9,4 % ($p<0,001$) and with concentric remodeling – decreased by 6,5 % ($p<0,05$). The index of LV end-diastolic size in these patients increased with eccentric hypertrophy by 4,7 % and concentric hypertrophy by 5,2 % ($p<0,05$) and decreased by 9,9 % ($p<0,01$) with concentric remodeling. LV end-systolic size in patients increased with eccentric hypertrophy by 15,8 % ($p<0,001$) and

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Table 1. Character of the structural and functional state of the heart in the examined patients 1 month after COVID-19

Indicators	Types of left ventricular geometry in patients			
	normal geometry	hypertrophy eccentric	concentric remodeling	concentric hypertrophy
Aortic root diameter	2,97±0,05	3,05±0,09	3,10±0,10	3,16±0,08*
Left atrial size	3,11±0,05	3,48±0,12***	3,18±0,12	3,59±0,08***
Left atrial index	1,57±0,01	1,72±0,05***	1,63±0,08	1,82±0,04***
Left atrial area	14,54±0,62	16,63±1,05	13,12±0,94	16,66±0,52*
Left atrial area index	7,59±0,24	9,12±0,47**	6,87±0,53	8,34±0,25
LV end-diastolic size	4,58±0,04	5,09±0,11***	4,24±0,16*	5,0±0,08***
LV end-diastolic size index	2,43±0,03	2,54±0,07	2,15±0,06**	2,54±0,02*
LV end-systolic size	2,84±0,06	3,23±0,16***	2,74±0,15	3,12±0,07***
LV end-diastolic volume	97,36±2,70	122,50±5,38***	83,31±7,47*	114,32±3,56***
LV end-diastolic volume index	50,80±1,04	62,14±2,70***	41,95±3,52**	57,27±1,64**
LV end-systolic volume	31,79±1,50	42,15±3,04**	30,23±3,49	40,32±2,15**
LV ejection fraction	68,78±0,86	65,12±1,89*	67,40±1,60	65,05±0,90*
LV posterior wall myocardial thickness	0,92±0,01	1,04±0,02***	0,98±0,01***	1,25±0,03***
Relative thickness of the posterior wall of the left ventricle	0,38±0,03	0,45±0,07	0,47±0,02***	0,51±0,02***
Interventricular septal thickness	1,06±0,5	1,27±0,30***	1,19±0,03	1,45±0,03***
LV myocardial mass	187,12±7,80	276,71±16,78***	187,94±15,65	307,78±13,24***
Myocardial mass index	95,83±3,54	136,07±5,58***	94,54±7,0	155,40±6,51***
Right atrial area	12,35±0,42	14,31±0,64*	10,57±0,98	13,76±0,42
Right atrial area index	6,60±0,21	7,51±0,25*	5,38±0,42*	6,84±0,27

Note: * – p<0.05, ** – p<0.01, *** – p<0.001

concentric hypertrophy by 11,1 % (p<0,001) and decreased by 14,5 % (p>0,05) with concentric remodeling. The LV end-diastolic volume in the examined patients increased with hypertrophy (eccentric – by 25,8% and concentric – by 17,4 % (p<0,001) and decreased by 14,4 % (p<0,05) with concentric remodeling. The LV end-diastolic volume index in patients increased with eccentric hypertrophy by 22,2 % (p<0,001) and concentric hypertrophy by 12,5 % (p<0,01) and decreased with concentric remodeling by 17,4 % (p<0,01). The LV end-systolic volume in patients after coronavirus disease increased with hypertrophy (eccentric – by 32,6 % and concentric – by 26,9 % (p<0,01) and decreased with concentric remodeling by 4,9 % (p>0,05). LV ejection fraction in such individuals decreased with eccentric hypertrophy by 5,3 % (p<0,05) and concentric hypertrophy by 5,4 % (p<0,05) and with concentric remodeling by 2,5 % (Table 1).

A number of researchers found that patients with chronic CHD, even without coronavirus disease, were characterized by pronounced LV remodeling (increased end-diastolic volume) and decreased systolic function (decreased ejection fraction and increased end-systolic volume) [24].

The thickness of the LV posterior wall in patients after coronavirus disease increased with eccentric hypertrophy by 14,3 % (p<0,001) and

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concentric hypertrophy by 32,6% (p<0,001), and with concentric remodeling by 9,9 % (p<0,001). The relative thickness of the posterior wall of the left ventricle in patients increased with concentric remodeling by 18,5 % (p<0,001), with hypertrophy (eccentric) by 3,2 % and concentric by 25,8 % (p<0,001). The thickness of the interventricular septum in patients increased with eccentric hypertrophy by 22,5 % (p<0,001) and concentric hypertrophy by 10,5 % (p<0,001) and with concentric remodeling by 9,7 %. The mass of the left ventricle in such individuals increased with hypertrophy (concentric) by 64,4 % and eccentric by 47,9 % (p<0,001), and had only a tendency with concentric remodeling by 0,4 %. The myocardial mass index in patients increased with eccentric hypertrophy by 43,7 % (p<0,001) and concentric hypertrophy by 62,0 % (p<0,001) and decreased with concentric remodeling by 1,2 %. The thickness of the LV posterior wall in patients after coronavirus disease increased with eccentric hypertrophy by 14,3 % (p<0,001) and concentric hypertrophy by 32,6 % (p<0,001), and with concentric remodeling by 9,9 % (p<0,001). The relative thickness of the posterior wall of the left ventricle in patients increased with concentric remodeling by 18,5 % (p<0,001), with hypertrophy (eccentric) by 3,2 % and concentric by 25,8 % (p<0,001). The thickness of the interventricular septum in patients increased with eccentric hypertrophy by 22.5% (p<0.001) and concentric hypertrophy by 10,5 % (p<0,001) and with concentric remodeling by 9,7 %. The mass of the left ventricle in such individuals increased with hypertrophy (concentric) by 64,4 % and eccentric by 47,9 % (p<0,001), and had only a tendency with concentric remodeling by 0,4 %. The myocardial mass index in patients increased with eccentric hypertrophy by 43,7 % (p<0,001) and concentric hypertrophy by 62,0 % (p<0,001) and decreased with concentric remodeling by 1,2 %.

The area of the right atrium in people after coronavirus disease increased with eccentric hypertrophy by 16,2 % (p<0,05) and concentric hypertrophy by 10,8 % and decreased by 14,2 % (p>0,05) with concentric remodeling. In these patients, the right atrial area index increased with hypertrophy (eccentric hypertrophy by 16,2 % (p<0,05) and concentric hypertrophy by 5,4 % (p>0,05)) and decreased by 18,0 % (p<0,01) with concentric remodeling (Table 1).

The presence of hypertrophy (eccentric and concentric), as well as concentric remodeling in people with Covid-19 on the background of existing hypertension and ischemic heart disease led to significant features of the daily blood pressure profile (Table 2).

Among individuals without LV hypertrophy, the over-dipper daily blood pressure profile occurred in 8,3 %, night-peaker in 12,5 %, non-dipper in 25,0 %, and dipper in 54,2 % of the examined individuals; however, the presence of any type of hypertrophy led to an increase in the prevalence of night-peaker to 15,4 % and non-dipper to 30,8 % (Fig. 2a and 2b).

Non-dipper daily blood pressure profiles were diagnosed in 36,4; 33,3 and 50,0 %, night-peaker – in 18,2; 11,2 and 16,7 %, dipper – in 45,4; 55,5 and 33,3 % of those examined with hypertrophy (eccentric and concentric) and in patients with concentric remodeling.

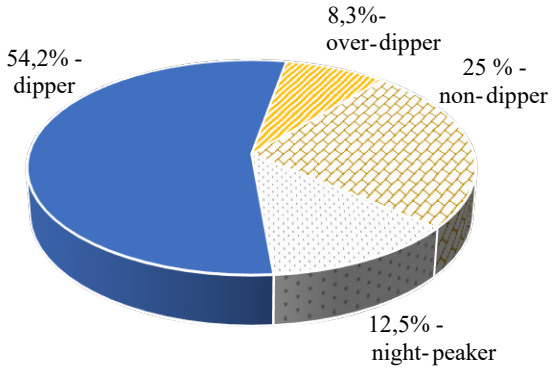

Fig. 2a. Prevalence of daily blood pressure profiles in individuals without LV hypertrophy who have undergone coronavirus disease

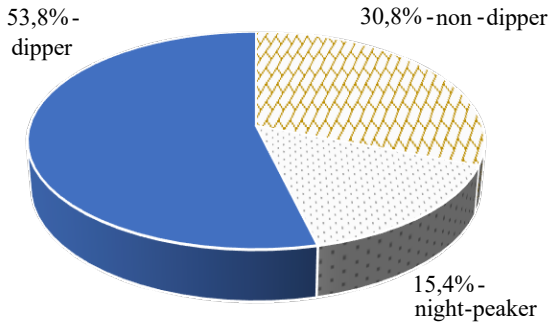

Fig. 2b. Prevalence of daily blood pressure profiles in individuals with LV hypertrophy who have undergone coronavirus disease

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Table 2. Features of the daily blood pressure monitoring in patients after suffering from coronavirus disease

Indicators daily blood pressure monitoring	Types of left ventricular geometry in patients after coronavirus disease			
	normal geometry	hypertrophy eccentric	concentric remodeling	concentric hypertrophy
Systolic blood pressure during the day	121,15±2,21	130,78±4,31*	131,54±3,36***	137,57±4,89*
Diastolic blood pressure during the day	78,17±1,37	83,74±2,11	89,20±3,31**	87,55±2,56**
Hypertension time index SBP during the day	11,29±3,58	21,31±7,56	11,78±6,13	42,56±8,35***
Daytime DBP hypertension index	12,46±3,79	24,53±5,62	23,12±9,54	37,16±8,21**
Daytime SBP variability	12,05±0,54	13,04±1,11	14,03±0,64	13,40±0,32
Daytime BP variability	9,69±0,35	11,646±1,21	11,56±0,85	10,08±0,43
Systolic blood pressure at night	114,68±1,79	122,19±5,52	120,48±3,76	131,29±6,17**
Diastolic blood pressure at night	70,48±2,05	72,05±2,34	76,89±2,72	79,14±3,52*
Nocturnal SBP Hypertension Time Index	11,37±3,54	23,34±8,15	21,84±9,24	45,84±10,62***
Nocturnal DBP hypertension time index	14,13±3,75	27,85±7,64	25,06±9,26	39,35±9,67**
Nocturnal blood pressure variability	9,79±0,72	10,53±0,84	9,78±1,14	10,85±1,21
Variability of DBP at night	7,81±0,62	7,52±0,48	8,72±1,04	9,08±0,76
Minimum SBP per day	90,80±2,35	93,56±4,34	96,16±4,23	95,18±5,60
Average SBP per day	119,79±1,67	128,83±4,25*	129,48±3,34*	136,86±4,59***
Maximum SBP per day	153,92±3,24	167,31±5,36*	174,09±7,11**	177,56±5,38***
Minimum daily blood pressure	53,18±1,59	53,24±3,18	53,07±3,51	52,84±3,23
Average DBP per day	77,10±1,34	81,07±2,11	86,75±3,09**	86,36±2,81***
Maximum DBP per day	102,61±1,54	113,10±4,04**	115,04±4,38**	119,82±4,24***
Minimum average blood pressure per day	67,23±1,18	69,53±3,24	67,45±4,73	75,61±4,03
Average blood pressure per day	91,37±1,75	97,07±3,29	101,26±3,46**	99,53±4,58*
Maximum average blood pressure per day	116,57±2,14	124,29±4,43	129,75±5,14	125,19±5,34
Minimum pulse pressure per day	22,42±1,39	23,74±1,95	20,52±1,47	23,07±3,82
Average pulse pressure per day	42,52±1,37	44,94±3,68	41,58±1,17	48,71±4,10*
Maximum pulse pressure per day	69,41±2,58	73,61±6,19	80,67±6,84	89,47±8,02**
Minimum heart rate	56,52±1,76	56,25±2,68	54,26±2,38	54,18±3,24
Average heart rate	73,78±1,35	72,45±2,78	73,09±2,78	72,54±3,36
Maximum heart rate	119,06±358,	116,81±6,24	120,94±5,17	116,37±8,41
Hypertension area index SBP per day	0,47±0,18	0,23±560,	0,34±0,15	0,31±0,28
Hypertension area index of DBP per day	27,42±2,54	18,65±3,27	24,84±4,37	17,58±3,08*

Note: * – $p<0.05$, ** – $p<0.01$, *** – $p<0.001$

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Daytime systolic (SBP) and diastolic (DBP) blood pressure in the examined subjects increased with eccentric hypertrophy by 8,0 ($p<0,05$) and 5,9 % ($p>0,05$) and concentric hypertrophy by 13,6 ($p<0,001$) and 11,9 % ($p<0,01$), and with concentric remodeling by 8,5 % ($p<0,001$) and 13,9 % ($p<0,01$). In the examined patients with hypertrophy (eccentric – by 88,2 and 93,2 % ($p>0,05$) and concentric – by 2,7 ($p<0,001$) and 1,9 ($p<0,001$) times, with concentric remodeling – by 0,2 and 82,0 %, the daily indices of hypertension time of SBP and DBP increased. There were tendencies to increase the daily variability of SBP (Var SBPd) and DBP (Var DBPd) in patients after coronavirus disease with concentric (hypertrophy – by 20,8 and 22,1 % and remodeling – by 12,5 and 3,9 %), with eccentric hypertrophy – by 8,9 and 19,1 %.

Certain features of nocturnal systolic and diastolic blood pressure were characteristic of our subjects. They were characterized by a probable increase in nocturnal systolic and diastolic blood pressure during hypertrophy (concentric – by 14,5 % ($p<0,01$) and 11,1 % ($p<0,05$) and a tendency to increase during eccentric – by 6,2 % and 1,6 %), as well as during concentric remodeling – by 5,1 % and 8,6 %. The time indices of hypertension, systolic and diastolic blood pressure at night, increased with concentric hypertrophy by 2,9 ($p<0,001$) and 1,7 ($p<0,01$) times, while with eccentric hypertrophy by 99,7 and 97,5% ($p>0,05$) and concentric remodeling by 88,6 and 77,6% ($p>0,05$). In such patients, nocturnal variability of SBP (VarSBPn) and DBP (VarDBPn) changed in different directions (with eccentric hypertrophy, VarSBPn decreased by 3,3% ($p>0,05$) and VarDBPn increased by 6,6 % ($p>0,05$); with concentric hypertrophy, they increased by 10,1 and 16,5 % ($p>0,05$), with remodeling – by 0,7 and 12,0 % ($p>0,05$). VarSBPd and (VarSBPn) were within normal limits in 76,6 and 70,0 % of the examined; while VarDBPd - only in 20,0 %, and VarDBPn – 6,6 %.

Daily systolic blood pressure (minimum (min SBP), average (serum SBP) and maximum (max SBP) in the examined patients increased with eccentric hypertrophy – by 4,9; 7,5 ($p<0,05$) and 8,6 % ($p<0,05$), with concentric hypertrophy – by 4,9; 14,3 ($p<0,001$) and 15,3 % ($p<0,001$), with concentric remodeling – by 5,9; 8,1 ($p<0,05$) and 13,1% ($p<0,01$). Minimum, average and maximum diastolic blood pressure (DBP per day) in patients increased with eccentric hypertrophy – by 0,3 and 5,1 % and 10,2 % ($p<0,01$) and changed in different directions with concentric hypertrophy and concentric remodeling. With concentric hypertrophy and remodeling, the minimum DBP per day decreased by 0,2 and 0,1 % and the average DBP per day increased by 12,1 ($p<0,001$) and 12,6 % ($p<0,01$) and the maximum DBP per day increased by 16,9 % ($p<0,001$) and 12,1 % ($p<0,01$). The daily minimum, average and maximum mean arterial pressure in patients after the coronavirus disease increased with eccentric hypertrophy by 2,9; 5,7 and 6,6 %, with concentric hypertrophy by 11,8; 8,2 ($p<0,05$) and 7,9 %, with concentric remodeling by 0,9; 10,7 ($p<0,01$) and 11,2 %. The minimum, average and maximum pulse blood pressure (BP per day) in such individuals increased with eccentric hypertrophy by 4,2; 5,8 and 5,9 % and with concentric hypertrophy by 3,8; 15,8 ($p<0,05$) and 29,1 % ($p<0,01$). With concentric remodeling, the minimum and average BP per day decreased by 6,8 and 1,1 % and the maximum BP per day increased by 15,8 %, but these changes were not significant. The differences in heart rate per day were not significant, so we did not analyze them in detail. The daily indices of hypertension area of systolic and diastolic blood pressure in patients decreased with eccentric hypertrophy by 52,5 and 32,0 % and with concentric hypertrophy by 32,6 and 35,7% ($p<0,05$), while with 25,1 and 9,3% – with concentric remodeling ($p>0,05$).

Patients a month after the coronavirus disease in the presence of eccentric and concentric hypertrophy, concentric remodeling were characterized by certain features of the morpho-functional state of the vessels, which are presented in Table 3. An increase in the intimate media complex (IMC) was observed in 46,0 % of the examined, however, there were certain differences in different types of LV remodeling: with concentric remodeling – in 50,0 % of the examined, with eccentric – in 36,3% and concentric hypertrophy – in 22,2 % (Fig. 3a and 3b).

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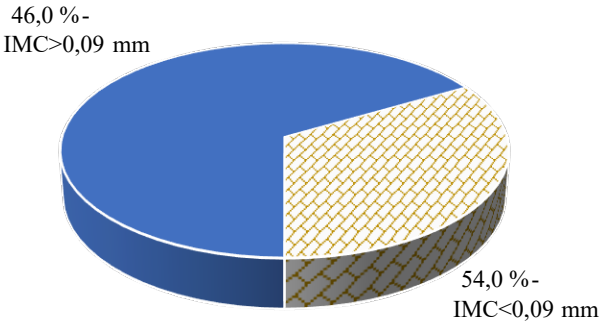

Fig. 3a. Prevalence of morphological changes functional state of blood vessels in people, who have had coronavirus disease

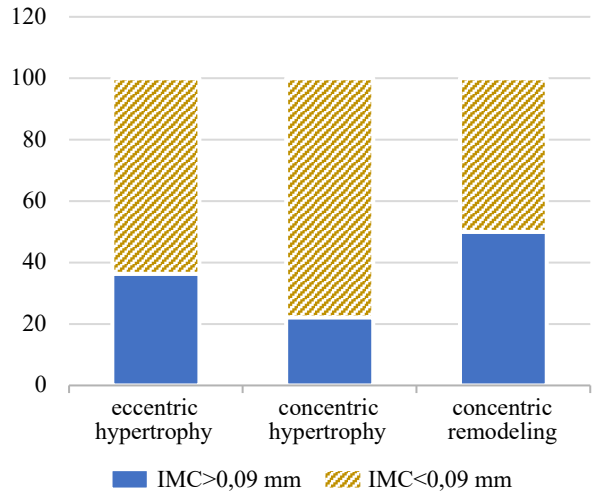

Fig. 3b. Prevalence of morphological changes functional state of blood vessels in people with various types of cardiac remodeling, who have had coronavirus disease

In the examined subjects with normal and increased IMC, the non-dipper daily BP profile was found in 29,4 and 35,0 %, in 11,7 and 20,0 % of cases – night-peaker, in 52,9 and 40,0 % – dipper, in 5,2 and 5,0 % – over-dipper.

With all types of LV remodeling, the diameters of the right common carotid arteries (RCCA) increased in patients (with concentric hypertrophy – by 12,4% (p<0,001), with eccentric hypertrophy – by 3,3 % and with concentric remodeling – by 0,7 % (p>0,05); resistance indices of the RCCA (with concentric hypertrophy – by 5,0 %, with eccentric hypertrophy – by 0,9 %, and decreased with concentric remodeling – by 3,5 % (p>0,05). With concentric hypertrophy – by 10,1 %, with eccentric hypertrophy – by 1,5 % and with concentric remodeling – by 3,5 % had a tendency to decrease the maximum blood flow velocities in the RCCA (Table 3).

There was a tendency to increase the diameters of the left common carotid arteries (LCCA) of patients with eccentric hypertrophy and concentric remodeling by 3,5 %, and by 2,5 % – with concentric hypertrophy. The maximum blood flow velocities and resistance indices on the left common carotid arteries in the examined patients decreased significantly only with concentric hypertrophy – by 14,7 (p<0,001) and 2,6 % (p>0,05) and had a tendency with concentric remodeling – by 5,6 and 2,9 % and eccentric hypertrophy – by 5,9 and 3,4 % (p>0,05).

In individuals after coronavirus disease, the diameters of the right internal carotid arteries increased with eccentric hypertrophy by 4,1 % and concentric hypertrophy by 8,8 % (p<0,05) and with concentric remodeling by 5,5 %, but this was only a trend. The maximum blood flow velocities in the right internal carotid arteries in the examined patients decreased with eccentric hypertrophy by 7,7 %, with concentric hypertrophy by 4,4 % and remodeling by 2,0 %, but these differences were not significant (Table 3).

In the examined patients with concentric hypertrophy – by 1,5 % and with concentric remodeling – by 0,3 %, the diameters of the left internal carotid arteries tended to increase, and with eccentric hypertrophy – to decrease by 0,7 %. The maximum blood flow velocity and resistance indices in the left internal carotid arteries decreased in patients after coronavirus disease with eccentric hypertrophy – by 10,5 (p<0,05) and 4,3 % (p>0,05) and concentric hypertrophy – by 5,5 and 0,5 % (both p>0,05), and with concentric remodeling they increased by 1,1 and 0,9 % (both p>0,05).

The diameters of the right vertebral arteries in the examined individuals did not change with eccentric hypertrophy and increased with concentric hypertrophy – by 0,5 % and with concentric remodeling – by 5,8 %. At the same time, the maximum blood flow velocities and resistance indices in the right vertebral arteries in these patients decreased with eccentric hypertrophy – by 12,4 (p<0,05) and 1,5 %, with

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Table 3. Structural and functional state of extracranial arteries in patients after coronavirus disease

Structural and functional state of extracranial vessels	Types of left ventricular geometry in patients after coronavirus disease			
	normal geometry	hypertrophy eccentric	concentric remodeling	concentric hypertrophy
Diameter of the RCCA	0,71±0,01	0,73±0,03	0,71±0,02	0,80±0,02***
Maximum blood flow velocity of the RCCA	87,60±2,38	86,15±2,09	84,45±4,12	78,77±3,24
RCCA resistance index	0,72±0,11	0,73±0,12	0,70±0,11	0,76±0,08
Diameter of the LCCA	0,70±0,11	0,72±0,20	0,72±0,12	0,72±0,14
Maximum blood flow velocity of the LCCA	90,68±2,15	85,32±2,46	85,75±4,34	77,41±3,15**
LCCA resistance index	0,74±0,11	0,71±0,11	0,72±0,11	0,72±0,02
Diameter of the RICA	0,50±0,11	0,52±0,12	0,53±0,12	0,55±0,02*
Maximum blood flow velocity of the RICA	74,28±1,34	68,45±2,26	72,64±2,75	70,79±4,65
RICA resistance index	0,72±0,11	0,73±0,12	0,73±0,02	0,67±0,11
Diameter of the LICA	0,53±0,01	0,51±0,11	0,52±0,02	0,52±0,12
Maximum blood flow velocity of the LICA	75,23±1,35	67,93±2,16*	76,18±2,52	71,17±3,44
LICA resistance index	0,73±0,11	0,70±0,12	0,74±0,04	0,73±0,13
Diameter of the RVA	0,35±0,11	0,36±0,11	0,38±0,12	0,36±0,12
Maximum blood flow velocity of the RVA	46,45±1,02	40,80±2,12*	44,85±3,15	37,62±2,45*
RVA resistance index	0,72±0,11	0,71±0,12	0,69±0,01	0,71±0,12
Diameter of the LVA	0,35±0,11	0,36±0,11	0,34±0,12	0,36±0,01
Maximum blood flow velocity of the LVA	46,64±1,38	39,28±2,16	42,050±3,19	38,54±2,18
LVA resistance index	0,73±0,11	0,71±0,01	0,72±0,12	0,70±0,02
Intimate media complex	0,09±0,003	0,085±0,004	0,093±0,022	0,098±0,016

Note: * – p<0.05, ** – p<0.01, *** – p<0.001

concentric hypertrophy – by 19,9 (p<0,05) and 1,3 % and with concentric remodeling – by 3,7 %.

The diameters of the left vertebral arteries in patients increased with eccentric hypertrophy by 2,5 % and concentric hypertrophy by 3,9 % and decreased with concentric remodeling by 2,6 %. At the same time, the maximum blood flow velocities and resistance indices in the left vertebral arteries decreased with eccentric hypertrophy by 15,7 and 2,4 %, concentric hypertrophy by 17,3 and 3,2 % and with concentric remodeling by 9,0 and 1,5 %, but these changes were not statistically significant.

In patients after coronavirus disease, the intimate media complex (IMC) increased with concentric hypertrophy by 10,0 % and remodeling by 1,0 % and decreased with eccentric hypertrophy by 5,5 % (p>0,05).

Discussion

Coronavirus disease is one of the greatest challenges for healthcare systems worldwide [1, 25]. Previous studies have shown that coronavirus disease can cause cardiovascular complications, such as acute coronary syndrome and myocardial infarction, myocarditis and Takotsubo cardiomyopathy, various rhythm and conduction disorders, thromboembolism (PE), and heart failure [25, 26, 27]. Although the prevalence of complications in COVID-19 is not known in detail, it has been shown that the presence of cardiovascular disease in the anamnesis is associated with a more severe course of infection [28]. Wu et al., 2019 showed a significant increase in mortality from COVID-19 in patients with existing CVD, which was 10,5 % versus 2,3 % [29].

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As Mahmoud-Elsayed HM et al., 2020 indicated, in patients with coronavirus disease, LV systolic function was hyperdynamic or normal in 89,0 %, while RV dilation was present in 41,0 %, and RV dysfunction was present in 27,0 % of those examined. RV systolic dysfunction is associated with PE, with elevated D-dimer and C-reactive protein levels in 20,0 % of cases [30].

Dweck MR et al., 2020 showed that more than half of patients with COVID-19 had cardiovascular abnormalities, most commonly left ventricular, although some individuals had myocardial infarction, myocarditis, and Takotsubo cardiomyopathy. Right ventricular (RV) abnormalities were more common in severe COVID-19 and were likely associated with severe pneumonia and PE [31]. While Szekely Y et al., 2020 emphasized that the most common abnormality in patients with COVID-19 was RV dilatation and/or dysfunction, followed by LV diastolic dysfunction. LV contractility [ejection fraction (EF)] remained normal in 90,0 % of the examined [32]. In patients with severe conditions, further deterioration of RV parameters was visualized, which could be associated with increased pulmonary resistance [26]. The study by Szekely Y. and Topilsky Y,2022 showed a significant decrease in both systolic and diastolic LV function; even subclinical changes in LV function are associated with a worse prognosis in other heart diseases [32].

As emphasized by Manuylov S, Mykhaylovska N, 2024, in people with coronary artery disease after a previous coronavirus disease, significant changes in cardiac remodeling indicators, an increase in the severity of LV hypertrophy, LV diastolic dysfunction and end-systolic pressure, and a decrease in LV ejection fraction were found, in contrast to people without Covid-19. The authors indicated that a previous coronavirus disease in people with coronary artery disease is associated with the risk of dilatation and hypertrophy of the LV myocardium, its diastolic dysfunction [33].

Our study showed that against the background of coronary artery disease, arterial hypertension and a previous coronavirus disease, 52,0 % of patients had left ventricular hypertrophy; eccentric and concentric hypertrophy were observed in 22,0 and 18, 0%, respectively. In patients with LV hypertrophy, the DBPP dipper was found in 53,8 %, non-dipper – in 30,8 %, night-peaker – in 15,4 % of cases. In individuals with eccentric and concentric LV hypertrophy, the diurnal BP profile dipper was most often found – in 45,4; 55,5 % of the examined. The intima-media complex >0,09 mm was found in eccentric and hypertrophy and concentric remodeling – in 36,3 and 50,0 %. Among individuals with thickened ICM, the DBPP dipper was diagnosed in 40,0 %, non-dipper – in 35,0 %, night-peaker – in 20,0 %, over-dipper – in 5,0 % of cases.

Szekely Y. and Topilsky Y, 2022 emphasize that the availability of echocardiographic examination and ultrasound examination of vessels, their ability to qualitatively and quickly assess the morpho-functional state of the heart and vessels, the nature of hemodynamics, and the risk of possible complications are significant advantages and must be used in the treatment of people with previous coronavirus disease [34].

Conclusions

Against the background of existing hypertension, ischemic heart disease, and previous coronavirus disease, 52,0 % of patients had left ventricular hypertrophy, 46,0 % had changes in vascular remodeling, and 52,0 % had disturbances in the circadian rhythm of blood pressure (night-peaker – 15,4 % and non-dipper – up to 30,8 %). Among all individuals with LV hypertrophy, eccentric was observed in 42,3 %, concentric – 34,6 %, concentric remodeling – 23,1 % of the examined. The non-dipper daily BP profile was diagnosed in 36,4; 33,3 and 50,0 %, night-peaker – in 18,2; 11,2 and 16,7 %, dipper – in 45,4; 55,5 and 33,3 %; thickening of the intima-media complex – in 36,3; 22,2 and 50,0 % of the examined with eccentric and concentric hypertrophy and with concentric remodeling. In patients with coronary artery disease with arterial hypertension, a month after the transferred coronavirus disease, diverse changes in the intima-media complex were observed (decrease in eccentric hypertrophy by 5,5 % and increase in concentric hypertrophy by 10,0 % and concentric remodeling by 1,0 %). In patients with thickened

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ICM, the non-dipper daily blood pressure profile was found in 35,0 %, night-peaker in 20,0 %, dipper in 40,0 %, and over-dipper in 5,0 % of the examined. Ultrasound examinations, their ability to qualitatively and quickly assess the morpho-functional state of the heart and vessels, the nature of hemodynamics, and the risk of possible complications should be used in the diagnosis and treatment of persons with transferred coronavirus disease at the stage of primary medical care.

Perspectives of subsequent scientific research

Further research will be aimed at developing an algorithm for the diagnosis and treatment of coagulopathy in people who have had coronavirus disease.

The results of the study were obtained by the authors during the research work of the Department of Family Medicine of Shupyk National University of Health of Ukraine on the topic «Development and Justification of Programs For the Prevention and Treatment of Patients With Comorbid Pathology of Organs and Systems» (state registration number 0122U-002416; term: 2022-2026 years).

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Conflicts of Interest

The author certify the absence of conflicts of interest.

Consent to publication

Informed consent was obtained from all subjects in accordance with the Declaration of Helsinki and ethical commission submission.

AI Disclosure

No AI tools were used in the preparation of this manuscript.

Author Contributions (CRediT taxonomy)

Conceptualization: Olga Vozniuk (ORCID: 0009-0001-4995-8581);
Methodology: Olga Vozniuk;
Software: Olga Vozniuk;
Validation: Olga Vozniuk;
Formal Analysis: Olga Vozniuk;
Investigation: Olga Vozniuk;
Resources: Olga Vozniuk;
Data Curation: Olga Vozniuk;
Writing – Original Draft Preparation: Olga Vozniuk;
Writing – Review & Editing: Olga Vozniuk;
Visualization: Olga Vozniuk;
Supervision: Olga Vozniuk;
Project Administration: Olga Vozniuk.

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Особливості ремоделювання серця та судин у хворих, що перенесли коронаровірусну хворобу

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Анотація: *Мета – вивчити вплив COVID-19 на стан ремоделювання серця та судин у пацієнтів з ішемічною хворобою серця та артеріальною гіпертензією. Протягом 2024-2025 років було обстежено 50 осіб (30 чоловіків і 20 жінок у віці 64,24±3,16 роки) з ішемічною хворобою серця та артеріальною гіпертензією через місяць після лікування коронаровірусної хвороби. У обстежених хворих після перенесеної коронаровірусної хвороби на тлі існуючих гіпертензії та ішемічної хвороби серця по 52,0 % зустрічались гіпертрофія лівого шлуночка та зміни циркадного ритму артеріального тиску, в 46,0 % – потовщення комплексу інтима-медіа. Серед всіх пацієнтів з гіпертрофією ЛШ зустрічались концентричні ремоделювання (у 23,1 %) та гіпертрофія (у 34,6 %), а також ексцентрична гіпертрофія (у 42,3 % випадків). Такі добові профілі АТ серед осіб з концентричними ремоделюванням і гіпертрофією, а також з ексцентричною гіпертрофією, як non-dipper зустрічалися у 50,0, 33,3 та 36,4%, night-peaker – у 16,7, 11,2 та 18,2%, dipper – у 33,3, 55,5 та 45,4% обстежених. Зростання товщини комплексу*

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інтима- медіа при ексцентричній і концентричній гіпертрофіях та у осіб з концентричним ремоделюванням спостерігалося у 36,3; 22,2 і 50,0 % випадків. При її збільшенні товщини КІМ у пацієнтів суттєво зростали поширеність dipper – у 40,0 %, non-dipper – у 35,0 %, тоді як night-peaker та over-dipper зустрічались у 20,0 і 5,0 % обстежених. Ультразвукові дослідження серця і судин, їх здатність якісно й швидко оцінити морфо- функціональний стан, характер гемодинаміки, ризик можливих ускладнень мають використовуватись при діагностиці та лікуванні осіб з перенесеною коронаровірусною хворобою на етапі первинної медичної допомоги.

Ключові слова: Коронавірусна хвороба, Серцево-судинні захворювання, Ехокардіографія, Шлуночки серця, Серцева недостатність, Серцево-судинні ускладнення, прогноз

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Features of Regional Antibiotic Resistance in Pharyngeal Infections

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Abstract: *Antibiotic resistance (ABR) is a global public health issue. The World Health Organization (WHO) predicts that by 2050, ABR could lead to 10 million deaths annually if no countermeasures are taken (WHO, 2019). The rise in multidrug-resistant (MDR) bacteria and fungi complicates treatment strategies, particularly in healthcare facilities where nosocomial infections are prevalent, according to various studies. To analyze the results of bacteriological examination of throat swabs with antibiograms in pharyngeal diseases and, based on the data analysis, develop recommendations for empirical antibiotic therapy. From 2024 to 2025, 255 throat swabs were collected and cultured at the Brovary Multidisciplinary Clinical Hospital to determine the bacteriological composition of the pharyngeal mucosa and antibiotic resistance. Isolates were identified using standard microbiological methods, such as culturing on nutrient media and biochemical tests. Antibiotic susceptibility was assessed using the minimum inhibitory concentration (MIC) method or the Kirby-Bauer disk diffusion method. Testing was conducted on a panel of antibiotics. Results were interpreted according to standards such as those of the Clinical and Laboratory Standards Institute (CLSI) to classify strains as susceptible, intermediate, or resistant. A multilevel statistical methodology was employed for comprehensive analysis of microbiological data and antibiotic resistance profiles. Data analysis was performed using Python 3.9 and specialized libraries for scientific data processing (NumPy, SciPy, Pandas, and scikit-learn; data visualization was conducted using Matplotlib and Seaborn). Antifungal drugs—clotrimazole (100%) and ketoconazole (90.0%)—demonstrated the highest efficacy in treating fungal infections. Ceftazidime, vancomycin, benzylpenicillin, and clindamycin showed low efficacy (less than 50%), which may indicate high microbial resistance to these drugs. Amikacin, ceftriaxone, and cefepime were the most effective antibiotics for β-hemolytic streptococcus in terms of susceptibility. Staphylococcus aureus exhibited complete susceptibility to levofloxacin, ofloxacin, and meropenem. The study highlights the severity of the antibiotic resistance problem and the need for rational use of antimicrobial agents in clinical practice.*

Keywords: Antibiotic Resistance, Antibiotics, Bacteria, Pharynx, Fungi, Pharyngeal Diseases, Tonsillitis, Oral Cavity, Pharyngitis.

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Introduction

Antibiotic resistance (ABR) is a global public health challenge. The World Health Organization (WHO) projects that by 2050, ABR could cause 10 million deaths annually if no countermeasures are implemented (WHO, 2019). The rise in multidrug-resistant (MDR) bacteria and fungi complicates treatment strategies, particularly in healthcare settings where nosocomial infections are more prevalent.

The clinical consequences of ABR are significant, as high resistance to commonly used antibiotics, such as amoxicillin-clavulanate and clarithromycin, limits treatment options, especially for bacterial infections caused by gram-positive bacteria. Regarding the distribution of bacteria by epidemiology, the most common gram-positive bacterium is *Staphylococcus aureus*. For instance, Jones et al. (2018) found that 30–50% of *S. aureus* isolates in European healthcare facilities were methicillin-resistant (MRSA), with high resistance to clarithromycin (60%) and clindamycin (40%) [6]. Meanwhile, the most frequent gram-negative pathogens include *Enterobacter* spp. Additionally, gram-negative bacteria such as *Pseudomonas aeruginosa* and *Enterobacter* spp. pose further challenges due to their acquired resistance mechanisms. *P. aeruginosa* is known for resistance to carbapenems and aminoglycosides [5]. *Citrobacter* spp. exhibit multidrug resistance to cephalosporins and amoxicillin-clavulanate [3]. Fungal pathogens, particularly *Candida albicans*, also show increasing resistance to azoles [5]. A global study by Pfaller et al. (2020) revealed that 10–15% of *C. albicans* isolates had acquired resistance to fluconazole, with higher resistance observed in immunocompromised patients [5].

Limiting the use of broad-spectrum antibiotics and regularly monitoring susceptibility are critical measures to combat antibiotic resistance. The WHO Global Action Plan on ABR emphasizes infection monitoring and control [1].

Materials and Methods

The study was approved by the Bioethics Committee of the Bogomolets National Medical University (protocol №187 23.09.2024) and complies with the requirements of the Helsinki Declaration. Since the study is retrospective, obtaining informed consent from patients was not required.

From 2024 to 2025, a study was conducted at the Brovary Multidisciplinary Clinical Hospital, where 255 throat swabs were collected and cultured to assess antibiotic resistance. The study investigated regional antibiotic resistance patterns in patients with pharyngeal infections from otolaryngology and infectious disease departments.

Isolates were identified using standard microbiological methods, including cultivation on nutrient media and biochemical tests. Antibiotic susceptibility was evaluated using the minimum inhibitory concentration (MIC) method or the Kirby-Bauer disk diffusion method. Testing was performed on a panel of antibiotics, and results were interpreted according to standards such as those of the Clinical and Laboratory Standards Institute (CLSI) to classify strains as susceptible, intermediate, or resistant.

A multilevel statistical methodology was employed for comprehensive analysis of microbiological data and antibiotic resistance profiles. Data analysis was conducted using Python 3.9 with specialized libraries for scientific data processing (NumPy, SciPy, Pandas, scikit-learn), and data visualization was performed using Matplotlib and Seaborn.

Microbiological data were analyzed using standard measures of central tendency (mean, median) and variability (standard deviation, range of minimum and maximum values). Categorical variables were evaluated using absolute frequencies and relative proportions (percentages). The distribution of microorganisms and colony-forming unit (CFU) levels were presented as absolute counts and percentages of the total sample.

Antibiotic resistance was assessed based on standard classifications (susceptible (S), intermediate (I), and resistant (R) strains). Percentages of susceptibility and resistance were calculated for each antibiotic. The multiple antibiotic resistance (MAR) index was calculated as the ratio of the number of antibiotics to which resistance was detected to the total number of antibiotics tested. Cross-

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resistance was evaluated using Spearman's rank correlation coefficient (ρ) with statistical significance determined by p-values. Antibiotic pairs with a correlation coefficient $\rho \geq 0.7$ and $p < 0.05$ were considered to have significant cross-resistance.

For comparing resistance profiles between different microorganisms, the chi-square (χ^2) test was used for categorical variables with large sample sizes, and Fisher's exact test was applied for small samples. Differences were considered statistically significant at $p < 0.05$. The relationship between CFU levels and antibiotic resistance was analyzed using Spearman's rank correlation coefficient.

The dynamics of antibiotic resistance were analyzed using time-series analysis methods. Trends were assessed via linear regression, calculating the slope, coefficient of determination (R^2), and statistical significance (p-value). Future resistance levels were predicted using linear extrapolation with the construction of 95% confidence intervals.

To identify subgroups of strains with similar resistance profiles, k-means clustering was applied with prior data standardization. The optimal number of clusters was determined using the "elbow method" by analyzing the within-cluster sum of squares. For bacterial isolates with sufficient data ($n \geq 20$), dendrograms of antibiogram similarity were constructed using hierarchical agglomerative clustering with Euclidean distance metrics.

The effectiveness of antibiotics for empirical therapy was evaluated based on the percentage of susceptible strains with 95% confidence intervals. Antibiotic combinations were analyzed using a methodology that calculated combined effectiveness, considering the probability of susceptibility to at least one of the paired antibiotics.

Various visualization methods were employed to present results: bar charts (for frequency comparisons), heatmaps (for resistance matrices), line graphs (for trend analysis), boxplot diagrams (for distribution comparisons), correlation matrices, and dendrograms (for cluster analysis).

Artificial intelligence was not used.

Results and Discussion

A total of 255 individuals were examined, comprising 156 males (61.1%) and 99 females (38.9%), with a mean age of 37 years.

Among all isolated strains, *Streptococcus* (gram-positive) was the most frequently encountered (72.1%), while *Pseudomonas aeruginosa* was the least common (0.4%). *Candida albicans* (12.1%) and *Staphylococcus aureus* (7.3%) were also relatively frequent. The complete distribution is presented in Figure 1.

The highest number of multidrug-resistant strains was observed in Citrobacter, which may be explained by its frequent presence in healthcare facilities and its association with nosocomial infections. Additionally, hemolytic *Staphylococcus* (30%) and *Escherichia coli* (16.7%) exhibited high levels of multidrug-resistant strains, necessitating attention in the treatment of these infections. The frequency of multidrug-resistant strains among the isolated isolates is presented in Figure 2.

Regarding the trends in the temporal distribution of microorganisms, hemolytic streptococcus exhibits significant fluctuations with two peaks (September 2024 and March 2025), followed by a sharp decline to a minimum value (2%) by the end of the period. *Candida albicans* shows one pronounced peak in September 2024 (15%), after which its share remains low (1–4%) with minor fluctuations. *Staphylococcus aureus* displays a relatively stable distribution (1–2%) with one notable peak in November 2024 (9%). The data are presented in Figure 3.

The highest level of multiple antibiotic resistance (MAR) is observed in *Citrobacter* (0.70), indicating a serious resistance issue. Moderately high resistance levels are seen in *Pseudomonas aeruginosa* (0.38) and *Staphylococcus haemolyticus* (0.27). An average resistance level is demonstrated by *Enterobacter* (0.23) and Streptococcus (gram-positive) (0.20). Low resistance levels are observed in Klebsiella spp. (0.12) and *Staphylococcus* aureus (0.10). *Citrobacter* and *Pseudomonas aeruginosa* are the most problematic due to their high levels of multiple resistance. The data can be reviewed in Figure 4.

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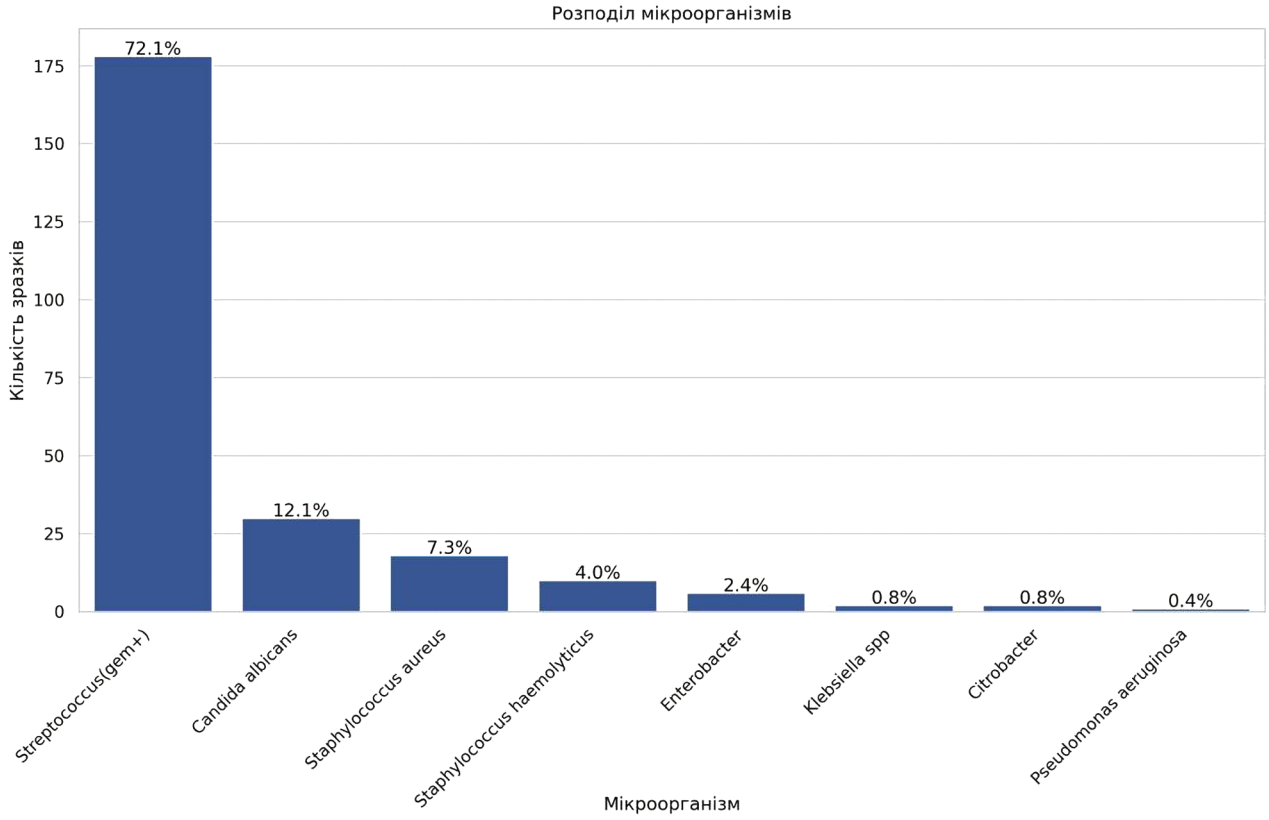

Figure 1. Distribution of Microorganisms

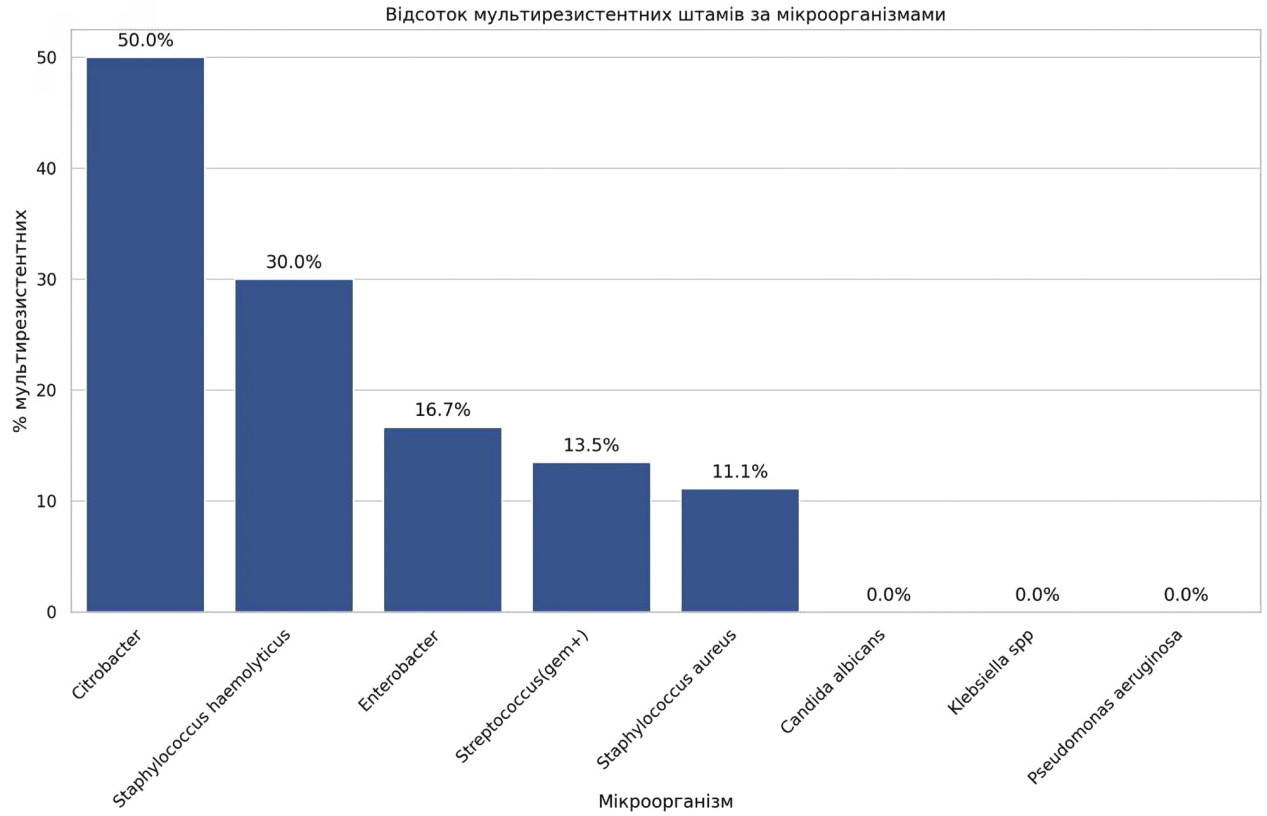

Figure 2. Percentage of Multidrug-Resistant Strains by Microorganism

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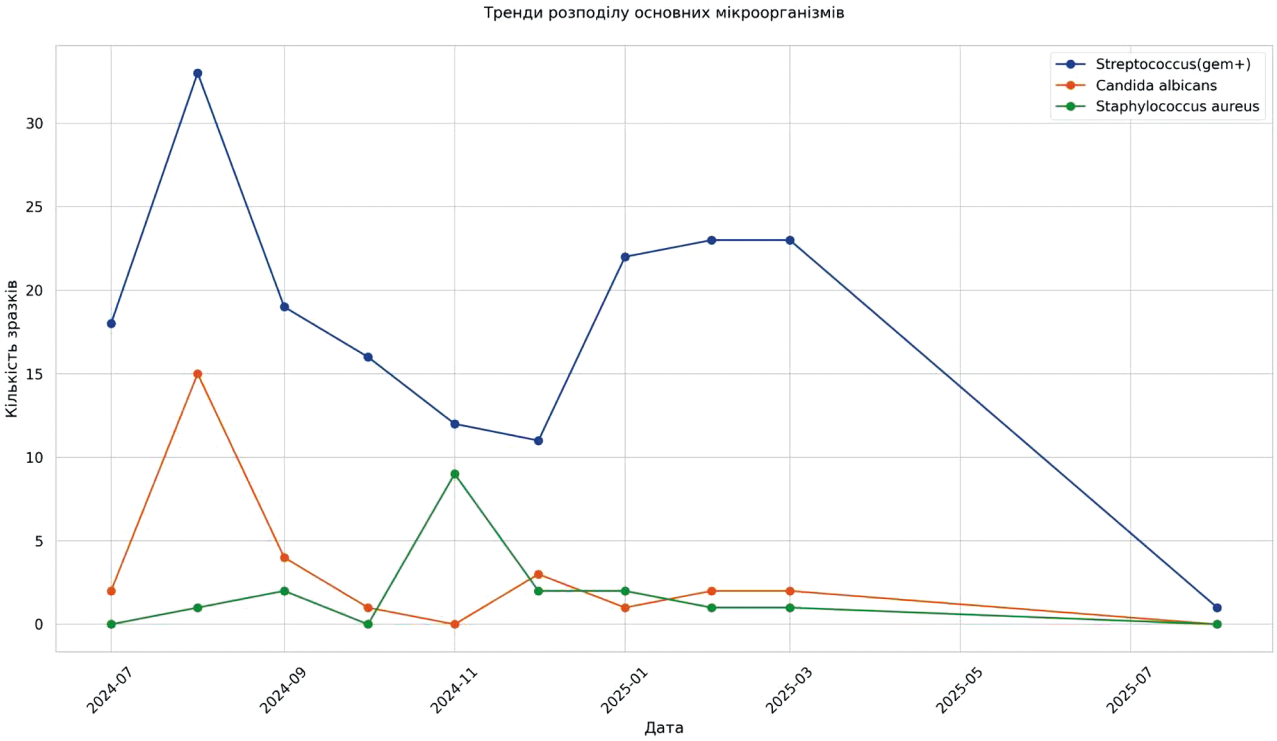

Figure 3. Trends in the Distribution of Major Microorganisms

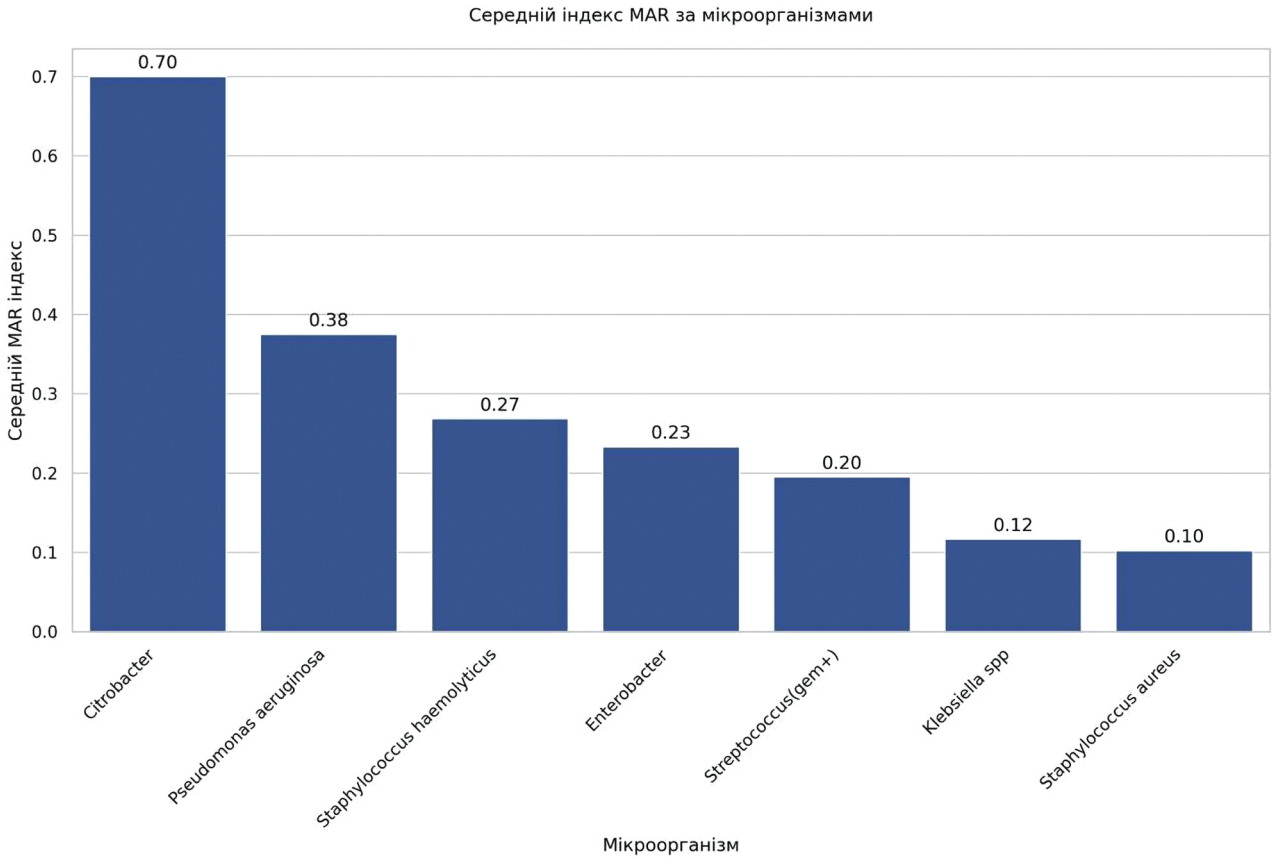

Figure 4. Average MAR Index by Microorganism

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Overall, only a small proportion of bacteria (less than 10%) have an MAR index ≥ 0.5. This means that approximately 90% of microorganisms predominantly exhibit monoresistance to a specific antibiotic. The final distribution of the MAR index can be reviewed in Figure 5.

Regarding fungi, the average MAR index is 0.32, which is higher than the average MAR index for bacteria (0.20), as shown in Figure 5. This suggests that fungi are more resistant than bacteria and require mandatory susceptibility testing for antifungal drugs for each fungal isolate. It is also important to implement resistance control measures and restrict the use of antifungal agents unless necessary. The data on the MAR index for fungi are illustrated in Figure 6.

In addition to evaluating the aforementioned parameters, a correlation heatmap of antibiotic

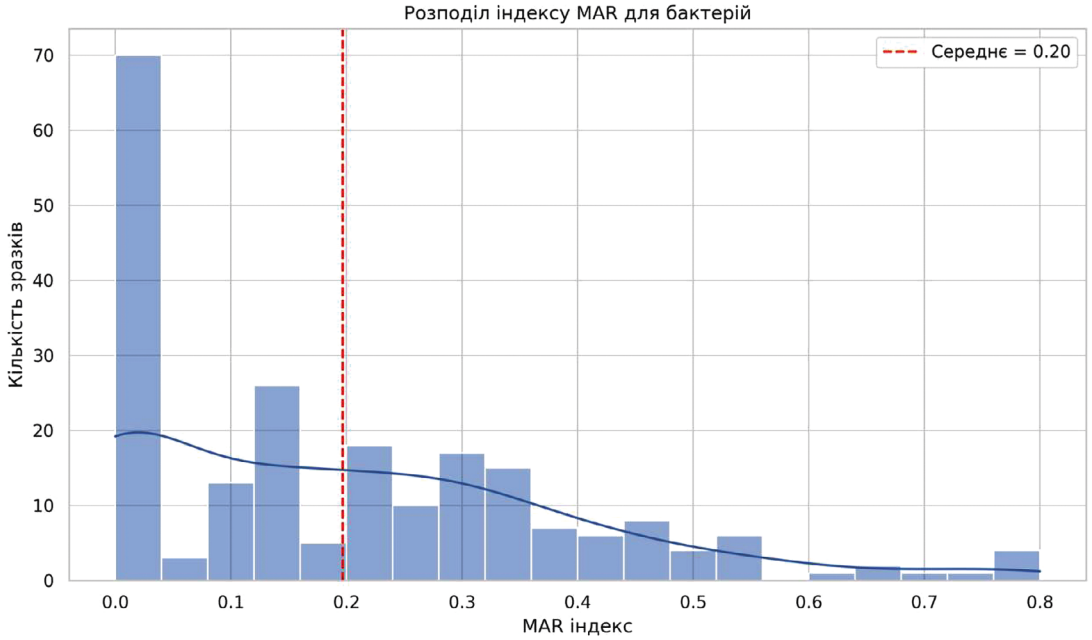

Figure 5. Distribution of MAR Index for Bacteria

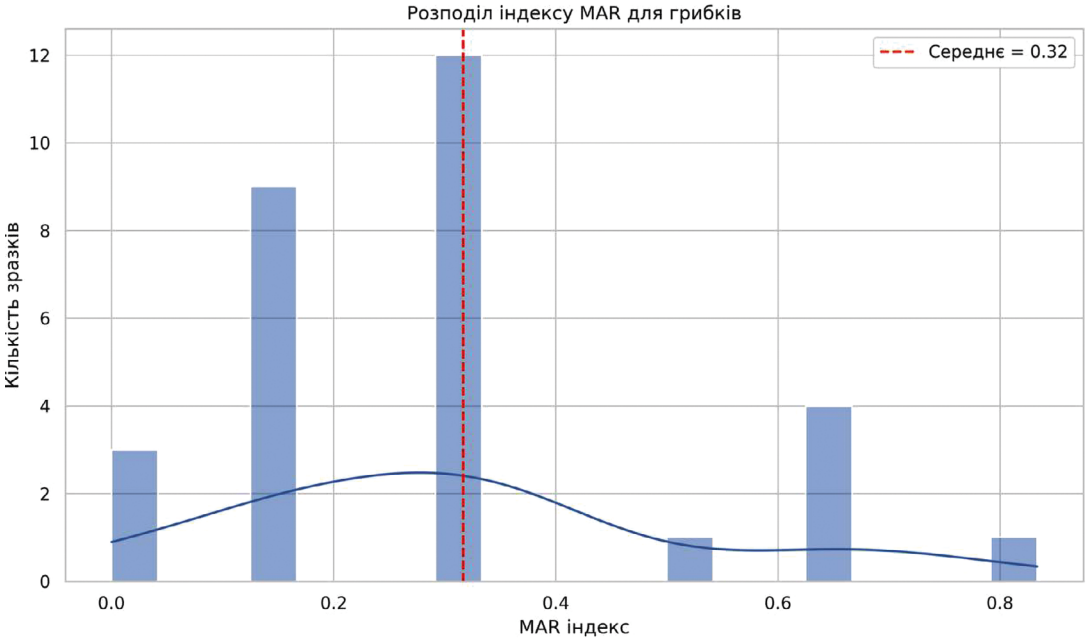

Figure 6. Distribution of MAR Index for Fungi

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resistance was constructed. The highest positive correlation is observed between fluconazole and ketoconazole (1.00), indicating that resistance to one of these antifungal agents is accompanied by resistance to the other. Surprisingly, strong correlational links were found between antibiotics within the same groups, such as levofloxacin and ofloxacin (0.77). Strong correlations were also observed between ofloxacin and linezolid (1.00), imipenem and clarithromycin (1.00), and imipenem and ceftriaxone (1.00).

The highest negative correlation was found between azithromycin and vancomycin (-0.35), meaning that microorganisms resistant to azithromycin were sensitive to vancomycin, and vice versa. A similar trend was noted with imipenem and vancomycin (-0.69), and imipenem and ampicillin (-0.43).

This correlation heatmap helps to understand which antibiotics share similar resistance profiles, which can be useful for selecting alternative drugs in the treatment of bacterial and fungal infections.

Based on the collected data, clotrimazole (100%) *and ketoconazole* (90.0%) demonstrated high effectiveness for the empirical treatment of fungal pharyngeal infections (Figure 8). Similarly, broad-spectrum antibiotics such as amikacin, ceftriaxone, and cefepime also showed high

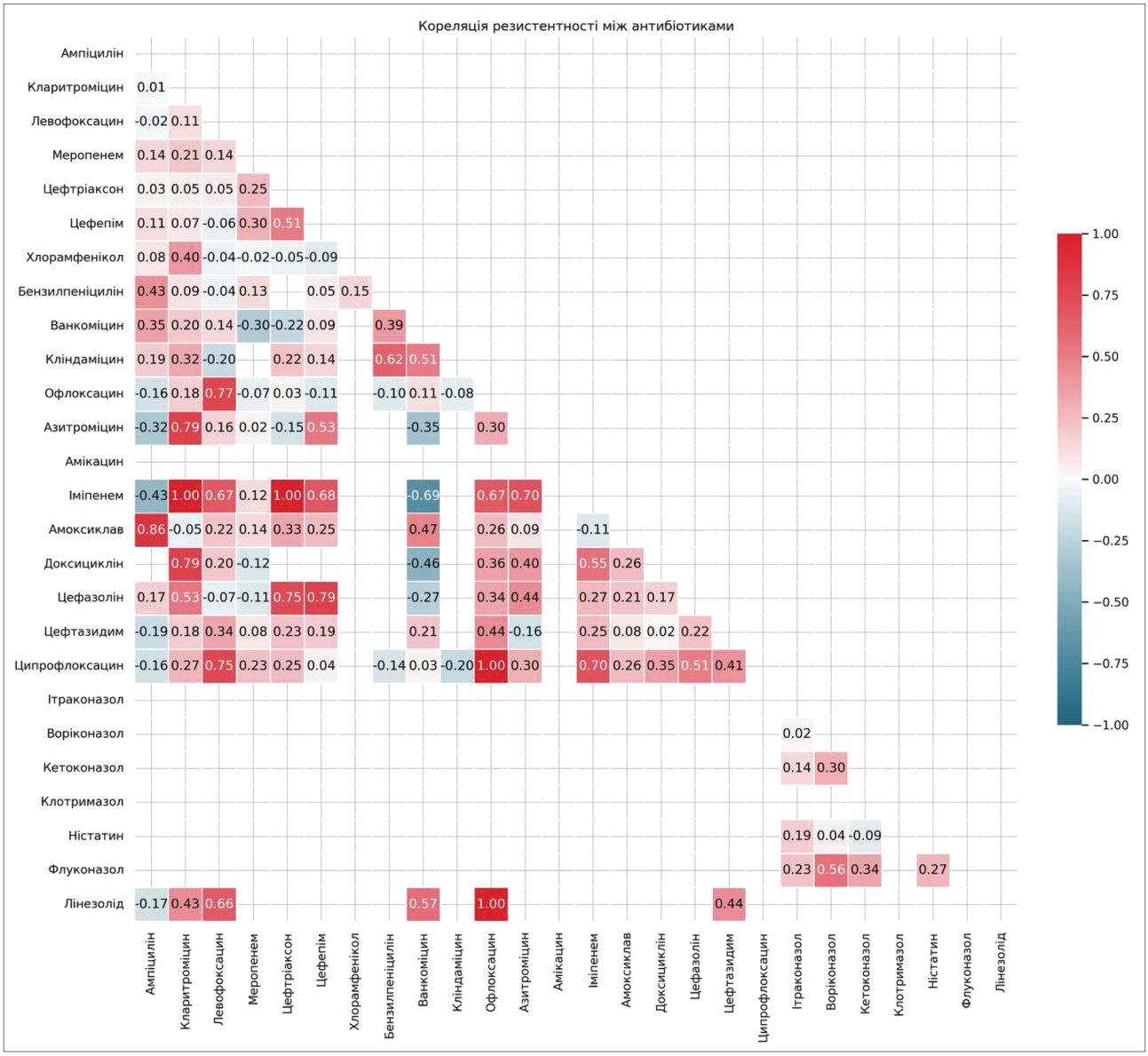

Figure 7. Correlation of Resistance Between Antibiotics

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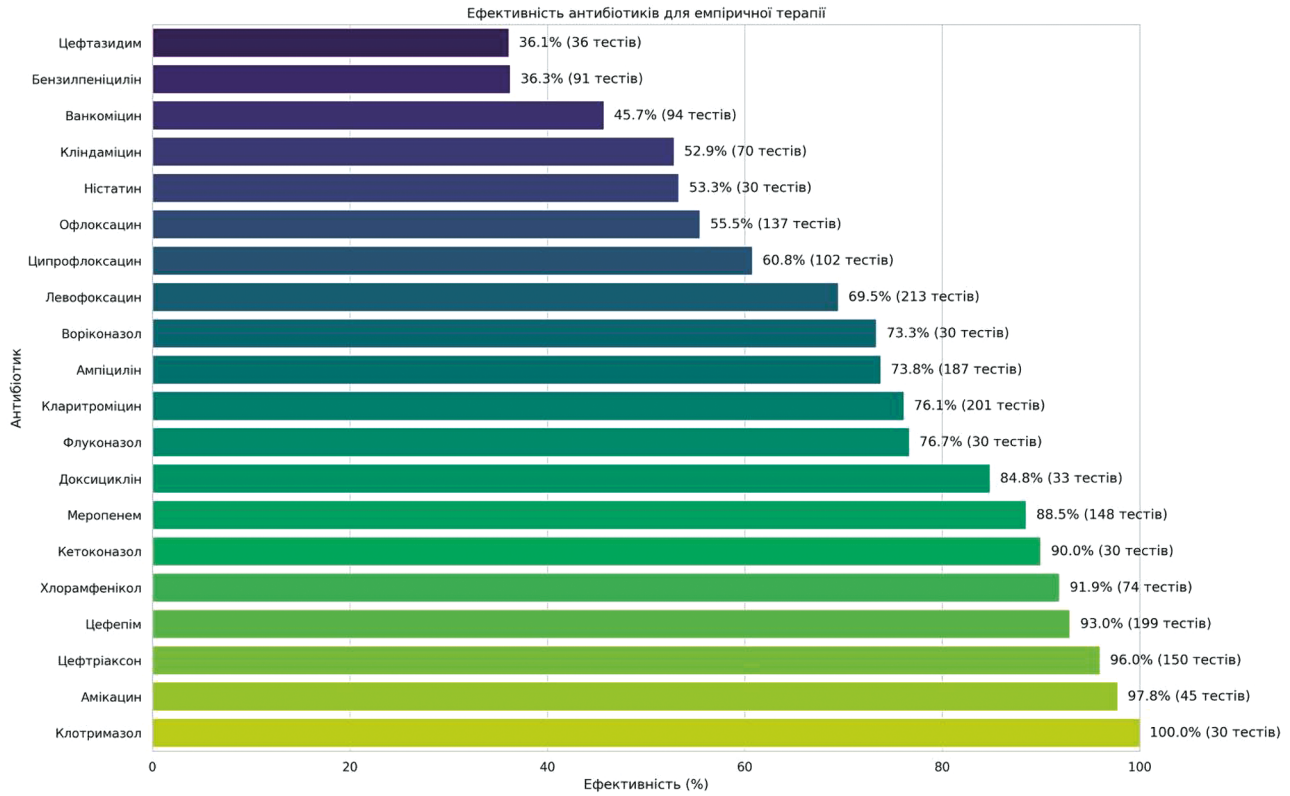

Figure 8. Effectiveness of Antibiotics for Empirical Therapy

effectiveness (over 90%). In contrast, ceftazidime, vancomycin, and clindamycin exhibited low effectiveness (less than 50%), which may indicate high resistance of microorganisms to these drugs.

It should be noted that for certain antibiotics, the number of tests was relatively low—fewer than 20 tests—which may affect the reported level of antibiotic resistance.

A detailed analysis of antibiotic resistance revealed that amikacin is the most effective antibiotic for *Streptococcus* (gram-positive) in terms of susceptibility (100%), though the small number of tests (8) suggests the need for further studies to confirm this finding. Meanwhile, ceftriaxone (98.5%, 131 tests) and cefepime (94.7%, 171 tests) also exhibit high effectiveness in treating pharyngeal bacterial infections caused by β-hemolytic streptococcus, with their results being more reliable due to the larger number of tests. The data are presented in Figure 9.

Figure 9. Most Effective Antibiotics for β-Hemolytic Streptococcus

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Three antibiotics (levofloxacin, meropenem, and ofloxacin) were found to have complete susceptibility for *Staphylococcus aureus*, with two belonging to the fluoroquinolone group. This is likely due to the similarity in the structural properties of these antibiotics. The data are presented in Figure 10.

Based on the statistical calculations conducted, clotrimazole was found to be the most effective antifungal agent with an effectiveness of 100% (30 tests), making it the best choice for empirical therapy. Ketoconazole (90.0%) is also highly effective and can serve as an alternative to clotrimazole. Fluconazole (76.7%) and voriconazole (73.3%) exhibit moderate effectiveness. Nystatin (53.3%) is the least effective, and its use may be limited in our context.

It is noted that an equal number of tests were conducted for all antifungal agents.

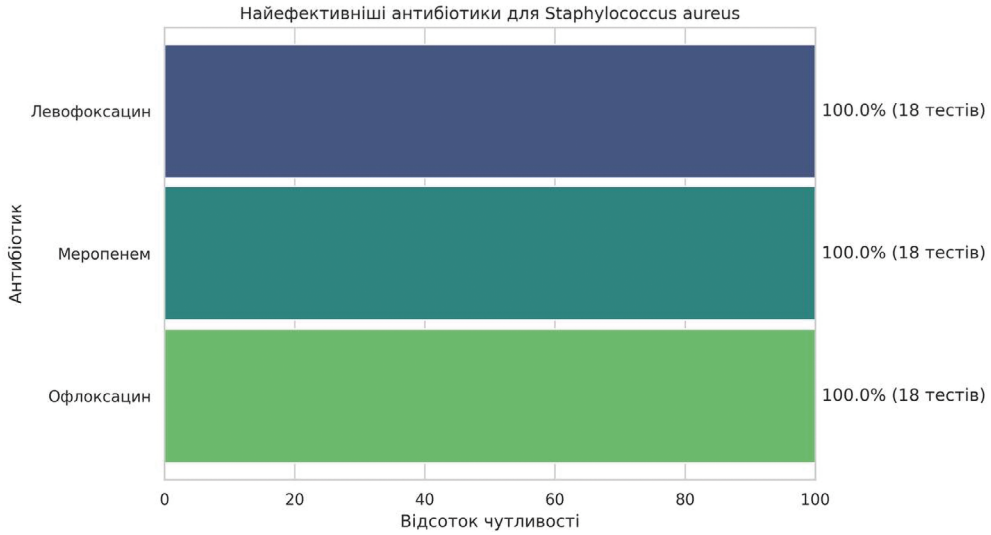

Figure 10. Most Effective Antibiotics for Staphylococcus aureus

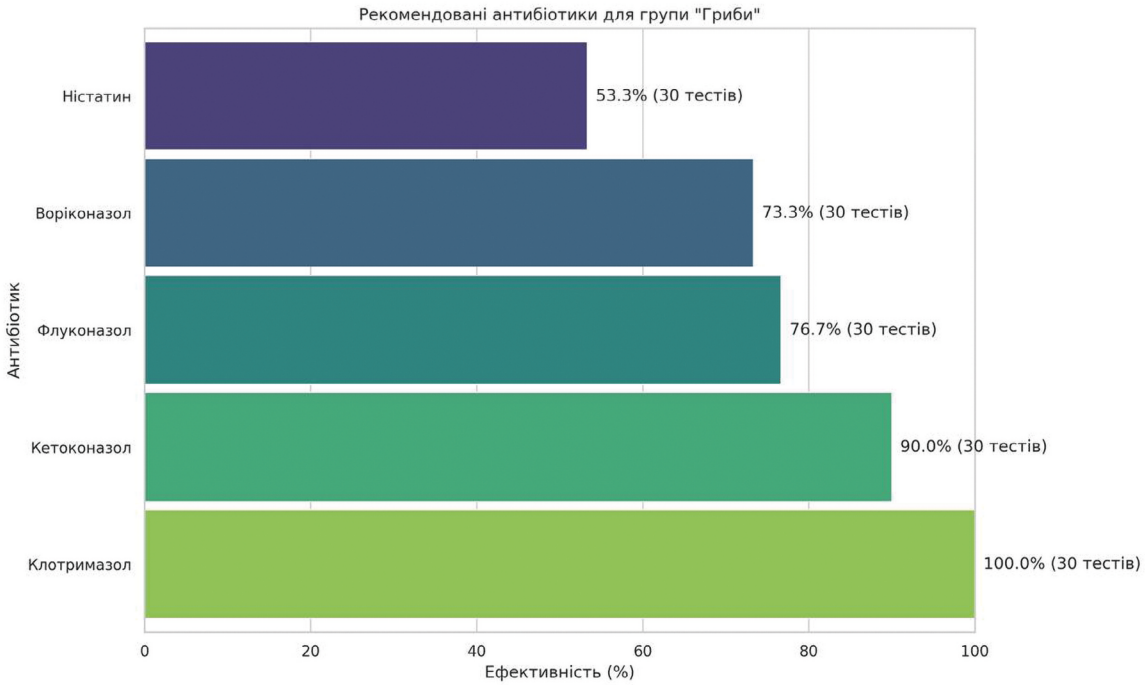

Figure 11. Recommended Antibiotics for the Fungi Group

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Upon group analysis, it was found that ampicillin exhibits the highest susceptibility (73.8%) and the lowest resistance (20%), whereas amoxicillin shows the lowest susceptibility (16.7%) and the highest resistance (78%) within the penicillin group. The data are presented in Figure 12.

Analysis of the macrolide group revealed that clarithromycin has higher susceptibility (76.1%) and lower resistance (14%), while azithromycin shows slightly lower susceptibility (69.6%) and higher resistance (25%). The data are presented in Figure 13.

An interesting finding is that levofloxacin exhibits the highest susceptibility among the studied drugs, whereas ofloxacin is the least effective in terms of the percentage of susceptible strains across various bacteria. The data are illustrated in Figure 14.

Among the cephalosporin group, ceftriaxone is the most effective. Ceftazidime, however, has the lowest effectiveness due to a high level of

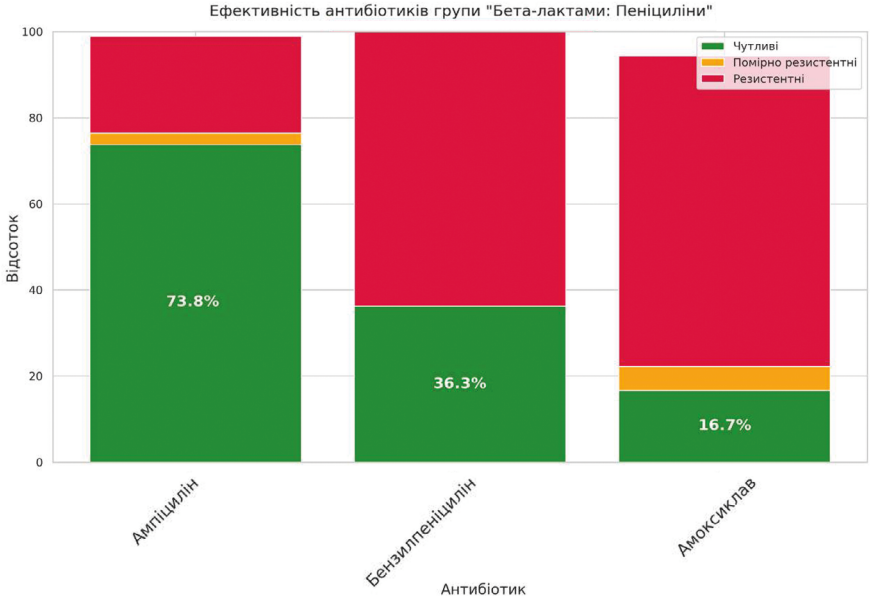

Figure 12. Effectiveness of Penicillin Group Antibiotics

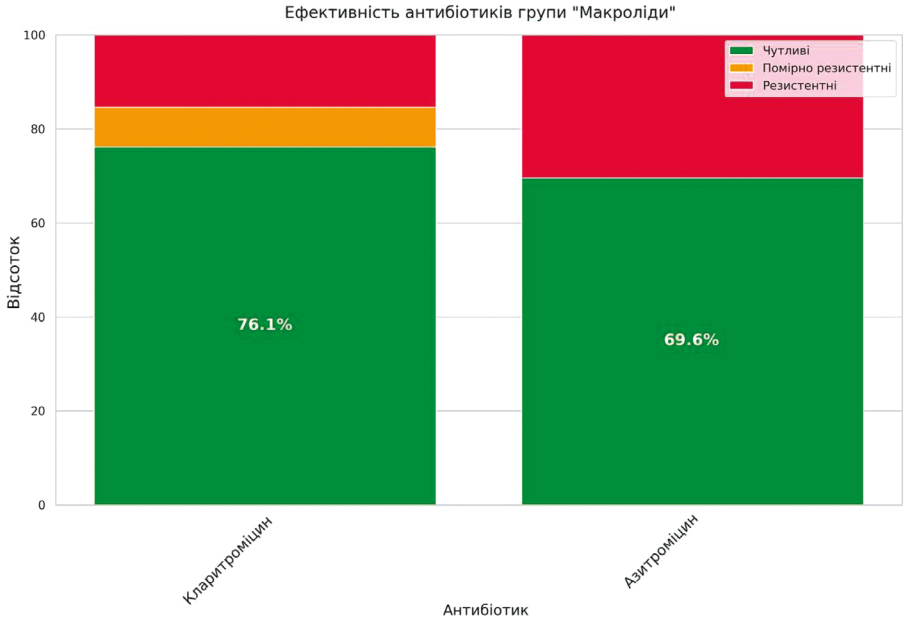

Figure 13. Effectiveness of Macrolide Group Antibiotics

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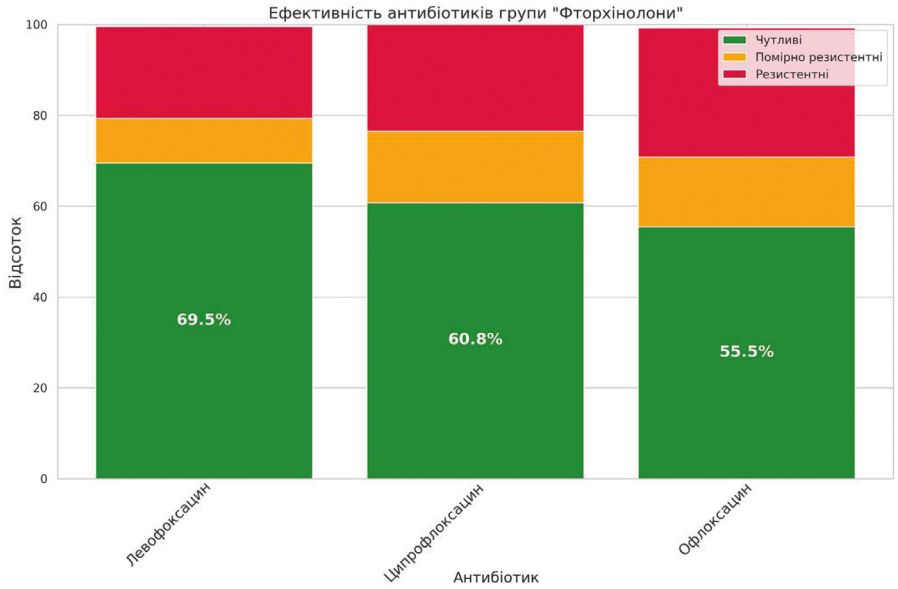

Figure 14. Effectiveness of Fluoroquinolone Group Antibiotics

resistance. The final distribution can be reviewed in Figure 15.

Regarding the carbapenem group, meropenem demonstrates significantly higher effectiveness compared to imipenem. Imipenem has a substantial level of resistance, which may limit its clinical applicability in some cases. The data are presented in Figure 16.

Regarding the azole group of antifungal agents, clotrimazole (100%) and ketoconazole (90%) exhibit the highest susceptibility, while itraconazole (13.3%) shows the lowest, making its use in clinical practice questionable. A detailed analysis is presented in the diagram (Figure 17).

After evaluating all baseline parameters, a linear regression model was developed to predict

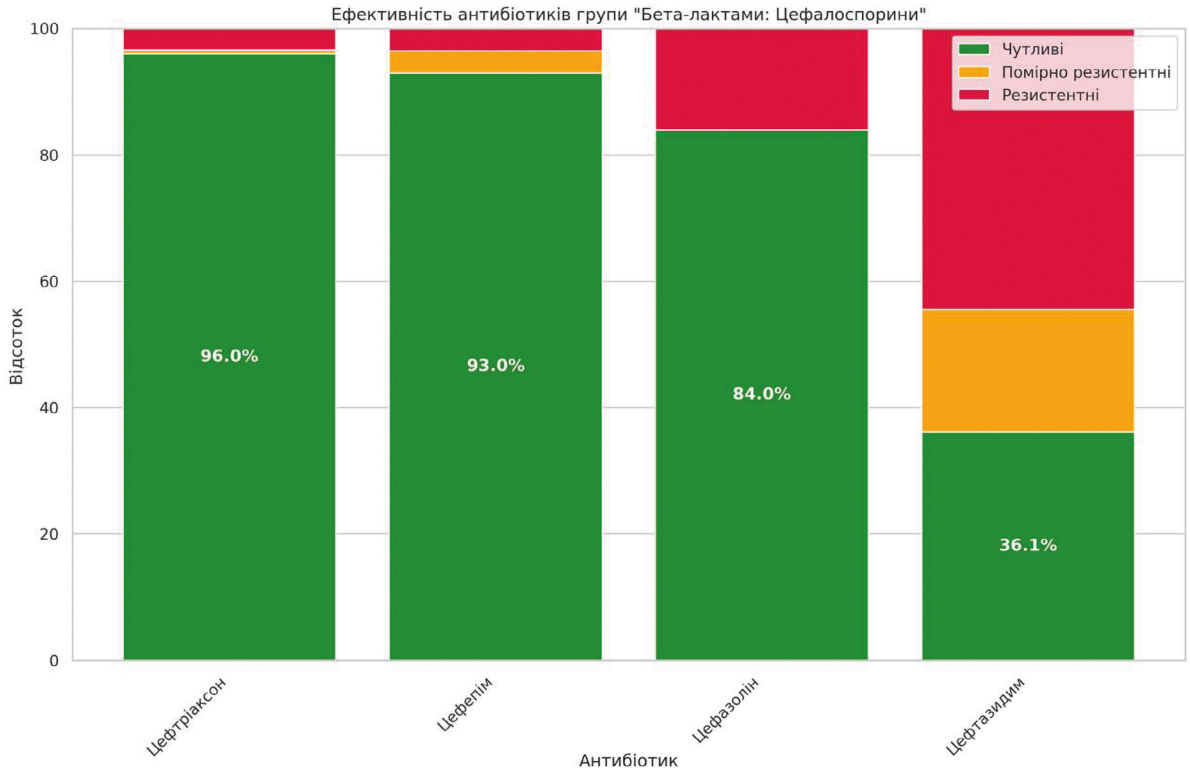

Figure 15. Effectiveness of Cephalosporin Group Antibiotics

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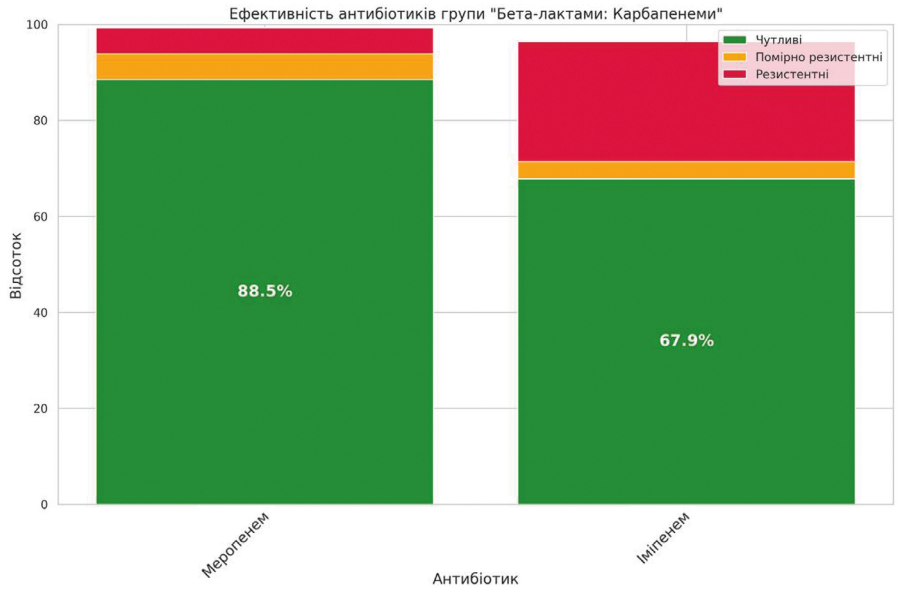

Figure 16. Effectiveness of Carbapenem Group Antibiotics

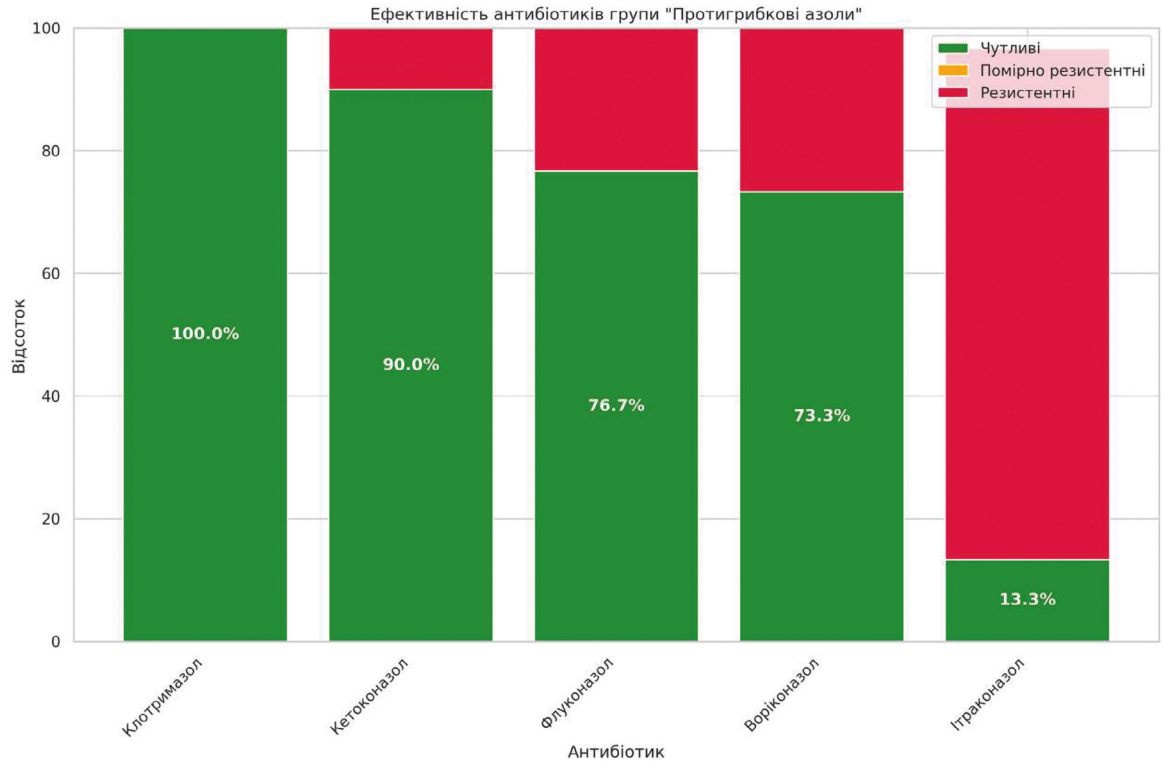

Figure 17. Effectiveness of Antifungal Agents

antibiotic resistance over time. Accordingly, the highest increase in resistance is forecasted for ampicillin (30.1%), which may indicate a rapid development of microbial resistance to this drug. In contrast, cefepime and clarithromycin show a predicted decrease in resistance levels, making them potentially more stable for future use (Figure 18).

Discussion

The study conducted at the Brovary Multidisciplinary Clinical Hospital between 2024 and 2025 highlights regional features of antibiotic resistance (ABR) in pharyngeal infections in the Kyiv region. Analysis of 255 throat swabs revealed a predominance of gram-positive bacteria, particularly *Streptoco-*

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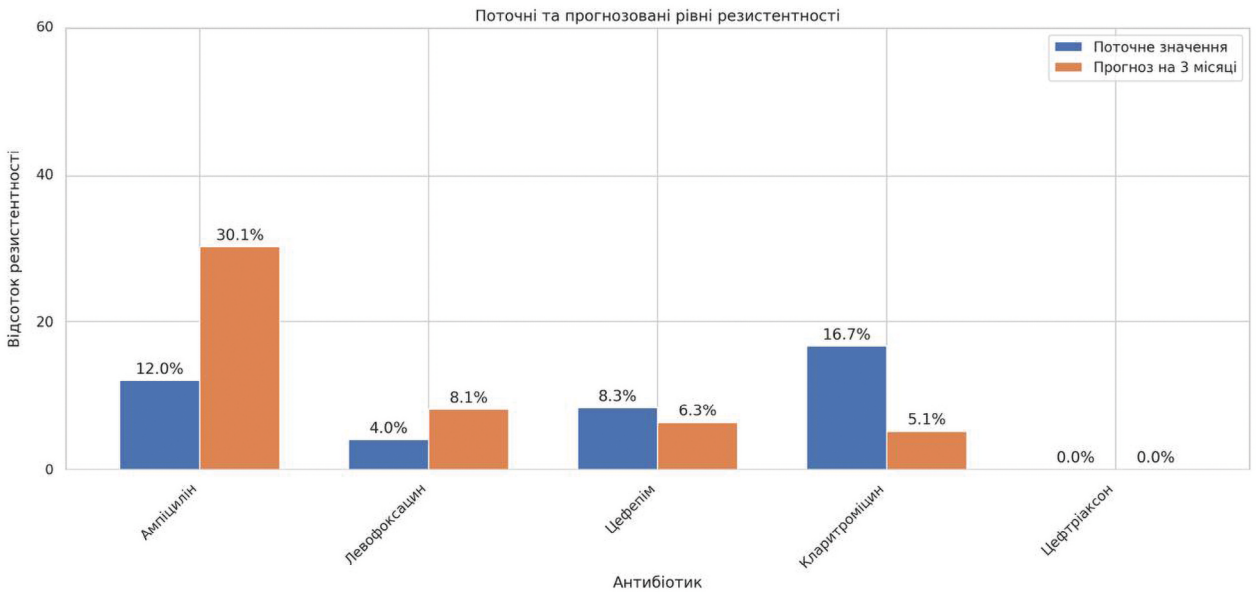

Figure 18. Current and Predicted Resistance Levels

ccus (gram-positive) (72.1%), which aligns with international data on the dominance of streptococci as the primary pathogens in pharyngitis and tonsillitis [8]. The low frequency of *Pseudomonas aeruginosa* (0.4%) reflects its greater prevalence in nosocomial settings, as noted by Bassetti et al. (2019), where gram-negative bacteria are more commonly associated with infections in intensive care units [1].

The seasonal dynamics identified in the study indicate peaks in activity for *Streptococcus* (gram-positive) in July (33%), *Candida albicans* in June (15%), and Staphylococcus aureus in August and November (9% and 8%, respectively). These fluctuations may be linked to climatic factors, including high temperatures and humidity during the summer, which promote microbial growth, as emphasized by Berkow and Lockhart (2017) for fungal infections [3]. The reduced activity of microorganisms in winter (December, 2%) may reflect lower circulation of pharyngeal infections during the cold season, warranting further investigation to develop seasonally adapted prevention strategies.

The high multiple antibiotic resistance (MAR) index in *Citrobacter* (0.70) confirms its status as a problematic pathogen, as noted by Gao et al. (2019), which highlights its multidrug resistance to cephalosporins and amoxicillin-clavulanate [7]. Moderate resistance in *Pseudomonas aeruginosa* (MAR 0.38) and *Staphylococcus haemolyticus* (MAR 0.27) points to challenges in treating infections caused by these microorganisms, especially in settings with limited access to broad-spectrum antibiotics [1]. The higher MAR index for fungi (0.32) compared to bacteria (0.20) is consistent with global trends of increasing resistance to azoles, particularly fluconazole, as confirmed by Castanheira et al. (2017) [5].

The effectiveness of antibiotics for empirical therapy varies by pathogen. For *Streptococcus* (gram-positive), amikacin (100%), ceftriaxone (98.5%), and cefepime (94.7%) showed high susceptibility, making them optimal for treating streptococcal infections. The complete susceptibility of *Staphylococcus aureus* to levofloxacin, meropenem, and ofloxacin (100%) aligns with findings by Diekema et al. (2019), which note the effectiveness of fluoroquinolones and carbapenems [6]. For fungal infections, clotrimazole (100%) and ketoconazole (90%) proved most effective, while the low susceptibility to nystatin (53.3%) and itraconazole (13.3%) suggests limited applicability, consistent with the rising resistance to azoles [5].

Correlation analysis revealed a high positive correlation between fluconazole and ketoconazole (1.00), imipenem and meropenem (0.69), levofloxacin and ciprofloxacin (0.44), levofloxacin and ofloxacin (0.77), ofloxacin and linezolid (1.00), imipenem and clarithromycin

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(1.00), and imipenem and ceftriaxone (1.00). A negative correlation between azithromycin and vancomycin (-0.35) supports the potential use of vancomycin as an alternative when resistance to azithromycin is present. High resistance to clarithromycin (54.3% in *Streptococcus* (gram+), 66.7% in *S. aureus*) and amoxicillin-clavulanate (83.3% in *Enterobacter*) underscores the need to limit their use, as recommended by ESCMID guidelines [8] and WHO [1].

Limitations of the study include the small number of tests for some antibiotics (e.g., amikacin for *Streptococcus* (gram+)) and the monocentric nature of the investigation. Therefore, further multicenter studies with larger samples are necessary to validate the findings.

Conclusions

The study revealed that *Streptococcus* (gram-positive) is the most common pathogen causing pharyngeal infections (72.1%), while *Pseudomonas aeruginosa* was the least frequent (0.4%), indicating the dominance of gram-positive bacteria in community-acquired pharyngeal infections in the region.

A clear seasonal dependency in the spread of microorganisms was identified: the peak activity of *Streptococcus* (gram-positive) occurs in July (33%), *Candida albicans* in June (15%), and *Staphylococcus aureus* in August and November (9% and 8%, respectively). The lowest activity of all microorganisms is observed in winter (December, 2%), highlighting the need for seasonally adapted prevention and treatment strategies.

The highest multiple antibiotic resistance (MAR) index was demonstrated by *Citrobacter* (0.70), followed by *Pseudomonas aeruginosa* (0.38) and *Staphylococcus haemolyticus* (0.27). The average MAR index for fungi (0.32) exceeds that for bacteria (0.20), indicating a higher resistance level among fungal pathogens, primarily to azoles.

Streptococcus (gram-positive) showed high susceptibility to amikacin (100%, 8 tests), ceftriaxone (98.5%, 131 tests), and cefepime (94.7%, 171 tests), making them optimal for empirical therapy, though the data for amikacin require further confirmation due to study limitations.

For *Staphylococcus aureus*, the most effective antibiotics were levofloxacin, meropenem, and ofloxacin (100% susceptibility).

Clotrimazole (100%) and ketoconazole (90%) emerged as the most effective antifungal agents. Nystatin (53.3%) and itraconazole (13.3%) have limited effectiveness due to high resistance.

A high positive correlation was found between fluconazole and ketoconazole (1.00), imipenem and meropenem (0.69), and levofloxacin and ciprofloxacin (0.44), reflecting shared resistance mechanisms. A negative correlation between azithromycin and vancomycin (-0.35) suggests the potential effectiveness of vancomycin as an alternative when resistance to azithromycin is present.

High resistance to clarithromycin (54.3% in *Streptococcus* (gram+), 66.7% in *S. aureus*), amoxicillin-clavulanate (83.3% in *Enterobacter*), and fluconazole (46.7% in *Candida albicans*) indicates the need to restrict their use in empirical therapy.

The highest increase in resistance is forecasted for ampicillin (30.1%), pointing to the need for enhanced control over its use. In contrast, cefepime and clarithromycin show a predicted decrease in resistance, which may reflect the effectiveness of local antibiotic therapy protocols.

Ethical Approval

The study was approved by the Bioethics Committee of the Bogomolets National Medical University (protocol №187 23.09.2024) and complies with the requirements of the Helsinki Declaration. Since the study is retrospective, obtaining informed consent from patients was not required.

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Conflict of Interest

The authors declare no conflicts of interest in conducting the research, authorship, or publication of this article.

Consent for Publication

All authors have reviewed the manuscript text and provided consent for its publication.

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Особливості регіональної антибіотикорезистентності при фарингеальних інфекціях

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Анотація: *Антибіотикорезистентність (АБР) є глобальною проблемою для населення. Всесвітня організація охорони здоров'я (ВООЗ) прогнозує, що до 2050 року АБР може спричинити 10 мільйонів смертей щорічно, якщо не вжити заходів протидії (WHO, 2019). Зростання кількості мультирезистентних (МР) бактерій і грибків ускладнює стратегії лікування, особливо в лікувально-профільних закладах, в яких за різними даними, поширені нозокоміальні інфекції. Проаналізувати результати бактеріологічного дослідження мазків із зіву з антибіотикограмою при захворюваннях глотки та на основі даних аналізу розробити рекомендації для емпіричної антибіотикотерапії. На базі КНП «Броварська багатопрофільна клінічна лікарня» з 2024 по 2025 роки було проведено 255 мазків із зіву з посівом для визначення бактеріологічного складу слизової оболонки глотки та антибіотикорезистентності. Ізоляти ідентифікували за допомогою стандартних мікробіологічних методів, таких як культивування на поживних середовищах і біохімічні тести. Для оцінки стійкості до антибіотиків використовували метод визначення мінімальної інгібуючої концентрації (MIC) або дискодифузійний метод (метод Кірбі-Бауера). Тестування проводили на панелі антибіотиків. Результати інтерпретували за стандартами, такими як CLSI (Clinical and Laboratory Standards Institute), щоб класифікувати штами як чутливі, помірно чутливі або стійкі. Для комплексного аналізу мікробіологічних даних та профілів антибіотикорезистентності використовувалась багаторівнева статистична методологія. Аналіз здійснювався з використанням мови програмування Python 3.9 та спеціалізованих бібліотек для наукової обробки даних (NumPy, SciPy, Pandas та scikit-learn; візуалізація даних проводилася засобами Matplotlib та Seaborn.). Протигрибкові препарати - клотримазол (100%) та кетоконазол (90.0%) - показали найвищу ефективність для лікування грибкових інфекцій. Цефтазидим, ванкоміцин, бензилпеніцилін та кліндаміцин показали низьку ефективність (менше 50%), що може свідчити про високу резистентність мікроорганізмів до цих препаратів. Амікацин, цефтріаксон та цефепім є найефективнішими антибіотиками для В-гемолітичного стрептококу з точки зору чутливості. Staphylococcus aureus має повну чутливість до левофлоксацину, офлоксацину та меропенему. Дослідження підкреслює серйозність проблеми антибіотикорезистентності та необхідність раціонального використання антимікробних препаратів у клінічній практиці.*

Ключові слова: антибіотикорезистентність, антибіотики, бактерії, глотка, грибки, захворювання глотки, тонзиліт, ротова порожнина, фарингіт

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Features of the concentration of vitamin and mineral compounds in women with antenatal fetal death in anamnesis at the pre-pregnancy stage

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Abstract: *Antenatal fetal death is one of the most severe obstetric condition, which has a significant impact on both somatic health and the psycho-emotional state of the woman. Recently, the data appeared that highlight the role of vitamin-mineral balance in the antenatal fetal death etiopathogenesis due to the influence on the angiogenesis and on the formation of placental blood flow processes. Therefore, studying the vitamin-mineral compounds levels in women with a history of antenatal fetal death is particularly relevant and prompted the formation of our study purpose: to determine the features of the folic acid, vitamins B, D, ferritin, homocysteine concentrations in women with antenatal fetal death in anamnesis at the stage of pre-pregnancy preparation. Materials and methods of the study – a prospective examination of 82 patients was conducted, of which 49 women (main group) with antenatal fetal death in anamnesis and 33 women (control group) with no late reproductive losses in anamnesis. In all patients, the levels of folic acid, vitamins B_1, B_6, B_{12}, 25-hydroxyvitamin D, ferritin, Mg^{2+}, Se^{2+} and homocysteine in the blood serum were determined. The concentration of vitamins D, B_1, B_6, B_{12}, folic acid, ferritin and homocysteine was determined using enzyme-linked immunosorbent assay (Monobind (USA)). The determination of Mg^{2+} concentration was carried out using the colorimetric method (Roche Diagnostics, Switzerland). Selenium was determined using atomic absorption spectrophotometry (PerkinElmer, USA). According to the results obtained, the women in the main group had statistically significant differences in compared with the control group women: lower concentration of folic acid by 28.2%, vitamin B_6 by 24.3%; B_{12} by 23.7%, Vitamin D was 18.4 ± 1.1 ng/ml, which is 15.6% less than in the control group and 38.7% less than the lower limit of reference values. The concentration of Mg^{2+} was recorded as 1.4 times lower, as well as Se^{2+} 1.2 times in the main group. Alterations in the vitamin and mineral profile can contribute to the activation of oxidative stress, endothelial dysfunction and, as a result, placental insufficiency, which are currently considered one of the key pathogenetic links of antenatal fetal death. The obtained results emphasize the feasibility of the vitamin and mineral compounds levels determination in the pre-pregnancy preparation of women with a burdened obstetric history, which will allow the formation of individual strategies to prevent pregnancy complications and repeated perinatal losses.*

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Keywords: Ferritins, Folic Acid, Homocysteine, Pregnancy Complications, Vitamin D, Vitamin B, Antenatal Fetal Death.

Introduction

Antenatal fetal death (AFD) is one of the most severe complications of pregnancy, which is recorded in 2-4 cases per 1000 births in a high level developed countries and in 10-20 cases per 1000 births in a low level developed ones [1]. The highest proportion of antenatal fetal deaths occurs between 32 and 36 weeks of gestation. In 2021, the global rate of preterm births beyond 22 weeks was 23.0 per 1000 births, equivalent to over 3 million cases per year, of which 77% occurred in South Asia and Africa [2, 3]. In Ukraine, the incidence of AFD ranges from 4 to 8 cases per 1000 live births [4, 5]. In the last 5 years, there has been a gradual decrease in perinatal losses, but the rates of AFD remain stably high.

The etiopathogenesis of stillbirth is multifactorial and includes factors such as infectious, chromosomal abnormalities, obstetric complications, thrombophilia, immune and endocrine disorders about 30% of stillbirths remain unexplained [6]. At the current stage of research, special attention is paid to the role of endothelial dysfunction in the pathogenesis of AFD, which can serve as a marker and a factor in gestational complications. It has been established that the state of the endothelium significantly depends on the balance of vitamin and mineral compounds, which play a key role in the processes of angiogenesis, blood clotting and the formation of placental blood flow [7].

During pregnancy, the need for micronutrients increases by 20–50%, while the nutritional security of women of reproductive age often remains insufficient. In 70–80% of pregnant women, a combination of deficiencies of three or more vitamins and minerals is recorded, in particular folate, vitamins of group B, D, iron, zinc, iodine, magnesium and selenium [8, 9]. Nutrient deficiencies are associated with an increased risk of preeclampsia, fetal growth restriction, congenital malformations, preterm birth, and stillbirth [10]. It is also known that reproductive loss in anamnesis significantly increases the risks of repeated obstetric complications in subsequent pregnancies, including perinatal mortality, preterm birth, and fetal growth restriction [11].

Currently, the role of folate during pregnancy is well understood, with the main focus being on preventing neural tube defects, congenital heart defects, and fetal growth retardation [12, 13]. In case of impaired folate metabolism, the need for folates and cofactors folate metabolism (vitamins B_2, B_6, B_{12}) increases significantly, the processes of DNA repair, cell proliferation and vascular remodeling are inhibited, which is especially critical in the conditions of placenta formation [14-16]. Decreased activity of folate enzymes metabolism disrupts the transformation of homocysteine into methionine and reduces the production of S- adenosylmethionine – a universal donor of methyl groups necessary for DNA methylation and epigenetic regulation of embryonic and placental development [17].

Vitamin D also plays an important role in the proper functioning of the maternal-placental-fetal system. 25(OH)D deficiency is associated with an increased risk of placental dysfunction, preeclampsia, fetal growth retardation, and AFD [18]. Combined deficiency of folate, vitamin D, and iron, a cofactor for vitamin D activation, is found in some pregnant women, especially those with low socioeconomic status [19, 20].

The use of multivitamin complexes with prophylactic dosage increases the effectiveness of eliminating deficiencies of folate, vitamin D, iron and other nutrients during the preconception stage, which has been demonstrated in many studies and confirmed by a decrease in the frequency of preterm birth, low birth weight of the newborn and a reduced risk of AFD [21-23].

Thus, assessment of vitamin and mineral status in women with AFD in anamnesis is of significant importance in the pre-pregnancy period. Insufficiency of vital trace elements and vitamins may be a hidden factor in disorders of placentation, uteroplacental blood flow and intrauterine development of the fetus. Detection

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and timely correction of micronutrient disorders in the pre-pregnancy period opens up the possibility of personalized prevention, reducing the risk of adverse reproductive outcomes and improving perinatal outcomes [24, 25].

Aim

To determine the concentrations of vitamin and mineral compounds, namely B vitamins, folic acid, vitamin D, ferritin, magnesium, selenium, and homocysteine, in women with antenatal fetal death in anamnesis on the pre-pregnancy stage.

Materials and methods

A prospective examination of 82 women who admitted in the pre-pregnancy period to plan their next pregnancy was conducted. The main group included women with AFD in anamnesis (n=49), the control group consisted of patients with no late reproductive losses in anamnesis (n=33). The examination was conducted on the basis of the outpatient department of obstetrics and gynecological observation of the Maternity and Childhood Center of the Municipal Non-Profit Enterprise «Kyiv City Clinical Hospital №5» in the period between 2022 and 2024 years. Patients of both groups were representatively compared by age and level of social security.

Inclusion criteria: childbirth in anamnesis, voluntary consent to participate in this study.

Exclusion criteria: oncological condition; severe somatic or mental illnesses; infectious diseases in the acute stage; taking medications that affect vitamin metabolism or hormonal levels; refusal to participate at any stage of the study.

All patients were tested for the concentration of B vitamins, namely: thiamine (B_1), pyridoxine (B_6), cyanocobalamin (B_{12}), folic acid, vitamin D (25(OH)D), ferritin, magnesium (Mg^{2+}), selenium (Se^{2+}), and homocysteine in their blood serum.

Venous blood was collected on an empty stomach, from the cubital vein into two test tubes. To determine the level of vitamins D, B_1, B_6, B_{12}, folic acid, ferritin, Se^{2+} and homocysteine, gel – free tubes were used. To determine Mg^{2+}, a tube with lithium heparin was used. After blood collection, the centrifuged serum was stored at -20 °C until analysis. The concentration of vitamins D, B_1, B_6, B_{12}, folic acid, ferritin, and homocysteine was determined by enzyme-linked immunosorbent assay (ELISA) using commercial kits according to the manufacturer's protocols (Monobind (USA)). Mg^{2+} concentration was determined by the colorimetric method (Roche Diagnostics, Switzerland). Se^{2+} was determined using atomic absorption spectrophotometry (PerkinElmer, USA).

Statistica 10 software (StatSoft, USA) was used on a personal computer with Microsoft Excel 2019 software using parametric and nonparametric analysis methods. Quantitative variables were presented as mean values (M) with the corresponding standard error (m). Student's t-test was used to assess the statistical significance of intergroup differences. Fisher's exact test was used to compare categorical variables. A statistically significant difference was considered a difference at $p<0.05$.

The study was conducted in accordance with the principles of the Declaration of Helsinki. The research protocol was approved by the Bioethics Committee of the Bogomolets National Medical University (protocol No. 181 dated 01/29/2024).

Results

The average age of patients in the main group was 29.6±2.3 years; in the control group – 30.2±2.4 years ($p>0.05$). All patients of both examined groups lived in the Kyiv region. The somatic anamnesis in the main group was burdened by condition of the cardiovascular system (19 (38.8%) women), thyroid gland (13 (26.5%) women); metabolic syndrome (7 (14.3%) patients); diseases of the gastrointestinal tract and hepatobiliary system (13 (26.5%) women) urinary tract infection (13 (26.5%) women). In the control group, pathology of the cardiovascular system was noted in 8 (24.2%) women; thyroid gland – in 6 (18.1%) patients, diseases of the urinary system – in 6 (18.1%).

Among gynecological pathologies, inflammatory diseases of the urogenital tract prevailed (main group – 19 (38.8%); control group – 11 (33.3%) women); uterine leiomyoma (main group – 11 (22.4%); control group – 4 (12.1%) women, $p<0.05$); menstrual cycle disorders, manifested by dysmenorrhea (main group – 15 (30.6%); control group – 8 (24.2%) women), irregular menstrual cycle (main group – 4 (8.2%); control group – 2 (6.1%) women).

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Analyzing the concentration of folic acid in the studied groups, as a key microelement for ensuring women's health and preventing perinatal pathology, it was found that the concentration of folic acid was found to be 1.5 times lower in patients of the main group, compared with the results in the control group ($p<0.05$) (Table 1).

Table 1. The content of markers of folate metabolism in women of the examined groups (M±m)

Indicator	Survey groups	
	Main group (n=49)	Control group (n=33)
Homocysteine (μmol/L)	16.7±1, 2*	8.7±0.7
Folic acid (ng /ml)	8.9±0.6 *	12.4±0.7

Note: * - statistically significant differences compared to the control group ($p<0.05$)

It is worth noting that one of the activators of oxidative stress and endothelial dysfunction is a high level of homocysteine, which is one of the markers of impaired folate metabolism. The average value of homocysteine in patients of the main group was significantly increased and exceeded the values of the control group by 1.6 times ($p<0.05$). In particular, a third of patients of the main group (17 (34.7%) women) had significant hyperhomocysteinemia in combination with a decrease in serum folic acid.

The results obtained regarding the violation of folate metabolism necessitated the assessment of the levels of B vitamins (B_1, B_6, and B_{12}), which participate in the biosynthesis of amino acids, purine, and pyramidine bases (Table 2).

According to the data obtained, patients in the main group had a significant decrease in vitamin B_6 levels by 24.2% compared to the control group, as well as a decrease in vitamin B_{12} concentration by 23.7% ($p<0.05$), which coincided with anamnestic data on pathology of the gastrointestinal tract and hepatobiliary system in 26.5% of women in the main group.

The average value of vitamin B_1 in both study groups was within the reference values (70–180 ng/ml) and the difference in the average value of thiamine between the study groups was

Table 2. Concentration of B vitamins in women of the examined groups (M±m)

Indicator	Survey groups	
	Main group (n=49)	Control group (n=33)
Pyridoxine (B_6) (ng/ml)	56.8±4.6*	74.9±5.3
Thiamine (B_1) (ng/ml)	106.3± 8.4	112.5±9.7
Cyanocobalamin (B_{12}) (pg/ml)	147.4±6.7*	193.2±10.3

Note: * - statistically significant differences compared to the control group ($p<0.05$)

5.5% ($p>0.05$). However, vitamin B_1 deficiency was detected in the main group, 14 (28.6%) women were found to have a deficiency state in relation to this micronutrient.

Given the significant percentage of women with chronic pathology of the gastrointestinal tract and hepatobiliary system in the main group (26.5%), the level of ferritin was determined – a cofactor of cytochrome P_{450} enzymes, which is involved in the conversion of vitamin D to the biologically active form of calcitriol. In women of the main group, the average ferritin level was 14.6±1.1 ng/ml, which is 1.8 times lower than in the control group (26.3±1.6 ng/ml, $p<0.05$).

Analyzing the results of the study of the content of cofactors with pronounced antioxidant and anti-inflammatory properties (25(OH)D, Mg^{2+}, Se^{2+}), a significant difference was established between the studied groups (Table 3).

Table 3. Concentration of cofactors with antioxidant properties in women of the examined groups (M±m)

Indicator	Survey groups	
	Main group (n=49)	Control group (n=33)
Vitamin D (25(OH)D), ng/ml	18.4±1.1 *	21.8±1.3
Magnesium (Mg^{2+}), mmol/l	0.69±0.06*	0.97±0.08
Selenium (Se^{2+}), μg/l	79.1±5.9	97.3±7.2

Note: * - statistically significant differences compared to the control group ($p<0.05$)

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The average value of the concentration of 25(OH)D in women of the main group was 18.4±1.1 ng/ml, which is 15.6% lower than the similar indicator in the control group (21.8±1.6 ng/ml; $p<0.05$) and 38.7% lower than the lower limit of the reference value (30–70 ng/ml). In particular, vitamin D deficiency (<20 ng/ml) was detected in 67.3% of women of the main group versus 24.2% in the control group. A similar situation was found in the study of Mg^{2+} in the examined groups, where the concentration of Mg^{2+} was 1.4 times lower in the main group compared to the control group ($p<0.05$). Clinically, we associated the high frequency of violation of menstrual function (30.6%) in the main group with this deficiency condition.

Selenium, as the main antioxidant micronutrient, deserved no less attention, where in both examined groups it was within the reference value (70–150 μg/l). However, the concentration of Se^{2+} in the main group was lower by 18.7% compared to the control group. This was clinically confirmed by the high incidence of thyroid disease (26.5%) in women of the main group.

Thus, the obtained results of the study of vitamin and mineral compounds demonstrate significant changes in micronutrient status in women with a history of antenatal fetal death and indicate a pathogenetically combined mechanism of the occurrence of deficient states, and also justify the feasibility of including an assessment of vitamin and mineral metabolism in the pre-pregnancy examination of women with a burdened obstetric history.

Discussion.

The results of the study indicate significant deviations in the concentrations of vitamin and mineral compounds in women with a history of ADP in the pre-pregnancy stage, which is consistent with the results of recent studies. In particular, reduced levels of folic acid, vitamin B_6, B_{12} and vitamin D in reproductive losses are consistent with the results obtained in the works of Lindqvist PG (2025), which indicated a correlation between folate and B vitamin deficiency, hyperhomocysteinemia and an increased risk of thrombotic complications. At the same time, Petersen JM et.al. (2023) emphasize that the best period for correcting deficiency states, in order to prevent perinatal pathology, is the pre-pregnancy period. A systematic review showed an association between low selenium levels and pregnancy loss, preeclampsia and premature birth. In the studies of Dahlen CR (2022), lower Se^{2+} values were found in the group with pregnancy losses compared to controls. The results obtained confirm the hypothesis of the study and also have practical significance for the formation of pregravid preparation algorithms. The limitation of our study at this stage is a relatively small sample and the lack of dynamic monitoring of the course of pregnancy after correction of deficiencies, which requires further research.

Conclusions

1. The study found that women with antenatal fetal death in anamnesis have significantly lower vitamin and mineral metabolism indicators, in particular, a 1.5-fold lower level of folic acid compared to women without a history of late reproductive losses, which coincides with an increased level of average homocysteine concentration (16.7±1.2 μmol/l versus 8.7±0.7 μmol/l, $p<0.05$) and indicates high alertness to oxidative stress and, as a prognostic factor, to the development of endothelial dysfunction and prompts the mandatory correction of deficient states during the preconception stage.

2. The concentration of vitamins B_6, B_{12}, 25(OH)D was recorded in a significantly lower concentration in the main group, namely: vitamin B_6 was reduced by 24.2%; vitamin B_{12} – by 23.7%; 25(OH)D – by 15.6% compared to the control group and by 38.7% compared to the lower limit of reference values ($p<0.05$).

3. The results of the analysis of the content of micronutrients with pronounced antioxidant and anti-inflammatory effects showed a reduced amount of Mg^{2+} by 1.4 times and Se^{2+} by 1,2 times compared to the value in the control group, which coincided with the clinical manifestations, namely thyroid pathology – 26.5%; metabolic syndrome – 14.3%.

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Conflict of interest

The authors declare that they have no conflicts of interest.

AI Disclosure

No AI tools were used in the preparation of this manuscript. All authors have read and approved the final version of the manuscript.

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Особливості концентрації вітамінно-мінеральних сполук у жінок з антенатальною загибеллю в анамнезі на прегравідарному етапі.

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Анотація: *Антенатальна загибель плода є однією з тяжких акушерських патологій, що має значний вплив як на соматичне здоров'я, так і на психоемоційний стан жінки. В сучасних джерелах з'являються дані щодо ролі вітамінно-мінерального балансу у етіопатогенезі*

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антенатальної загибелі плода шляхом впливу на процеси ангіогенезу та формування плацентарного кровотоку. Тому, дослідження рівня вітамінно-мінеральних сполук у жінок із антенатальною загибеллю плода в анамнезі набуло особливої актуальності та спонукало до формування мети нашого дослідження: визначити особливості концентрації фолієвої кислоти, вітамінів групи В, D, феритину гомоцистеїну у жінок із антенатальною загибеллю плода в анамнезі на етапі прегравідарної підготовки. Матеріали та методи дослідження – проведено проспективне обстеження 82 пацієнток, з яких 49 жінок (основна група) з антенатальною загибеллю плода в анамнезі та 33 жінки (контрольна група), у яких відсутні пізні репродуктивні втрати в анамнезі. У всіх пацієнток визначено рівень фолієвої кислоти, вітамінів B_1, B_6, B_{12}, 25-гідроксивітаміну D, феритину, Mg^{2+}, Se^{2+} та гомоцистеїну в сироватці крові. Концентрацію вітамінів D, B_1, B_6, B_{12}, фолієвої кислоти, феритину, та гомоцистеїну визначали за допомогою імуноферментного аналізу (Monobind (США)). Визначення концентрації магнію поводили за допомогою колометричного методу (Roche Diagnostics, Швейцарія). Селен визначали за допомогою атомноабсобційної спектрофотометрії (PerkinElmer, США). Згідно отриманих результатів, у жінок основної групи виявлено статистично достовірно нижчу концентрації фолієвої кислоти в 1,5 разів , вітаміну B_6 на 24,3%; B_{12} на 23,7% відносно контрольної групи. Вітамін D становив 18,4±1,1 нг/мл, що на 15,6% менше ніж в контрольній групі та на 38,7% відносно нижньої межі референтних значень. Концентрація Mg^{2+} зареєстрована нижчою в 1,4 разів, а також Se^{2+} на 18,7% в основній групі. Порушення показників вітамінно-мінерального профілю можуть сприяти активації оксидативного стресу, ендотеліальної дисфункції та, як наслідок, плацентраної недостатності, які наразі розглядаються як одні з ключових патогенетичних ланок антенатальної загибелі плода. Отримані результати підкреслюють доцільність включення визначення рівнів вітамінно-мінеральних сполук до структури прегравідарної підготовки жінок із обтяженим акушерським анамнезом, що дозволить сформувати індивідуальні стратегії профілактики ускладнень вагітності та повторних перинатальних втрат.

Ключові слова. Антенатальна загибель плода, вітамін Д, вітаміни групи В, гомоцистеїн, ускладнення вагітності, феритин, фолієва кислота.

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Laboratory Markers of Chronic and Acute Stress: Diagnostic Value and Clinical Implications (Part 2: Neuroendocrine, Immunological and Metabolic Biomarkers of Chronic Stress in the Context of Its Influence on Cardiovascular System)

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Abstract: *Chronic stress (CS) is a powerful factor that silently, but persistently undermines human health by dysregulating the hypothalamic-pituitary-adrenal (HPA) axis and autonomic nervous system (ANS). Its manifestation goes far beyond emotional experiences, shaping profound physiological changes that affect the endocrine, immune and metabolic systems. Modern biomarkers allow us both to visualize these changes and measure their intensity, making them quantifiable and clinically relevant. A comprehensive literature review was conducted, encompassing 76 English-language sources identified through PubMed, Scopus, Web of Science and Google Scholar. The analysis focused on the interplay between the hypothalamic–pituitary-adrenal (HPA) axis, the autonomic nervous system (ANS), and stress-related conditions (CS). The search strategy targeted peer-reviewed publications from 2020 to 2025 using the following keywords: "cardiovascular system", "acute stress", "chronic stress", "cortisol", "epinephrine", "norepinephrine", "dehydroepiandrosterone", "dopamine", "aldosterone", "tumor necrosis factor alpha", "interleukin-1", "interleukin-6", "C-reactive protein", "cholesterol", "albumin" and "glycosylated hemoglobin". Inclusion criteria comprised original research articles, systematic and narrative reviews, meta-analyses and clinical guidelines, while non-peer-reviewed sources and non-English publications were generally excluded. The article summarizes key laboratory markers of stress, from classical hormones (cortisol, epinephrine, ACTH) to immune and metabolic indicators (cytokines, C-reactive protein, oxidative stress markers), with particular attention to hair cortisol as an innovative tool for long-term stress assessment. Stress-related biomarkers provide an integrated view of CS pathophysiology, demonstrating how neuroendocrine, immune and metabolic dysregulation drives hypertension, cardiovascular events, insulin resistance, systemic inflammation and neuropsychiatric disturbances. Early detection and management of CS are essential to prevent cumulative damage that can progress to obesity, metabolic syndrome, atherosclerosis, neurodegeneration and increased morbidity and mortality.*

Key words: Cortisol, Oxidative Stress, Immune System, Endocrinology, Biomarkers, Chronic Stress.

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Introduction

Stress is an unavoidable part of life that in small doses enhances focus and adaptation, but when prolonged, becomes harmful, destabilizing core regulatory systems and raising the risk of cardiovascular, endocrine, psychiatric and autoimmune disorders. Elevated cortisol levels promote the generation of reactive oxygen species (ROS) [1], which can induce damage to DNA, RNA and proteins, thereby accelerating cellular aging and predisposing to age-related pathologies [2]. Oxidative stress, further amplified by sustained catecholamine activity, contributes to vascular inflammation and facilitates the progression of atherosclerosis [3,4]. Additionally, chronic stress (CS) induces neurobiological alterations that may underlie anxiety and depression [5], disrupts reproductive function [6] and plays a role in the pathogenesis of autoimmune and inflammatory disorders [7, 8]. The diagnosis of CS requires a multifaceted approach that integrates neuroendocrine, immunological and metabolic biomarkers. Hair cortisol is especially promising, as it provides a long-term record of stress exposure while remaining non-invasive and practical. Such comprehensive biomarker analysis enhances diagnostic accuracy, supports individualized prevention and therapy, and reframes stress as a measurable process that can be effectively managed.

Materials and methods

A comprehensive literature search was conducted using PubMed, Scopus, Web of Science and Google Scholar to gather relevant articles for this manuscript. The keywords “cardiovascular system“, “acute stress“, “chronic stress“, “cortisol“, “epinephrine“, “norepinephrine“, “dehydroepiandrosterone“, “dopamine“, “aldosterone“, “tumor necrosis factor alpha“, “interleukin-1“, “interleukin-6“, “C-reactive protein“, “cholesterol“, “albumin“ and “glycosylated hemoglobin“ were utilized. The search was restricted to peer-reviewed articles published between 2020 and 2025. However, older articles were also considered and included when deemed relevant to the topic. The inclusion criteria encompassed original research studies, systematic and narrative reviews, meta-analyses, and clinical guidelines, while non-peer-reviewed articles and publications in languages other than English were mainly excluded. Articles were initially screened based on their titles and abstracts, and those meeting the inclusion criteria were further assessed through a full-text review to ensure relevance to the manuscript’s objectives.

Laboratory Markers of Stress: Overview

The identification of specific biomarkers is crucial for assessing stress levels, understanding individual susceptibility and developing targeted therapeutic interventions. Biomarker-based diagnostics offer objective and quantifiable insights into stress-related pathophysiological changes, allowing for early detection of maladaptive responses and guiding clinical decision-making. Stress biomarkers are classified into three primary categories based on their physiological roles: neuroendocrine markers, immunological markers, and metabolic markers [9] (Table 1). These categories correspond to key physiological systems that mediate the stress response, including the HPA axis, the ANS and immune/metabolic pathways.

Neuroendocrine biomarkers primarily reflect the activation of the HPA axis and the sympathetic nervous system, which are central to the physiological response to stress [10, 11].

Cortisol is the primary glucocorticoid hormone released by the adrenal cortex in response to ACTH stimulation [12, 13, 14]. This hormone regulates glucose metabolism, immune function and blood pressure. CS leads to a dysregulated cortisol secretion, manifesting as either hypercortisolemia or hypocortisolemia [15, 16]. Cortisol is the main stress hormone that takes a vital role in the regulation of various physiological processes, including metabolism, immune response, and blood pressure [17, 18]. Its concentration serves as a reliable biomarker for assessing both acute and CS [19]. In clinical diagnostics acute stress is typically evaluated through cortisol levels in saliva or blood, as these fluids reflect immediate hormonal responses triggered by the activation of the HPA axis [20]. Cortisol levels can be measured in saliva, blood serum, sweat, urine and hair [21]. The measurement of free cortisol

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Table 1. Laboratory markers of CS

Name	Sample	Units of measurement	Method for detection	Time of material collection	Number of samplings	References
Neuroendocrine markers (the main ones)						
Cortisol	Hair	pg/mg	ELISA[a], LC-MS[b]/MSc RIA[d]	Anytime	Single sample	10, 11, 12
	Saliva	ng/mL	ELISA, LFIA[e]	Anytime	Single sample	11, 13
	Serum	µg/dL	CLIA[f], RIA	Morning (7:00-9:00)	Single sample	14, 15
	Sweat	µg/L; µM	ELISA, FET[g]	Anytime	Single sample	16, 17
	Urine	µg/24h	LC-MS/MS	24-hour collection	Single sample	18
Dehydroepia ndrosterone sulfate (DHEA-S)	Serum	µg/dL	ELISA, LC-MS/MS	Morning (7:00-9:00)	Single sample	19
	Saliva	pg/mL	ELISA	Morning	Single sample	20
	Urine	µg/24h	LC-MS/MS	24-hour collection	Single sample	21
	Hair	pg/mg	RIA	Anytime	Single sample	12
Cortisol/DHEA-S	Saliva	Ratio	ELISA	Morning	Single sample	12, 20
Epinephrine (adrenalin)	Plasma	pg/mL	HPLC[h], LC-MS/MS	Morning (fasting)	Single sample	22, 23
	Urine	µg/24h	HPLC, LC-MS/MS	24-hour collection	Single sample	24, 25, 26
Norepinephrine (norepinephrine)	Plasma	pg/mL	HPLC, LC-MS/MS	Morning (fasting)	Single sample	27, 23
	Urine	µg/24h	HPLC, LC-MS/MS	24-hour collection	Single sample	24, 25, 26
Dopamine	Plasma	pg/mL	HPLC, LC-MS/MS	Morning (fasting)	Single sample	22, 28
	Urine	µg/24h	HPLC, LC-MS/MS	24-hour collection	Single sample	24, 29
	Cerebro-spinal fluid	pg/mL	HPLC, LC-MS/MS	Lumbar puncture	Single sample	30
Aldosterone	Serum	ng/dL	RIA, CLIA	Morning (upright position)	Single sample	31, 32
	Plasma	ng/dL	RIA, CLIA	Morning (upright position)	Single sample	33

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Name	Sample	Units of measurement	Method for detection	Time of material collection	Number of samplings	References
	Urine	µg/24h	LC-MS/MS	24-hour collection	Single sample	34
Immunological biomarkers (additional ones)						
TNF-α	Serum	pg/mL	ELISA	Morning (fasting)	Single sample	35
IL-1	Serum	pg/mL	ELISA	Morning (fasting)	Single sample	36
IL-6	Serum	pg/mL	ELISA	Morning (fasting)	Single sample	36
CRP	Serum	mg/L	Immuno-turbidimetry	Morning (fasting)	Single sample	36
ILG-1	Serum	ng/mL	ELISA	Morning (fasting)	Single sample	35
Metabolic biomarkers (additional ones)						
Cholesterol	Serum	mg/dL	Enzymatic colorimetric	Morning (fasting)	Single sample	36
Albumin	Serum	g/dL	Bromocresol Green	Morning (fasting)	Single sample	36
Glycosylated hemoglobin	Serum	% (mmol/mol)	ELISA, HPLC	Anytime	Single sample	36

Legend of the table: [a]The enzyme-linked immunosorbent assay; [b]Liquid chromatography-mass spectrometry; [c]Mass spectrometry; [d]Radioimmunoassay; [e]Lateral flow immunoassay; [f]Chemiluminescent Immunoassay; [g]Aptamer-field-effect transistor; [h]High-performance liquid chromatography.

in response to awakening should be considered a potential biomarker of CS, and salivary cortisol is a suitable medium for this purpose [22, 23]. Utilizing salivary cortisol as a stress biomarker enhances the reliability and informativeness of cortisol assessments obtained through saliva samples [24, 25, 26, 27, 28]. Previous studies have demonstrated that salivary cortisol levels are elevated in individuals experiencing CS compared to those without such stress exposure [29]. However, in cases where cortisol is assessed through saliva, serum, or urine, these methods face limitations due to the significant diurnal fluctuations in cortisol levels, making it difficult to rely on a single measurement [30]. Hair cortisol serves as a retrospective indicator of cumulative HPA axis activity over previous months, similar to how hemoglobin A1c reflects average glucose levels over the past three months. The purpose of this review is to explore hair cortisol as an innovative and practical biomarker for assessing long-term cortisol exposure linked to CS in older adults. Measuring cortisol in hair enhances our understanding of aging by providing a more accurate marker for CS both as a contributor to disease progression and as a means of evaluating the success of stress-reduction strategies [31]. Conversely, CS assessment is more accurately achieved through hair cortisol analysis. Given that human hair grows at approximately one centimeter per month, segmented hair samples allow for retrospective evaluation of cortisol exposure over extended periods [32]. Among biological matrices, saliva and blood are primarily used to measure short-term cortisol fluctuations, while hair provides insight into long-term hormonal accumulation [33]. Hair cortisol measurement offers several distinct advantages: it allows for long-term stress monitoring, involves a non-invasive sample collection process, and ensures sample stability over time, facilitating

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both storage and transportation. The use of hair cortisol as a diagnostic tool holds considerable promise in medical practice. It enables continuous stress monitoring, supports the prevention and management of stress-related disorders, and provides a means to evaluate the effectiveness of therapeutic interventions [33, 34]. Furthermore, it contributes to psychosocial research by linking physiological stress markers to psychological and social variables. Thus, cortisol remains a critical biomarker for stress evaluation, and its measurement in hair presents significant opportunities for advancing the diagnosis and treatment of stress-associated conditions in clinical settings [34]. As a key regulator of cortisol secretion, ACTH levels provide insights into upstream HPA axis function. Elevated ACTH with normal or low cortisol levels suggests adrenal insufficiency, while suppressed ACTH with high cortisol may indicate HPA axis hyperactivity [34]. It is confirmed that under prolonged exposure to stressors, the level of ACTH significantly increases alongside epinephrine and corticosterone, while monoaminergic transmitters (5-hydroxytryptamine (5-HT), dopamine, norepinephrine) simultaneously decrease [35]. There is a documented association between plasma ACTH levels and the severity of suicidal ideation in patients with major depressive disorder who are resistant to antidepressant therapy, as well as with the overall severity of depression. This finding highlights the potential role of ACTH in understanding the consequences of stress and mental disorders [36]. Because of its connection with the level of cortisol and possible relation to development of mental problems, ACTH stays an important marker of CS too.

Dehydroepiandrosterone sulfate (DHEA-S) is a steroid hormone synthesized in the zona reticularis of the adrenal cortex in response to ACTH, and it plays an immunomodulatory role that counteracts the effects of cortisol. It contributes significantly to tissue regeneration and protective functions that support overall health. Both elevated and reduced DHEA-S levels are often linked to various health conditions and clinical outcomes. DHEA-S is most commonly assessed in saliva, urine, and blood serum, though studies have also explored its measurement in hair samples [36]. In CS DHEA-S levels progressively decline despite cortisol fluctuations, and although its reliable assessment requires frequent time-specific sampling, the cortisol/DHEA-S ratio remains a valuable indicator of the HPA axis imbalance and prolonged stress-related neurodegeneration risk [36]. Prolonged activation of stress pathways can contribute to immunosuppression or chronic inflammation. That is why the importance of immunological markers is present.

Epinephrine and norepinephrine mediate the sympathetic nervous system's response to stress [27]. CS induces adaptive changes in hormonal regulation, where responsiveness to epinephrine decreases due to habituation, yet overall levels may remain elevated because of slower metabolism [38]. Although epinephrine reliably rises under stress, its diagnostic value is limited by non-specificity, as it also increases during general arousal and mental activity. Nevertheless, catecholamines remain important for understanding how prolonged stress contributes to oxidative damage, cellular senescence and long-term health risks [38]. Acute or short-term stress can alter dopamine levels and midbrain dopaminergic neuronal activity. These changes typically enhance reward-related neural circuits, such as improving the learning of cue-reward associations. Such stress episodes do not usually lead to depressive behavior. In contrast, chronic and repeated stress exposure has been consistently shown, especially in animal studies, to induce behaviors resembling depression. Established models for studying CS include chronic restraint stress, chronic social defeat stress, and chronic unpredictable mild stress. Acute stress appears to temporarily heighten sensitivity to rewards, facilitating the engagement of reward-related neural networks. However, prolonged exposure to CS dampens this sensitivity, which may lead to anhedonia – a core symptom of depression, marked by diminished pleasure and motivation. Prolonged, uncontrollable, and unpredictable stressors exert an inhibitory effect on dopamine release, contributing to the neurochemical foundation of stress-induced mood disorders [39].

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A key acute-phase protein and marker of systemic inflammation. Having been traditionally utilized as a marker of infection and cardiovascular events, there is now growing evidence that CRP plays important roles in inflammatory processes and host responses to infection including the complement pathway, apoptosis, phagocytosis, nitric oxide (NO) release, and the production of cytokines, particularly interleukin-6 and tumor necrosis factor-α [40]. CS is associated with persistently elevated CRP levels, which correlate with an increased risk of cardiovascular disease and metabolic syndrome [41].

CS profoundly alters immune regulation by elevating pro-inflammatory cytokines such as IL-6, TNF-α and IL-1β [42], while simultaneously suppressing anti-inflammatory mediators like IL-10 and TGF-β, thereby promoting neuroinflammation, mood disorders and autoimmune susceptibility [42]. In parallel, CS disrupts lymphocyte homeostasis, as reflected by a decreased CD4+/CD8+ ratio and diminished natural killer (NK) cell activity, which together weaken immune surveillance and heighten vulnerability to infections and chronic disease [42]. Stress also influences metabolic homeostasis through alterations in glucose metabolism, lipid profiles and oxidative stress regulation. Acute stress induces transient hyperglycemia due to increased hepatic gluconeogenesis and insulin resistance. CS contributes to persistent insulin resistance, predisposing individuals to type 2 diabetes mellitus [43]. Dysregulation of lipid metabolism caused by stress is characterized by increased levels of triglycerides and decreased levels of high-density lipoprotein cholesterol, which contribute to the development of fatty plaques in the blood vessels and elevate the risk of cardiovascular disease [44]. CS also promotes oxidative damage by increasing the production of highly reactive molecules that can damage cells. Elevated levels of malondialdehyde indicate lipid peroxidation, while decreased levels of superoxide dismutase and glutathione reflect a weakened antioxidant defense system, leading to increased cellular damage [45].

Conclusions

CS disrupts neuroendocrine, immune and metabolic regulation, thereby increasing the risk of cardiovascular and systemic diseases. Laboratory biomarkers, including cortisol, DHEA, catecholamines, cytokines and oxidative stress indicators, are essential for translating the physiological burden of stress into measurable parameters. Hair cortisol provides a particularly valuable long-term marker, complementing conventional biofluids in both research and clinical practice. The integration of diverse biomarkers enhances early diagnosis, supports individualized interventions and strengthens strategies for the prevention and management of stress-related disorders.

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Conflict of interests

The authors declare no conflict of interest.

Consent to publication

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AI Disclosure

The authors used ChatGPT (OpenAI, San Francisco, CA, USA) for language editing of the English text. The authors reviewed and verified all AI-generated content to ensure accuracy and integrity.

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Лабораторні маркери хронічного та гострого стресу: діагностична цінність та клінічні наслідки (Частина 2: Нейроендокринні, імунологічні та метаболічні біомаркери хронічного стресу у контексті його впливу на серцево-судинну систему)

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Анотація: *Хронічний стрес (ХС) є потужним чинником, який непомітно, але наполегливо підриває здоров’я людини шляхом порушення регуляції гіпоталамо-гіпофізарно-надниркової (ГГН) осі та автономної нервової системи (АНС). Його прояви виходять далеко за межі емоційних переживань, формуючи глибокі фізіологічні зміни, що впливають на ендокринну, імунну та метаболічну системи. Сучасні біомаркери дають змогу не лише візуалізувати ці зміни,*

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а й вимірювати їхню інтенсивність, роблячи їх кількісно оцінюваними та клінічно значущими. Було здійснено ґрунтовний огляд літератури, що охопив 76 англомовних джерел, відібраних у базах даних PubMed, Scopus, Web of Science та Google Scholar. Аналіз був зосереджений на взаємодії ГГН осі, АНС та ХС. Стратегія пошуку включала рецензовані публікації за 2020-2025 роки з такими ключовими словами: «серцево-судинна система», «гострий стрес», «хронічний стрес», «кортизол», «епінефрин», «норепінефрин», «дегідроепіандростерон», «дофамін», «альдостерон», «фактор некрозу пухлини альфа», «інтерлейкін-1», «інтерлейкін-6», «С-реактивний білок», «холестерин», «альбумін» та «глікозильований гемоглобін». Критерії включення охоплювали оригінальні наукові статті, систематичні та наративні огляди, метааналізи й клінічні настанови, тоді як нерецензовані матеріали та публікації іншими мовами, окрім англійської, загалом виключалися. У статті подано огляд основних лабораторних маркерів стресу: від класичних гормонів, таких як кортизол, адреналін та адренокортикотропний гормон (АКТГ), до імунних і метаболічних показників, включаючи цитокіни, С-реактивний білок і маркери оксидативного стресу. Особливу увагу приділено визначенню рівня кортизолу у волоссі як інноваційному методу довгострокової оцінки стресу, що відкриває перспективи для вдосконалення ранньої діагностики, профілактичних стратегій, терапевтичного моніторингу та персоналізованих медичних втручань. Оцінка стрес-асоційованих біомаркерів дає змогу всебічно зрозуміти патофізіологію ХС, демонструючи, як порушення регуляції нейроендокринної, імунної та метаболічної систем сприяє розвитку гіпертензії, серцево-судинних подій, інсулінорезистентності, системного запалення та нейропсихіатричних порушень. Відтак раннє виявлення та контроль ХС мають вирішальне значення, оскільки своєчасні втручання можуть запобігти його кумулятивним наслідкам, які інакше призводять до ожиріння, метаболічного синдрому, атеросклерозу, нейродегенерації та суттєвого зростання захворюваності й смертності.

Ключові слова. Хронічний стрес, кортизол, оксидативний стрес, імунна система, ендокринологія

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Magnetic Resonance Imaging (MRI) Technology in the Diagnosis of Rectal Cancer

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Abstract: *The article is devoted to the study of the use of magnetic resonance imaging technology (MRI) in the diagnosis of rectal cancer, which is an important stage in modern cancer. The purpose of the article is to carry out a systematic review of scientific sources that highlight the effectiveness of MRI in determining the stage of the tumor process, evaluation of lesions of lymph nodes and accuracy in planning treatment approaches, in particular surgery. The task is to analyze the accuracy of modern MRI methods for the diagnosis of rectal cancer and to consider technological solutions to improve MRI in the diagnosis of rectal cancer. A comprehensive analysis of publications in databases such as Google Scholar, PubMed, Scopus and IEEE XPlore was conducted on the basis of scientific research. The data revealed is systematized to highlight key technical and clinical aspects that require further development. The main attention is paid to the methods of contrast enhancement and diffusion-weighted MRI, which showed a high level of sensitivity (90-95%) and specificity (85-90%) in the detection of tumor invasion and metastases into lymph nodes. The advantages of methods that allow to accurately evaluate the blood supply to the tumor and the invasiveness of the process are considered, which is especially important for choosing the appropriate treatment tactics. Analysis of scientific works indicates that 1) MRI, due to high accuracy and safety, plays a key role in determining the localization and stage of the tumor process and is an indispensable method of diagnosis of rectal cancer, which provides accurate visualization Treatment and reduces the risk of relapse; 2) Modern MRI methods show high accuracy in the diagnosis of rectal cancer. In particular, highly separated MRI and dynamic contrast MRI have high sensitivity (90-95%) and accuracy (90%), which makes them effective for preoperative stages and tumor invasion. MRI with diffusion-weighted images also has high sensitivity and is useful for evaluating the response to therapy, which is important for monitoring the progress of the disease; 3) methods of contrast enhancement and advanced analysis of images significantly increase the accuracy of diagnosis, especially when predicting the effectiveness of neoadjuvant therapy; 4) there is a need to further improve MRI methods to reduce the frequency of false positive results in the early stages, which will improve the quality of treatment and increase the life expectancy of patients. 5) The development of artificial intelligence and the use of combined methods of diagnosis, in particular with other visualization technologies, will significantly increase the accuracy and availability of MRI in cancer diagnosis.*

Keywords: Magnetic resonance imaging, Rectal cancer, Diagnosis, Oncology, General surgery, surgical practice.

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Introduction

Modern trends in the diagnosis of cancer show significant technological progress made through the development of magnetic resonance imaging (MRI), which has become an integral part of clinical practice in oncology [1]. In particular, in the work [9] it is noted that MRI plays a special role in the assessment of rectal cancer, providing accurate visualization of the tumor and adjacent anatomical structures. The above mentioned results are the results of the studies that have conducted the above researchers according to which in the diagnosis of rectal cancer, the accuracy of MRI in the assessment of the tumor stage and the involvement of lymph nodes usually ranges from 70-95%, depending on the experience of the radiologist and used techniques. Similar results are also obtained in research [8], according to which MRI accuracy in determining the T3 and T4 tumor stage can reach about 85-95%, and to detect metastases in lymph nodes − 70-85%. The above level of accuracy makes MRI a key tool for making therapeutic solutions and planning surgical tactics. According to [4], MRI allows you to evaluate the tumor stage, which is key to determining the optimal treatment strategy, especially when planning surgery. In accordance with [5] the use of MRI, as the main method in the initial diagnosis and monitoring of the response to therapy allows to reduce the risk of relapse and increase patient survival. The work [1] states that the development of image methods and their adaptation to the needs of oncology made an MRI gold standard for local stage of rectal cancer. According to [12] Consideration of MRI capabilities and restrictions in the diagnosis of rectal cancer is extremely important for clinical practice. Therefore, from the surveyed research work it follows that the diagnosis of rectal cancer emphasizes the urgent need for accurate information to make therapeutic decisions, which in turn emphasizes the relevance of the search for the latest ways in improving MRI technologies used in cancer diagnosis rectum.

Aim

The purpose of the article is to carry out a systematic review of scientific sources that highlight the effectiveness of MRI in determining the stage of the tumor process, evaluation of lesions of lymph nodes and accuracy in planning treatment approaches, in particular surgery.

The way to achieve the goal: The task is to analyze the accuracy of modern MRI methods for the diagnosis of rectal cancer and to consider technological solutions to improve MRI in the diagnosis of rectal cancer.

Materials and methods

A comprehensive analysis of publications in databases such as Google Scholar, PubMed, Scopus and IEEE XPlore was conducted on the basis of scientific research. The data revealed is systematized to highlight key technical and clinical aspects that require further development.

Review and discussion

According to [9] magnetic resonance imaging (MRI) is a leading technology in the diagnosis and stage of rectal cancer due to its ability to provide detailed images of tissues, which greatly facilitates the determination of the degree of tumor spread and damage to the surrounding structures. Within the framework of consideration of the questions raised in this article, it is important to note that analyzing the main aspects of MRI technologies in the context of diagnosis of rectum cancer, it is advisable to emphasize the importance of a multidisciplinary approach in diagnosis and treatment. In the study [14] describes a multidisciplinary approach to the treatment of rectal cancer, which includes the use of MRI as a central method for evaluating tumor spread before the treatment begins. This approach allows you to better develop individualized treatment plans for patients aimed at maximizing the preservation of healthy tissues and optimizing the results of treatment for Watch-and-Wait treatment and the role of MRI in monitoring. In accordance with [2] during the precision evaluation of the spread of the MRI tumor allows you to evaluate the tumor's localization, its size, the involvement of surrounding tissues, as well as the presence of metastases, which is especially important for cancer, because accurate assessment makes it possible to choose the most appropriate treatment tactics In particular, determine the feasibility of surgery or the use of other methods of therapy. The work [3] also noted that MRI is an important

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tool for monitoring the effectiveness of treatment, in particular when using neoadjuvant therapy. In addition, the author's team of this work is noted that dynamic monitoring of tissue changes allows doctors to evaluate how successfully the treatment reduces tumor formations. The work [15] describes in detail the strategy "Watch-and-Wait" for rectal cancer, which involves the absence of immediate surgery in cases of complete clinical response to neoadjuvant therapy. According to the above work, MRI helps to evaluate the presence or absence of a residual tumor after treatment, which allows oncologists and surgeons to make informed decisions on further steps. In work [12], it is stated that high-separated MRI (HR-MRI) is extremely accurate for preoperative staging of rectum cancer, allowing radiologists specializing in abdominal and oncological visualization to determine the depth mesorectal fascia (an important factor for surgery planning). The study described in the work [5] found that dynamic contrast-induced MRI (DCE-MRI) can be used by radiologists and medical visualization specialists to identify key prognostic factors in patients with patients with patients primary rectal cancer. DCE-MRI provides extended tumor visualization and allows you to evaluate the degree of blood flow in it, which is important for prognosis and further treatment. In the work [13] clearly demonstrated the prospects of radio mines in predicting the effectiveness of therapy and survival of patients with colorectal cancer (this technology includes the selection and analysis of a large number of parameters that are not visible to the human eye, but may be significant medicinal results). It should also be noted that [9] focus on the importance of MRI to evaluate the effectiveness of neoadjuvant therapy, which is often performed before surgery. According to the views of the above researchers, the use of MRI allows you to control the size of the tumor after therapy and to determine the residual tumor, which helps to evaluate the full clinical response. Instead, in the work [8] emphasizes the need for accurate local stage of rectal cancer by means of MRI to determine the presence of local invasion and metastases in lymph nodes. According to the above work, the MRI allows you to determine the anatomical features that are critical for the choice of the appropriate method of treatment.

Table 1 shows the results of the analysis of the accuracy of modern MRI methods for the diagnosis of rectal cancer.

The results of the analysis given in Table 1. show that modern MRI methods demonstrate high accuracy in the diagnosis of rectal cancer.

Instead, the analysis showed that the use of radio masters and functional methods of MRI allows to improve the accuracy of prediction of treatment results and the prediction of relapses, which is important for individualization of therapy. However, in accordance with [10] for modern MRI methods, which are used in the diagnosis of rectal cancer there are a number of problems (hereinafter consider in more detail these problems). It is also advisable to note that one of the characteristic problems for the MRI method with contrast is its low specificity, which can lead to false positive results, especially when tumors are detected in the early stages, when pathological changes are not yet sufficiently expressed in the images. The above problem can also be observed in other MRI methods, such as:

− diffusion-weight mRI (DWI): tumors in rectangular lid cancer can be poorly distinguished from other tissues in the early stages, which leads to the risk of false positive results, in particular because water diffusion in tissues may be similar in some inflammatory processes or benign processes or benign processes neoplasms [3];

− MRI-collateral tomography: since the method is focused on the assessment of anatomy and structural changes, there may be difficulties with accurate determination of the tumor boundaries in the early stages, which sometimes leads to incorrect diagnosis, or errors in determining the localization of the tumor [6];

− MRI perfusion: it can be problematic due to limited specificity in the differentiation between tumor and inflammatory processes in the early stages, which sometimes leads to false results due to similar perfusion patterns [12].

As we can see in all of the above methods, the problem of low specificity is associated with difficulties in the recognition of early changes, or differentiation between different types of tissues or pathologies, which occurs when

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Table 1. The results of the analysis of the accuracy of modern MRI methods for diagnosis of rectal cancer

MRI method	Application	Sensitivity	Specificity	Precision	Notes
HR-MRI	Preoperative stage of rectal cancer. Assessment of the depth of invasion and mesorectal fascia.	90-95%	85-90%	90%	Particularly accurate to determine the involvement of the mesorectal fascia.
DCE-MRI	Evaluation of blood flow in the tumor to predict metastases and prognosis of the disease.	85-92%	80-88%	85%	High sensitivity in predicting a tumor progression and efficacy of therapy.
DWI	Determination of tumor evaluation and reaction to neoadjuvant therapy.	80-90%	75-85%	80%	Useful for assessing the response to therapy in the postoperative period.
MRI using radio	Forecasting of treatment results, determination of clinical response to therapy, early diagnosis of recurrence.	85-95%	80-90%	87%	Used to analyze a large number of images to predict results.
MRI with functional analysis	Analysis of tumor structure, differentiation of malignant and benign formations.	88-94%	85-92%	91%	It is used for better differentiation of types of tumors and tissues.
MRI after neoadjuvant therapy	Residual tumor evaluation and response to treatment after chemotherapy.	90-96%	80-85%	90%	Used to determine a complete clinical response to therapy.

changes are not pronounced or clearly defined on the images. In practice, the problem of low specificity in MRI can be partially corrected or reduced by several methodological and technical approaches, namely:

− Improving the contrast and resolution of the image: the use of the latest technologies, such as high-resolution MRI and improving contrast (eg, the use of new contrast agents), can improve tumors visualization in the early stages and reduce the number of false positive results [7];

− The use of combined diagnostic methods: the use of MRI in combination with other methods, such as CT, ultrasound, or RET-MRI, can increase the accuracy of diagnosis [11]. In turn, it is advisable to note that according to [15] above the specified approach allows doctors to get a more complete picture of the nature of the formation and reduce the risk of false positive results;

− use of artificial intelligence and machine training: introduction of artificial intelligence algorithms for MRI image processing can help automatically detect and classify tumors with high accuracy, reducing the likelihood of erroneous results, especially in the early stages;

− Improvement of image processing algorithms: the use of advanced MRI algorithms, such as diffusion-weight mRI (DWI) or MRI perfusion, can help determine the borders of tumors and avoid errors;

− involvement of experienced specialists: advanced training of doctors, use of additional training programs and professional consultations with other medical specialists allows to improve the interpretation of MRI results and reduce the likelihood of erroneous diagnoses;

− Extended use of diffusion-weight methods: it is advisable to use methods that evaluate the structure of tissues, not just their abnormal changes, for more accurate assessment in the

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early stages of tumor development. For example, a diffusion-weight mRI can be improved for better detection of early cell mixes that may not be noticeable in standard contrast.

It should also be noted that the above approaches can reduce false positive results, improve the accuracy of diagnosis and increase the effectiveness of MRI in early detection of rectal cancer. According to [4] when applying diffusion-weight mRI (DWI) quite often in practice there is a problem that is reduced to the fact that this method may be less effective for detecting small tumors, or to determine the exact limit of neoplasm, which sometimes leads to errors in determining the stage of cancer. In the general case, the above problem associated with less efficiency of diffusion-weight mRI (DWI) to detect small tumors or accurate assessment of the boundaries of the neoplasm can be solved by several approaches, namely:

− Applying the DWI combination with other methods of visualization: PET scan (PET) or computed tomography (CT) can be used together with DWI for more accurate detection of small tumors or their boundaries. PET allows to evaluate the metabolic activity of the tissues, and CT scans in more detail the image of the tissue structure, which can help in the more accurate localization of the tumor;

− the use of functional and parametric maps: the use of parametric maps (for example, ADC cards − the diffusion coefficient) may allow to better evaluate the diffusion properties of tissues and, thus, to determine the boundaries of neoplasm even in late stages or in small tumors;

− Improvement of image resolution: high quality and highly separated DWI methods, for example, using a larger number of diffusion directions, or reduced sections thickness, can help to detect small tumors and their boundaries accurately.

− Use of machine learning and artificial intelligence algorithms (AI): AI algorithms, in particular deep training, can be used to analyze DWI images and automatically identify tumor boundaries. Such technologies can improve the accuracy of detection of even very small tumors and increase the efficiency of cancer;

− joint use with histological studies: in some cases it is important to combine DWI results with histological or molecular analyzes to determine the exact nature and boundaries of the neoplasm;

− Clinical adjustment and interpretation: qualified doctors who have experience in interpreting DWI results can adjust the boundaries of tumors by comparing the data obtained with other clinical features and indicators.

As we can see, the combination of the above approaches can significantly increase the efficiency of the DWI method in oncology, in particular to accurately detect small tumors and determine their stage. According to [14], for the use of MRI-collapse method, this method is a high-cost problem and requires special equipment that makes it less accessible in remote or insufficiently equipped medical institutions. The following innovative approaches can be used to improve the availability and efficiency of diagnosis of rectal cancer using MRI-collapse:

− Integration with less expensive diagnostic methods: a combination of MRI with markers in the blood or fecal tests for blood for primary screening. This will allow the preliminary selection of patients with suspected rectal cancer, which reduces the load on the MRI examination and improves the efficiency of use of expensive equipment;

− Development of mobile or compact MRI devices that can be used to diagnose rectal cancer in regions where there is no access to stationary medical institutions. Mobile devices can be equipped with specific programs for colorectal diagnostics, which reduces the cost and time for examination.

− Use of machine learning algorithms (AI) for automatic processing of MRI images in order to detect tumors and determine their stage. This can significantly reduce the time spent on the interpretation of images and increase the accuracy of diagnosis, especially in remote or low-income medical institutions;

− introduction of TV to ensure access to MRI analysis of rectal cancer in remote regions, which allows doctors from large medical centers to remotely analyze images and make accurate diagnoses that reduces the need for qualified specialists in each medical institution [4];

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− IRT integration with other screening methods: the use of hybrid methods such as MRI with CT, ultrasound, or colonoscopy for a more detailed study of anatomy and stage of rectum cancer. Combined methods allow to increase the accuracy of diagnosis with less use of expensive MRI [13];

− introduction of modular systems that allow you to adapt MRI devices for specialized examinations, in particular for diagnosis of rectum cancer. This will reduce the total cost of equipment and increase the availability of these services for medical institutions [5];

− development of short scan protocols that allow to reduce the time for MRI examination and image processing. This approach will reduce the cost of procedures and increase the number of patients who can be examined per day [10];

− the use of machine learning to predict the development of the disease based on MRI results. This will allow doctors to better plan the tactics for the treatment of rectal cancer and improve the personalized approach to therapy, as well as reduce the cost of long -term patient monitoring.

To improve MRI perfusion in the diagnosis of rectal cancer, following improvements:

− optimization of protocols for the specificity of the organ: development of MRI perfusion protocols, adapted specifically for the diagnosis of rectal cancer, taking into account its anatomical features, will help to obtain more detailed images for more accurate determination of tumor size, invasion and involvement of adjacent tissues;

− Improving contrast agents for hypersensitivity: the introduction of contrast agents, which are especially effective for rectum tissues, can increase the sensitivity and specificity of perfusion MRI. This will allow the doctors to determine the degree of blood supply to the tumor more clearly, which is important for assessing the aggression and stage of cancer;

− artificial intelligence algorithms for detection and classification: the use of deep learning algorithms for automated Image analysis of MRI perfusion can help identify early tumor signs, determine local invasion and metastasis, which will increase the accuracy of diagnosis. These algorithms can be tuned to identify specific markers of rectal cancer, simplifying the interpretation of results;

− Integration with other methods of visualization: the use of MRI perfusion together with PET-CT or conventional MRI with high resolution (HR-MRI) can provide a multifaceted approach to tumor evaluation. This will allow to evaluate both functional and anatomical aspects of the tumor, which will contribute to a more accurate stage of treatment;

− Expanding availability through broadcasting systems: to overcome the scarcity of qualified specialists, remote access to images interpretation through television and radiology can allow doctors from smaller medical institutions to consult with specialists of large oncological centers, which will increase the accuracy of diagnosis and provide more patients with qualitative patients.

Marking steps can contribute to a more accurate and accessible diagnosis of rectum cancer by MRI perfusion, which is important for early detection and effective treatment planning. Similar approaches can be offered by improving MRI (FMRI).

Conclusions

Analysis of scientific works indicates that 1) MRI, due to high accuracy and safety, plays a key role in determining the localization and stage of the tumor process and is an indispensable method of diagnosis of rectal cancer, which provides accurate visualization Treatment and reduces the risk of relapse; 2) Modern MRI methods show high accuracy in the diagnosis of rectal cancer. In particular, highly separated MRI and dynamic contrast MRI have high sensitivity (90-95%) and accuracy (90%), which makes them effective for preoperative stages and tumor invasion. MRI with diffusion-weighted images also has high sensitivity and is useful for evaluating the response to therapy, which is important for monitoring the progress of the disease; 3) methods of contrast enhancement and advanced analysis of images significantly increase the accuracy of diagnosis, especially when predicting the effectiveness of neoadjuvant therapy; 4) there is a need to further improve MRI methods to reduce the frequency of false positive results in the early stages, which will improve the quality of treatment and increase the

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life expectancy of patients. 5) The development of artificial intelligence and the use of combined methods of diagnosis, in particular with other visualization technologies, will significantly increase the accuracy and availability of MRI in cancer diagnosis.

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Conflict of Interest

The authors declare that they have no financial, academic, or personal conflicts of interest related to the publication of this article.

Consent to publication

The author has read and approved the final version of the manuscript. All authors consented to the publication of this manuscript.

AI Disclosure

The authors used ChatGPT (OpenAI, San Francisco, CA, USA) for language editing of the English text. The authors reviewed and verified all AI-generated content to ensure accuracy and integrity.

Ethical approval

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki (2013). The study protocol was reviewed and approved by the Ethics Committee of P. L. Shupyk National Healthcare University of Ukraine (Protocol No. 3, 07 February 2017). All participants provided informed voluntary consent for participation.

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Технології магнітно-резонансної томографії (МРТ) у діагностиці раку прямої кишки

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Анотація: *Стаття присвячена дослідженню використання технології магнітно-резонансної томографії (МРТ) у діагностиці раку прямої кишки, що є важливим етапом у сучасній онкологічній практиці. Мета статті – здійснити системний огляд наукових джерел, що висвітлюють ефективність МРТ у визначенні стадії пухлинного процесу, оцінці ураження лімфатичних вузлів та забезпеченні точності при плануванні лікувальних підходів, зокрема хірургічних втручань. Висувається завдання провести аналіз точності сучасних методів МРТ для діагностики раку прямої кишки та розглянути технологічні рішення для поліпшення МРТ при діагностиці раку прямої кишки. На основі узагальнення наукових досліджень було проведено комплексний аналіз публікацій у таких базах даних, як Google Scholar, PubMed, Scopus та IEEE Xplore. Виявлені дані систематизовано для виокремлення ключових технічних і клінічних аспектів, що потребують подальшого розвитку. Основну увагу приділено методам контрастного підсилення та дифузійно-зваженого МРТ, які показали високий рівень чутливості (90-95%) та специфічності (85-90%) у виявленні інвазії пухлини та метастазів у лімфатичні вузли. Розглянуто переваги методів, що дозволяють здійснювати точну оцінку кровопостачання пухлини та інвазивності процесу, що особливо важливо для вибору відповідної тактики лікування. Аналіз наукових праць свідчить про те, що 1) МРТ, завдяки високій точності та безпеці, відіграє ключову роль у визначенні локалізації та стадії пухлинного процесу та є незамінним методом діагностики раку прямої кишки, який забезпечує точну візуалізацію пухлинного процесу, сприяє вибору оптимальних методів лікування та знижує ризик рецидивів;2) сучасні методи МРТ демонструють високу точність у діагностиці раку прямої кишки. Зокрема, високороздільна МРТ та динамічна контраст-індукована МРТ мають високі показники чутливості (90-95%) і точності (90%), що робить їх ефективними*

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для передопераційного стадіювання та оцінки інвазії пухлини. МРТ з дифузійно-зваженими зображеннями також має високу чутливість і корисна для оцінки відповіді на терапію, що важливо для моніторингу прогресу захворювання; 3) методи контрастного підсилення та розширеного аналізу зображень значно підвищують точність діагностики, особливо при прогнозуванні ефективності неоад'ювантної терапії; 4) існує необхідність у подальшому вдосконаленні методик проведення МРТ для зменшення частоти хибнопозитивних результатів на ранніх стадіях, що забезпечить покращення якості лікування та збільшення тривалості життя пацієнтів. 5) Розвиток штучного інтелекту та використання комбінованих методів діагностики, зокрема з іншими візуалізаційними технологіями, дозволить значно підвищити точність і доступність МРТ в онкологічній діагностиці.

Ключові слова: магнітно-резонансна томографія, рак прямої кишки, діагностика, онкологія, загальна хірургія, хірургічна практика.

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Quality of life assessment in patients after laparoscopic cholecystectomy

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Abstract: *Laparoscopic cholecystectomy is widely recognized as the gold standard for surgical treatment of gallstone disease. Despite its high efficacy and low rate of early complications after surgery, some patients still experience abdominal symptoms after surgery. The results of some studies show that approximately 25% of patients experience abdominal complaints requiring medical assessment one month after surgery. Active postoperative follow-up is considered to play a key role in improving patients' quality of life and identifying symptoms that remain after surgery for various reasons. With the growth of digitalization in health care, telemedicine technologies are opening up new opportunities to improve the effectiveness of postoperative monitoring. However, telemedicine services also face a number of challenges, including technical limitations, unequal access to digital technologies, the need to adapt clinical protocols, and the potential threat to patient data security. The present prospective study was conducted between 2024 and 2025 at two medical institutions in Ukraine. The study comprised 70 patients who underwent laparoscopic cholecystectomy for gallstone disease. The age of participants ranged from 24 to 67 years, with a mean age of 44.3 ± 10.8 years. Exclusion criteria included performing open instead of laparoscopic cholecystectomy, complicated intraoperative course, severe comorbidities (decompensated diabetes mellitus, malignancies, advanced heart failure), psychiatric disorders, lack of internet access, or refusal to participate in telemedicine follow-up. The patients were divided into two groups: the main group received postoperative support using telemedicine, while the control group received traditional outpatient care. Patients in the main group were at liberty to seek face-to-face outpatient care at any time. Quality of life was assessed using validated Ukrainian versions of the EQ-5D-5L and SF-36 questionnaires 1, 6, and 12 months after surgery. The results showed positive changes in quality of life for the entire group during the year after the intervention. The average EQ-5D-5L index increased from 0.90 to 0.95 over 11 months, and the physical and psycho-emotional components of the SF-36 increased from 70.3 to 82.6 and from 73.0 to 85.0, respectively. It is worth noting that at no stage of the observation were there any statistically significant differences between the main and control groups in terms of quality of life as assessed by the above-mentioned questionnaires. This finding indicates that telemedicine tools may be as effective as traditional postoperative supervision in terms of quality of life. The introduction of telemedicine into postoperative care is safe, effective and patient-centered, especially in cases where in-person consultations are not possible or require additional financial or time costs. The study suggests that telemedicine could be a valuable option of postoperative management for patients who have undergone laparoscopic cholecystectomy, highlighting its potential for wider integration into routine postoperative management.*

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Keywords: Cholecystectomy, Cholelithiasis, Postoperative Care, Quality of Life, Remote Consultation, Telemedicine, Treatment Outcome, Laparoscopic.

Introduction

Gallstone disease (GSD) is one of the most common disorders of the liver and bile ducts and affects 10–20% of adults in developed countries. Observations have shown that GSD is more common as people get older, and its prevalence is twice as high among women. This discrepancy is primarily attributed to hormonal factors, including estrogen levels, pregnancy, and the utilisation of hormonal contraceptives [1]. There are some other risk factors to consider, which include obesity, a sedentary lifestyle, and genetic predisposition.

Symptomatic gallstone disease can have a significant impact on patients' quality of life, often resulting in chronic pain, dyspepsia, and the potential for acute complications. Most medical researchers agree that laparoscopic cholecystectomy (LC) is the best option for treating cholelithiasis because it is safe, effective, relatively low-risk and patients make a quick recovery.

In Ukraine the number of cholecystectomies performed each year has increased over the past decade reaching a record high of 160.5 operations for every 100,000 people in 2023. Concurrently, the mortality rate showed stability, maintaining a consistent range of 0.21-0.25% [3].

Despite the LC proving successful in most cases, some patients experience ongoing or new abdominal symptoms in the postoperative period. The most prevalent complaints encompass intermittent abdominal pain, dyspeptic syndrome, bloating, and disturbances in bowel movements.

According to international studies, up to 13% of patients report symptoms six months after surgery, although an organic cause can be identified in less than 1% of cases [4]. Based on our preliminary findings [3], approximately 25% of patients experience intermittent abdominal complaints one month after surgery, requiring medical attention.

The pathogenesis of postoperative abdominal disorders in patients after LC is multifactorial. Symptoms can originate by both biliary and non-biliary factors. One of the common causes is dysfunction of the sphincter of Oddi, which can lead to intermittent or persistent pain, elevated liver enzymes, bile duct dilatation, or even recurrent pancreatitis [5].

Postoperative management of patients involves a multifaceted approach, encompassing meticulous monitoring of the patient's condition, expeditious identification of any potential complications, and the judicious implementation of both pharmacological and non-pharmacological interventions when deemed necessary. In the context of the ongoing digitalisation of healthcare and the imperative to optimise resource utilisation, there has been an increasing use of telemedicine technologies in clinical practice. The use of teleconsultations has the potential to reduce the number of in-person visits, save time for both patients and healthcare providers, and ensure timely access to medical care. [6-8]

Telemedicine presents several challenges, including technical limitations, unequal access to digital technologies, the need to adapt clinical protocols, a potential increase in overall healthcare expenditures due to overutilisation of medical services, and additional risks to patient safety [9]. However, when these technologies are implemented in the appropriate manner, there is a possibility that they may not compromise the quality of life of patients in the postoperative period [10].

Aim

The aim of this study is to assess the impact of using telemedicine tools on patient`s quality of life in the postoperative management after LC.

Materials and Methods

The prospective study was conducted during 2024–2025 at two healthcare institutions: St. Paraskeva Medical Center (Lviv) and the University Clinic of Bogomolets National Medical University (Kyiv). The study included 70 patients who had LC for GSD. The inclusion criteria were patient age between 18 and 75 years; LC performed no more than 4 weeks prior to enrollment; confirmed diagnosis of

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GSD as the primary condition; signed informed consent to participate in the study; and access to a mobile phone or computer suitable for remote monitoring. Exclusion criteria: complicated surgical course (conversion to laparotomy or extended surgical intervention); early postoperative complications; confirmed malignant neoplasm of any localization; severe decompensated comorbid conditions (cardiac, renal, or hepatic failure); pregnancy or lactation; refusal to participate in the study; or inability to comply with the study protocol (lack of access to digital communication tools or limited ability to use them).

Patients were divided into two groups. The main group received postoperative care using telemedicine tools, including asynchronous remote questionnaires, teleconsultations, and video consultations (n = 35). The control group received standard outpatient follow-up without the use of telemedicine tools (n = 35). Patients were allocated to the main and control groups using stratified randomization to ensure balanced distribution between the two study sites (Lviv and Kyiv). Within each stratum, a computer-generated randomization sequence (Microsoft Excel, RAND function) was used to assign participants in a fixed 1:1 ratio. Allocation was implemented immediately after confirming eligibility and obtaining informed consent.

The EQ-5D-5L and SF-36 questionnaires, validated in Ukrainian, were used to assess quality of life. The validated forms were uploaded using Google Forms and distributed by email. Assessments were carried out 1, 6, and 12 months after surgery. Participants in the main group completed the questionnaires online via Google Forms, while patients in the control group completed paper-based versions during in-person visits to their physician. A visual analogue scale (VAS) ranging from 0 to 10 was used to evaluate overall patient satisfaction with medical care. Patients were asked to respond to the question: “How satisfied are you with postoperative care and the treatment process?” where 0 indicated complete dissatisfaction and 10 indicated maximum satisfaction.

The sample was characterized through the utilization of descriptive statistical methods, encompassing the calculation of mean values, standard deviations, frequencies, and percentages. The t-test for independent samples was utilized to compare the indicators between independent groups (main and control). In order to assess changes in quality of life over time (1, 6 and 12 months) within the same group, a paired t-test was used, as well as an analysis of variation with repeated measures (Repeated Measures ANOVA) to identify the dynamics of changes at three time points. Post-hoc pairwise comparisons following Repeated Measures ANOVA were performed using the Bonferroni correction to adjust for multiple comparisons. Effect sizes were calculated using Cohen’s d for t-tests and partial eta-squared (η^2p) for Repeated Measures ANOVA. The analysis of the obtained results was performed using the statistical software packages MedStat v.5.2 and EZR version 4.1.2. The study materials were reviewed and approved by the Commission on Bioethical Expertise and Research Ethics of the Bogomolets National Medical University (Protocol № 195 dated May 26, 2025). The study was conducted in full accordance with the ethical principles outlined in the Declaration of Helsinki (2013 revision). Personal data were anonymized and handled confidentially.

Results

Among the participants of the study, 45 (64.3%) were women and 25 (35.7%) were men, which is consistent with epidemiological data indicating a higher prevalence of GSD in women. The main group included 21 women and 14 men, while the control group consisted of 23 women and 12 men. There was no statistically significant difference in sex distribution between the groups ($p = 0.805$).

The mean age of participants was 49.3 ± 13.1 years, ranging from 23 to 74 years. The mean age in the main group was 48.8 ± 13.2 years, and in the control group, 49.1 ± 12.7 years. There was no statistically significant difference in age between the main and control groups ($p = 0.919$). Table 1 and figure 1 show the mean EQ-5D-5L quality of life scores 1, 6, and 12 months after cholecystectomy in both groups. Despite a slight tendency toward higher scores in the main group, the difference between

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Table 1. Mean EQ-5D-5L quality-of-life scores (utility index) at 1, 6, and 12 months after laparoscopic cholecystectomy in the main and control groups

Group	1 month mean ± SD (utility index)	6 months mean ± SD (utility index)	12 months mean ± SD (utility index)
Main	0.91 ± 0.05	0.94 ± 0.04	0.96 ± 0.03
Control	0.89 ± 0.06	0.92 ± 0.05	0.94 ± 0.04

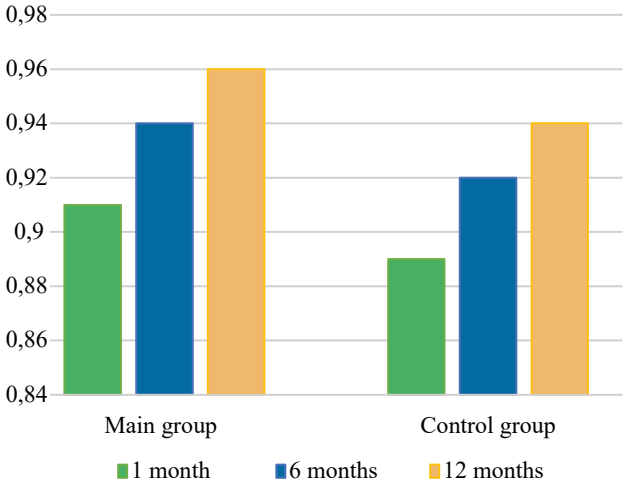

Figure 1. Mean quality of life scores according to the EфQ-5D-5L questionnaire (utility index) at 1, 6, and 12 months after laparoscopic cholecystectomy.

the groups was not statistically significant at any time point ($p > 0.05$).

Table 2 shows the mean scores of the physical (PCS) and mental (MCS) components according to the SF-36 questionnaire in the main and control groups 1, 6, and 12 months after LC.

Table 2. Mean SF-36 physical (PCS) and mental (MCS) component scores (points) at 1, 6, and 12 months after LC

Group	Time after surgery	PCS, Mean ± SD (points)	MCS, Mean ± SD (points)
Main	1 month	72 ± 9	74 ± 8
	6 months	80 ± 7	83 ± 6
	12 months	83 ± 6	86 ± 5
Control	1 month	70 ± 10	72 ± 9
	6 months	78 ± 8	81 ± 7
	12 months	82 ± 7	84 ± 6

None of the differences between the main and control groups reached statistical significance ($p > 0.05$).

Among the total sample ($n = 70$), a statistically significant improvement in quality of life was observed between 1 and 12 months after LC. Both groups showed an improvement in physical and psychoemotional components of quality of life, as measured by the SF-36 questionnaire, over the one-year period after the intervention ($p < 0.001$), which is consistent with the natural course of recovery after cholecystectomy. A statistically significant difference was also observed according to the EQ-5D-5L questionnaire between 1 and 12 months after surgery ($p<0.001$). These findings are presented in Table 3, Figure 2, and Figure 3.

The distribution of satisfaction values on the visual analogue scale (VAS) was found to be non-normal ($p< 0.00001$, according to the Shapiro-Wilk test). The mean level of satisfaction in the

Table 3. Statistically significant changes in quality-of-life indicators according to the SF-36 (points) and EQ-5D-5L questionnaires (utility index) between 1 and 12 months after laparoscopic cholecystectomy in the total sample

	Mean ± SD	p
EQ-5D-5L		
1 month	0.90 ± 0.06	p<0.001
12 months	0.95 ± 0.03	
SF-36 Physical Health		
1 month	70.3 ± 4.7	p<0.001
12 months	82.6 ± 3.7	
SF-36 Mental Health		
1 month	73.0 ± 4.3	p<0.001
12 months	85.0 ± 3.7	

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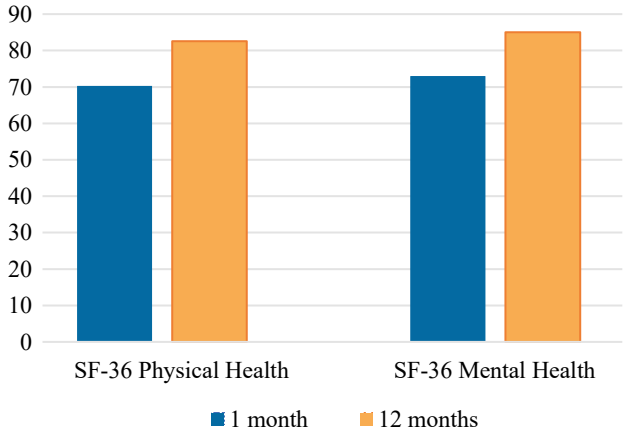

Figure 2. Mean quality of life scores according to the SF-36 questionnaire (points) in the total sample 1 and 12 months after laparoscopic cholecystectomy in the total sample

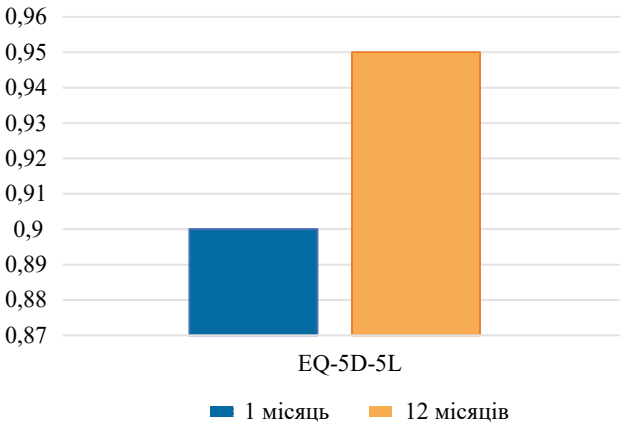

Figure 3. Mean quality of life scores according to the EQ-5D-5L questionnaire (utility index) 1 and 12 months after laparoscopic cholecystectomy in the total sample

total sample is Me (QI-QIII) 8.0 (8.0 - 9.0). The main group is characterised Me (QI-QIII) 9.0 (8.0 - 9.5) while the control group exhibits an average score of Me (QI-QIII) 8.0 (8.0 - 9.0). The data show a slight tendency for a higher median in the main group, but these differences are not statistically significant (p = 0.49).

Discussion

Since its introduction in the early 1990s, LC has gradually become the preferred method for gallbladder removal, largely due to the many advancements in medical technology that have taken place over the years. In the current medical practice, LC is considered the standard of care for a range of conditions, including symptomatic cholelithiasis, chronic cholecystitis, and even complications like gallstone pancreatitis. LC has been adopted in a number of high-income countries, where it appears to offer a number of advantages, including shorter hospital stays, faster recovery, and reduced overall healthcare costs. Its safety profile is well-established, with a reported mortality rate as low as 0.22%–0.4%, which further supports its role as a first-line surgical intervention. [11]

The findings of this study demonstrate that the use of telemedicine in the postoperative management of patients after LC provides outcomes that are comparable to those achieved through conventional outpatient follow-up. Both groups demonstrated statistically significant improvements in EQ-5D-5L and SF-36 scores over the 12-month period following surgery, which appears to be consistent with the natural course of postoperative recovery.

These results are consistent with previous research indicating a gradual enhancement of health-related quality of life after surgical treatment of gallstone disease. According to a meta-analysis by Deborah et al. (2022), postoperative EQ-5D utility scores typically approach 0.93, which aligns well with the values observed in this study and supports the external validity of our findings. [12]

Our study did not reveal clinically meaningful differences between telemedicine-based and traditional follow-up formats. This finding indicates that telemedicine support may serve as a viable alternative to conventional postoperative monitoring, aligning with current trends in the digitalisation of healthcare [6, 13].

According to recent studies, postoperative care incorporating telemedicine technologies offers several potential advantages, including a reduction in the number of in-person visits [7, 8], time and resource savings for both patients and healthcare providers [14], and high levels of patient satisfaction while maintaining clinical effectiveness [13, 15]. The aforementioned benefits of telemedicine-based approaches suggest their potential as a promising strategy in the postoperative management of patients with gallstone disease. The findings of this study demonstrate the high level of quality of life, which is consistent with the results reported by Taha

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et al. (2024). These researchers demonstrated a high level of satisfaction and improved quality of life among patients undergoing LC in Saudi Arabia [11].

Conclusions

Telemedicine can be a reliable and convenient alternative to conventional follow-up for patients after LC. Over the course of one year, patients in both the telemedicine and traditional care groups reported significant improvements in their quality of life after surgical treatment. Specifically, the EQ-5D-5L index rose from 0.90 to 0.95, and the SF-36 scores improved in both physical (from 70.3 to 82.6) and mental health domains (from 73.0 to 85.0), all with high statistical significance ($p < 0.001$).

There were no significant differences between the groups at any stage of follow-up, which suggests that remote monitoring is just as effective as in-person visits in supporting recovery and well-being after surgery.

Further implementation of telemedicine in postoperative management protocols for gallstone disease appears justified. Such an approach may improve continuity of care, reduce the burden on healthcare system, and provide flexible, patient-centered follow-up options, particularly in settings with limited access to in-person consultations.

Financing

This study did not receive funding.

Conflict of interests

The authors declare no conflict of interests.

Consent to publication

Consent was obtained from participants included in the study.

AI Disclosure

The authors used ChatGPT (OpenAI, San Francisco, CA, USA) for language editing of the English text. The authors reviewed and verified all AI-generated content to ensure accuracy and integrity.

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Formal Analysis: Starodub Tetiana;

Investigation: Starodub Tetiana, Bogomaz Volodymyr;

Resources: Bogomaz Volodymyr;

Data Curation: Starodub Tetiana;

Writing – Original Draft Preparation: Starodub Tetiana;

Writing – Review & Editing: Bogomaz Volodymyr;

Visualization: Starodub Tetiana;

Supervision: Bogomaz Volodymyr;

Project Administration: Bogomaz Volodymyr;

All authors have read and approved the final version of the manuscript.

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Оцінка якості життя пацієнтів після лапароскопічної холецистектомії

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Анотація: *лапароскопічна холецистектомія широко визнана золотим стандартом хірургічного лікування жовчнокам'яної хвороби. Незважаючи на високу ефективність операції та низький рівень ранніх ускладнень, згідно з результатами попередніх досліджень, приблизно 25% пацієнтів відчувають абдомінальні скарги, що вимагають медичного обстеження через місяць після операції. Активне післяопераційне спостереження вважається ключовим фактором у поліпшенні якості життя пацієнтів та виявленні симптомів, що залишаються після операції з різних причин. З розвитком цифровізації в галузі охорони здоров'я технології телемедицини відкривають нові можливості для підвищення ефективності післяопераційного спостереження. Однак послуги телемедицини також стикаються з низкою викликів, серед яких технічні обмеження, нерівний доступ до цифрових технологій, необхідність адаптації клінічних протоколів та потенційна загроза безпеці даних пацієнтів. Дане проспективне дослідження проводилося в період з 2024 по 2025 рік у двох медичних закладах України. У дослідженні брали участь 70 пацієнтів, яким було проведено лапароскопічну холецистектомію з приводу жовчнокам'яної хвороби. Вік учасників коливався від 24 до 67 років, середній вік – 44.3 ± 10.8 року. Критеріями виключення були: проведення відкритої холецистектомії замість лапароскопічної, ускладнений перебіг операції, тяжкі супутні захворювання (декомпенсований цукровий діабет, злоякісні новоутворення, виражена серцева недостатність), психічні розлади, відсутність доступу до Інтернету або відмова від участі у телемедичному спостереженні. Пацієнтів було розподілено на дві групи: основна отримувала*

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післяопераційний супровід із використанням телемедицини, а контрольна - мала традиційне амбулаторне спостереження. За потреби пацієнти основної групи могли в будь-який час звернутися за очною амбулаторною допомогою. Якість життя учасників дослідження оцінювалася за допомогою валідованих українських версій опитувальників EQ-5D-5L та SF-36 через 1, 6 та 12 місяців після операції. Результати показали позитивні зміни в якості життя загальної вибірки протягом року після втручання. Середній індекс EQ-5D-5L зріс з 0.90 до 0.95 за 11 місяців, а фізичний та психоемоційний компоненти SF-36 зросли з 70.3 до 82.6 та з 73.0 до 85.0 відповідно. Варто зазначити, що на жодному етапі спостереження не було статистично значущих відмінностей між основною та контрольною групами за якістю життя, оціненою за допомогою вищезазначених анкет. Цей висновок свідчить про те, що засоби телемедицини можуть бути настільки ж ефективними, як і традиційний післяопераційний нагляд, з точки зору якості життя. Загалом вважається, що впровадження телемедицини в післяопераційний догляд є безпечним, ефективним і орієнтованим на пацієнта, особливо в тих випадках, коли очні консультації неможливі або вимагають додаткових фінансових або часових витрат. Проведене дослідження показує, що телемедицина може бути ефективною альтернативою післяопераційному веденню пацієнтів після лапароскопічної холецистектомії, підкреслюючи її потенціал для більш широкої інтеграції в рутинну клінічну практику.

Ключові слова: Дистанційна консультація; Жовчнокам’яна хвороба; Лапароскопічна холецистектомія; Післяопераційний догляд; Результати лікування; Телемедицина; Якість життя.

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The role of galectin-3 in lipid metabolism disorders in patients with chronic heart failure of ischemic origin and concomitant metabolic pathology

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Abstract: *Chronic heart failure of ischaemic origin remains a leading cause of morbidity and mortality, and its course is significantly aggravated by concomitant metabolic pathology (type 2 diabetes mellitus and obesity). The role of galectin-3 in the mechanisms of direct participation in lipid metabolism disorders in this vulnerable cohort of patients remains insufficiently studied, which justifies the relevance of the study. The aim of the work was to study the role of galectin-3 as a potential diagnostic and prognostic marker of lipid metabolism disorders in patients with chronic heart failure of ischemic origin against the background of concomitant metabolic pathology. The study examined 225 patients with chronic heart failure with coronary artery disease, who were divided into four groups based on the presence of a combined course of diabetes mellitus and obesity (n=75), type 2 diabetes mellitus (n=50), obesity (n=50), isolated course of coronary artery disease (n=50), and 30 practically healthy individuals who were included in the control group. A biochemical study of lipid metabolism indicators was carried out, including total cholesterol, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, very low-density lipoprotein cholesterol and atherogenic index, as well as determination of serum galectin-3 levels by enzyme-linked immunosorbent assay. The results showed that the concentration of galectin-3 in the blood serum significantly increases in proportion to the degree of metabolic burden, reaching the highest values in patients with a combination of chronic heart failure, type 2 diabetes mellitus, and obesity, which was more than twice as high compared to patients without concomitant metabolic pathology ($p<0.05$). In the same group, the most pronounced deterioration of the lipid profile was found: low-density lipoprotein cholesterol increased by 99.2% compared to the group without metabolic pathology, and the atherogenic coefficient increased by 300.9% ($p<0.001$). At the same time, a significant decrease in antiatherogenic high-density lipoprotein cholesterol was recorded. Correlation analysis confirmed that serum galectin-3 has close links with dyslipidemic processes, and the strength of the correlation depends on the comorbid status. The strongest direct correlations with proatherogenic fractions, such as triglycerides and low-density lipoprotein cholesterol, were found in patients with comorbid obesity. These associations indicate that galectin-3 is actively involved in the mechanisms of dyslipidaemia and reflects a triglyceride-dependent aspect of the disorders, closely related to insulin resistance and chronic inflammation. The study also showed that even in patients without comorbid metabolic pathology, a statistically significant association of galectin-3 with total cholesterol and triglycerides persists, which emphasises its role as a marker of fundamental inflammation and fibrosis, independent of external metabolic factors. Thus, the results obtained expand the understanding of the role of galectin-3 as a key mediator integrating inflammatory, fibrotic, and dyslipidemic processes, providing*

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a strong rationale for including galectin-3 in cardiometabolic risk stratification strategies and the search for new therapeutic targets in patients with chronic heart failure.

Keywords: Heart failure, Coronary Disease, Lipid metabolism, Galectin-3, Obesity, Diabetes Mellitus Type 2, Coronary Artery Disease.

Introduction

Chronic heart failure (CHF) caused by coronary artery disease (CAD) has remained one of the leading causes of morbidity, hospitalisation and mortality worldwide for many decades, despite significant advances in treatment. The importance of the problem increases many times over in the context of comorbidity, namely when CHF is combined with metabolic pathology, in particular type 2 diabetes mellitus (T2DM) and obesity [1]. This concomitant pathology not only complicates the clinical course and worsens the prognosis of CHF, but also significantly modifies its pathogenesis, largely due to lipid metabolism disorders and the development of dyslipidaemia [2].

In recent years, researchers have focused their attention on galectin-3, a multifunctional β-galactoside-binding lectin that is a key mediator of inflammation and fibrosis [3]. Galectin-3 is expressed by activated macrophages and fibroblasts and plays a critical role in the processes of adverse remodelling, myocardial fibrosis and the progression of CHF, regardless of its ejection fraction [4]. Recent studies show that galectin-3 is not only a marker of myocardial damage, but also has the ability to actively influence metabolic dysregulation [3, 5].

Despite significant evidence of the association of galectin-3 with overall metabolic risk and cardiac fibrosis, the mechanisms of its direct involvement in lipid metabolism disorders in an extremely vulnerable cohort of patients — those with ischaemic CHF and concomitant metabolic pathology – remain poorly understood. Understanding this interaction is crucial, as dyslipidaemia is a powerful modified risk factor that exacerbates atherogenesis and the progression of CAD, and galectin-3 may act as a common link connecting inflammatory, fibrotic and metabolic disorders.

Aim

The aim of this study is to investigate the role of galectin-3 as a potential diagnostic and prognostic marker of lipid metabolism disorders in patients with chronic heart failure of ischaemic origin against the background of concomitant metabolic pathology.

Materials and methods

According to the study design, 225 patients undergoing inpatient treatment in the cardiology department of Kharkiv City Hospital No. 27 were divided into groups as follows: Group 1 included patients with CHF against the background of CAD with concomitant T2DM and obesity (n=75), Group 2 included patients with ischaemic CHF with T2DM (n=50), Group 3 included patients with CHF against the background of CAD with concomitant obesity (n=50), the comparison group (Group 4) consisted of patients with CHF and CAD without comorbid metabolic pathology (n=50). The control group included 30 practically healthy individuals. The groups of examinees were comparable in terms of age (63.44±2.06; 64.47±1.88; 60.59±2.43 and 63.27±1.72 years, respectively) and gender.

The diagnosis of CAD was verified in accordance with current international and national clinical protocols: the standards of the European Society of Cardiology (ESC) and the Unified Clinical Protocol of the Ministry of Health of Ukraine "Stable Ischemic Heart Disease" (Order No. 2857 of 23 December 2021). The presence of CHF was determined according to the classification of the Working Group on Heart Failure of the Association of Cardiologists of Ukraine, and its functional class was assessed according to the NYHA (New York Heart Association) criteria. T2DM was diagnosed based on the Unified Clinical Protocol of the Ministry of Health of Ukraine "Diabetes mellitus" (Order No. 1300 of 24 July 2024). To

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diagnose abdominal obesity, anthropometric indicators of waist and hip circumference and body mass index (BMI) were determined using the following formula:

$$BMI = m / h^2,$$

where

BMI – body mass index (kg/m^2);
m – body weight (kg);
h – height (m).

The inclusion criteria were age over 18 years, CAD with signs of CHF with or without excess body weight, grade 1-3 obesity, type 2 diabetes mellitus, and voluntary written consent to participate in the study.

Exclusion criteria were based on the need to minimise the influence of extraneous factors on the assessment of biomarkers and cardiometabolic status. Pregnant women were not included in the study, nor were patients with acute infectious and autoimmune diseases, diffuse connective tissue diseases, oncological diseases, diseases of the pituitary gland and hypothalamus, chronic renal failure with a GFR of less than 35 ml/min/1.73 m^2, symptomatic hypertension, acute coronary syndrome and acute cerebrovascular accident within the last 6 months, exacerbation of chronic or acute inflammatory diseases; patients with a history of alcohol abuse or mental illness; patients who were likely to violate the study protocol and individuals who are not citizens of Ukraine.

Biochemical testing included determination of total cholesterol (TC) and high-density lipoprotein cholesterol (HDL-C) levels, which were performed using the peroxidase method with the Cholesterol Liquicolor reagent kit from Human (Germany) in heparin-stabilised blood serum. Triglyceride (TG) levels were determined by an enzymatic colorimetric method using the Triglycerides 105 GPO reagent kit from Human (Germany). The atherogenicity coefficient (AC) was calculated using the Klimov A.M. formula:

$$AC = (TC – HDL\text{-}C)/HDL\text{-}C$$

The level of very low-density lipoprotein cholesterol (VLDL-C) was calculated using the following formula:

$$VLDL\text{-}C = TG/2.2 \times 0.45, (mmol/L)$$

Low-density lipoprotein cholesterol (LDL-C) levels were determined using the Friedwald formula:

$$LDL\text{-}C = TC – (VLDL\text{-}C + HDL\text{-}C), (mmol/L)$$

The level of galectin-3 in blood serum was determined by immunoenzymatic method. For quantitative measurement, a commercial Human Galectin-3 ELISA Kit (eBioscience, Austria) was used. The study was conducted on a Labline–90 immunoenzymatic analyser (Austria Lab Technologies, Austria) at the biochemical department of the Central Research Laboratory of Kharkiv National Medical University.

Statistical analysis was performed using parametric statistics methods with the use of Microsoft Excel 2010 software. The normality of the distribution of quantitative data was checked using the Kolmogorov–Smirnov criterion. If normal distribution was confirmed, the data were presented as M±m (mean ± standard error of the mean). The comparison of mean values was performed using Fisher's criterion (F). Spearman's rank correlation coefficient (r) was used to assess the correlation between samples. The difference was considered statistically significant at $p<0.05$.

The study was approved by the Ethics and Bioethics Committee of the Kharkiv National Medical University (protocol №2, dated 12.10.2022). All procedures were performed in accordance with the written informed consent of the participants. The study fully complies with the international standards of bioethics established in the Helsinki Declaration («Ethical Principles for Medical Research Involving Human Subjects») and the Universal Declaration on Bioethics and Human Rights (UNESCO).

Results. Analysis of lipid metabolism indicators and galectin-3 levels in patients in the study groups revealed significant differences that correlate with the deterioration of the metabolic status of patients. The data obtained, illustrating the dynamics of metabolic parameters and serum galectin-3 levels, are presented in Table 1.

While analysing lipid metabolism indicators, we found a significant increase in TC (by 19.1%; 18.3%; 21.2% and 72.3%) and TG (by

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Table 1. Analysis of lipid metabolism indicators and serum galectin-3 levels in patients in the study groups

Parameter, Units Measurement	Patients with CHF				
	CAD + T2DM + obesity (n=75)	CAD + T2DM (n=50)	CAD + obesity (n=50)	CAD without metabolic pathology (n=50)	Control group (n=30)
	1	2	3	4	5
TC, mmol/l	6.41±0.08	5.38±0.07	5.42±0.11	5.29±0.09	3.72±0.11
		P_{1-2} <0.05 P_{2-3} >0.05 P_{2-4} >0.05 P_{2-5} <0.05	P_{1-3} <0.05 P_{3-4} >0.05 P_{3-5} <0.05	P_{1-4} <0.05 P_{4-5} <0.05	P_{1-5} <0.05
TG, mmol/l	2.84±0.07	1.81±0.08	1.91±0.09	1.44±0.05	1.31±0.03
		P_{1-2} <0.05 P_{2-3} >0.05 P_{2-4} <0.05 P_{2-5} <0.05	P_{1-3} <0.05 P_{3-4} <0.05 P_{3-5} <0.05	P_{1-4} <0.05 P_{4-5} <0.05	P_{1-5} <0.01
HDL-C, mmol/l	1.15±0.03	1.77±0.04	1.74±0.03	2.47±0.07	2.86±0.05
		P_{1-2} <0.05 P_{2-3} >0.05 P_{2-4} <0.05 P_{2-5} <0.05	P_{1-3} <0.05 P_{3-4} <0.05 P_{3-5} <0.05	P_{1-4} <0.05 P_{4-5} <0.05	P_{1-5} <0.01
LDL-C, mmol/l	4.68±0.05	2.74±0.04	2.94±0.06	2.35±0.04	0.82±0.03
		P_{1-2} <0.05 P_{2-3} >0.05 P_{2-4} <0.05 P_{2-5} <0.05	P_{1-3} <0.05 P_{3-4} <0.05 P_{3-5} <0.05	P_{1-4} <0.05 P_{4-5} <0.05	P_{1-5} <0.01
VLDL-C, mmol/l	0.58±0,05	0.37±0.04	0.39±0.03	0.30±0.04	0.16±0.04
		P_{1-2} <0.05 P_{2-3} >0.05 P_{2-4} <0.05 P_{2-5} <0.05	P_{1-3} <0.05 P_{3-4} <0.05 P_{3-5} <0.05	P_{1-4} <0.05 P_{4-5} <0.05	P_{1-5} <0.01
AC	4.57±0.04	2.04±0.05	2.15±0.07	1.14±0.06	0.51±0.04
		P_{1-2} <0.05 P_{2-3} >0.05 P_{2-4} <0.05 P_{2-5} <0.05	P_{1-3} <0.05 P_{3-4} <0.05 P_{3-5} <0.05	P_{1-4} <0.001 P_{4-5} <0.05	P_{1-5} <0.001
Galectin-3, ng/ml	29.66±1.37	27.14±1.63	20.22±1.87	14.54±1.48	10.07±1.02
		P_{1-2} > 0.05 P_{2-3} <0.05 P_{2-4} <0.05 P_{2-5} <0.01	P_{1-3} <0.05 P_{3-4} <0.05 P_{3-5} <0.05	P_{1-4} <0.05 P_{4-5} <0.05	P_{1-5} <0.01

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56.9%; 48.7%; 97.2% and 116.8%), LDL-C (by 70.8%; 59.2%; 99.2% and 407.7%), VLDL-C (by 56.8%; 58.7%; 93.3% and 262.5%), AC (by 124.0%; 112.6%; 300.9% and 796.1%), as well as a decrease in HDL-C (by 35.0%; 33.9%; 53.4% and 59.8%) in patients with CHF against a background of CAD combined with T2DM and obesity, compared with patients with CAD and T2DM, CAD and obesity, CAD without concomitant metabolic pathology ($p<0.05$) and with individuals from the control group ($p<0.001$), respectively.

It should be noted that no lipid profile parameters showed significant changes between patients with CAD and concomitant T2DM and patients with CAD and obesity ($p>0.05$). These results can be explained by common mechanisms of insulin resistance (IR) in both obese patients and patients with T2DM which is a key mechanism of dyslipidaemia. Systemic inflammation also has a significant impact, affecting lipid metabolism and contributing to the progression of atherosclerosis.

Among patients with CAD and concomitant T2DM, there was a significant increase in LDL levels by 30.9% compared to the control group ($p<0.05$). Compared to the comparison group (with isolated CAD) and the control group, the indicators changed as follows: there was an increase in TG concentrations by 20.4% and 27.6%, LDL-C by 50.7% and 70.1%, VLDL-C by 18.9% and 56.8%, AC by 44.1% and 75%, and a decrease in HDL-C by 28.3% and 38.1%, respectively ($p<0.05$).

Patients with CHF against the background of CAD with concomitant obesity also showed a significant increase in TG levels by 24.6% and 31.4%, LDL-C by 54.1% and 72.1%, VLDL-C by 23.1% and 59%, AC by 54.4% and 76.3%, as well as a decrease in HDL-C concentration by 29.6% and 39.2% compared to patients with isolated CAD and healthy volunteers from the control group, respectively ($p<0.05$).

Serum galectin-3 showed significant differences in the form of concentration increase in the main study group (group 1) by 8.5%, 31.8%, and 51% compared to groups 2, 3, and 4, respectively ($p<0.05$) and by 66.1% compared to the control group ($p<0.01$). Such changes in this indicator are likely due to the fact that in patients with obesity and T2DM, chronic low-level inflammation is a key pathogenetic factor. It should also be noted that this lectin is actively involved in the processes of fibrogenesis, stimulating the activation of fibroblasts and enhancing collagen synthesis. In patients with concomitant T2DM and obesity, this profibrotic effect is further enhanced by the accumulation of advanced glycation end products, which have a direct damaging effect on cardiac and vascular structures.

A correlation analysis was performed to establish the presence and nature of relationships between serum galectin-3 levels and lipid metabolism indicators.

Table 2. Relationships between galectin-3 levels and lipid metabolism indicators in patients with chronic heart failure against a background of coronary artery disease with concomitant obesity and type 2 diabetes mellitus ($r_{crit}=0.34$)

Parameter, units	r	p
TC, mmol/l	0.42	<0.05
TG, mmol/l	0.51	<0.05
HDL-C, mmol/l	-0.35	<0.05
LDL-C, mmol/L	0.56	<0.05
VLDL-C, mmol/l	0.59	<0.05
AC	0.22	>0.05

Thus, in a group of patients with CAD against the background of concomitant T2DM and obesity, moderate direct correlations were found between galectin-3 concentration and TC level ($r=0.42$; $p<0.05$), LDL-C ($r=0.56$; $p<0.05$), VLDL-C ($r=0.59$; $p<0.05$) TG ($r=0.51$; $p<0.05$) and an inverse relationship with HDL-C ($r= -0.35$; $p<0.05$), indicating an increase in atherogenic fractions of the lipid profile in response to galectinemia, along with a decrease in antiatherogenic components of the lipid profile. The correlation with the atherogenicity coefficient was not statistically significant ($r=0.22$; $p>0.05$). The data are presented in Table 2. These results confirm that galectin-3 not only reflects fibrotic changes but is also actively

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involved in the mechanisms of dyslipidaemia, making it a key biomarker of cardiometabolic risk in this cohort of patients.

The results of the correlation analysis presented in Table 3 allowed us to identify statistically and clinically significant associations between galectin-3 levels and key indicators of lipid metabolism in patients with CAD against the background of T2DM.

Table 3. Correlations between galectin-3 levels and lipid metabolism indicators in patients with chronic heart failure against a background of coronary artery disease with concomitant type 2 diabetes mellitus (r_{crit}=0.34)

Parameter, units	r	p
TC, mmol/l	0.42	<0.05
TG, mmol/l	0.61	<0.05
HDL-C, mmol/l	-0.19	>0.05
LDL-C, mmol/L	0.30	>0.05
VLDL-C, mmol/l	0.26	>0.05
AC	0.31	>0.05

In this group of patients, statistically significant direct correlations were found between serum galectin-3 concentration and two main proatherogenic indicators. A strong direct correlation (r=0.61; p<0.05) with TG levels was established, emphasising the close relationship between the fibrosis biomarker and TG metabolism disorders characteristic of insulin resistance and T2DM. A moderate direct correlation (r=0.42; p<0.05) with TC was also determined, indicating the clinical significance of the association of serum galectin-3 with total lipidemia. For the remaining indicators, the correlations were statistically insignificant (p>0.05). Therefore, the data obtained suggest that in the context of metabolic pathology galectin-3 primarily reflects the TG-dependent aspect of dyslipidaemia, which is closely associated with chronic inflammation and insulin resistance.

In the group of patients with CHF against the background of CAD with concomitant obesity, strong statistically significant associations were found between serum galectin-3 levels and TG (r=0.76; p<0.05), LDL-C (r=0.69; p<0.05) and

Table 4. Correlations between galectin-3 levels and lipid metabolism indicators in patients with chronic heart failure against a background of coronary artery disease with concomitant obesity (r_{crit}=0.34)

Parameter	r	p
TC, mmol/l	0.46	<0.05
TG, mmol/l	0.76	<0.05
HDL-C, mmol/l	-0.28	>0.05
LDL-C, mmol/L	0.69	<0.05
VLDL-C, mmol/l	0.27	>0.05
AC	0.26	>0.05

a moderate direct correlation with TC (r=0.46; p<0.05). At the same time, HDL-C (r=-0.28; p>0.05), VLDL-C (r=0.27; p>0.05) and AC (r=0.26; p>0.05) had weak correlations that did not reach statistical significance. In this cohort of patients, the presence of strong and moderate associations with key proatherogenic cholesterol fractions emphasises that serum galectin-3 is a powerful biomarker that integrates inflammatory, fibrotic and dyslipidaemic processes characteristic of the comorbidity of heart failure and obesity, signalling a high cardiometabolic risk.

The results of the correlation analysis demonstrate that even in the absence of concomitant metabolic pathology, serum galectin-3 levels in patients with heart failure of ischemic origin maintain statistically significant associations with major proatherogenic fractions (Table 5).

Table 5. Correlations between galectin-3 levels and lipid metabolism indicators in patients with chronic heart failure against a background of coronary artery disease without concomitant metabolic pathology (r_{crit}=0.34)

Parameter, units	r	p
TC, mmol/l	0.38	<0.05
TG, mmol/l	0.43	<0.05
HDL-C, mmol/l	-0.28	>0.05
LDL-C, mmol/L	0.26	>0.05
VLDL-C, mmol/l	0.27	>0.05
AC	0.32	>0.05

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A weak direct correlation was established with TG levels ($r=0.43$; $p<0.05$) and TC ($r=0.38$; $p<0.05$). The results obtained prove that serum galectin-3 is closely associated with TG metabolism disorders regardless of the presence of obesity or T2DM and indicate a significant relationship between the studied indicator and general lipid dysregulation in this group of patients. The remaining indicators did not show statistically significant correlations ($p>0.05$). The results indicate that in a group of patients with CAD without concomitant metabolic pathology, serum galectin-3 likely acts as a marker of fundamental inflammation and fibrosis, which partially overlaps with basic dyslipidaemia, but is not as closely associated with specific proatherogenic fractions as in groups with pronounced metabolic disorders.

Discussion

The study, aimed at investigating the relationship between serum galectin-3 and lipid metabolism parameters in patients with CHF against the background of CAD with concomitant metabolic pathology, confirmed the hypothesis about the integrative role of this biomarker in the cardiometabolic continuum. Our results demonstrate that the concentration of serum galectin-3 increases significantly in proportion to the degree of metabolic burden, which is consistent with most current studies. In their study on mouse models, Du XJ et al. found that galectin-3 has a direct effect on the transcription of genes associated with lipid metabolism and influences its disruption at the cellular level [7]. Taking into account the study by Du XJ et al. is fundamental, and lipidomics, which allows detecting profound changes at the cellular level, prevailed among the research methods, while our clinical indicators are an integral assessment of systemic lipid metabolism, it should be noted that the pathophysiological mechanisms of galectin-3 in fibrogenesis and lipid metabolism are universal.

In turn, Storman M et al. considered galectin-3 as a biomarker, particularly in the presence of other established factors such as age, body weight, and abdominal obesity. This confirms our concept that this lectin is an integrative marker of comorbidity of CHF and obesity [8].

Lin D et al. in their work associate an increase in serum galectin-3 with the presence or risk of T2DM, which is a key link in the cardiometabolic continuum, and also prove that lipids and galectin-3 should be assessed together for better prediction of metabolic risk, which once again confirms the importance of galectin-3 not only as a marker of fibrosis, but also as an integrative biomarker that plays a key role in the early stages of cardiometabolic dysfunction, including the development of T2DM [9]. This further substantiates its significance as a prognostic marker for assessing the risk of dyslipidaemia in patients with CHF burdened by metabolic pathology.

Some researchers like Schmitt et al. [10] and Lorenzo-Almorós A et al. [11] argue that higher serum galectin-3 levels are associated with a higher prevalence of prediabetes, T2DM, and other cardiovascular risk factors and comorbidities. The authors also believe that this lectin is cross-linked with impaired systolic and diastolic function in patients with T2DM and reduced systolic function in prediabetes, and is prospectively associated with systolic dysfunction and cardiovascular and all-cause mortality in T2DM. This is fully consistent with our results and confirms the role of galectin-3 as a link between metabolic disorders and myocardial damage. The study by Schmitt et al. also states that N-terminal pro B-type natriuretic peptide (NT-proBNP) was superior to galectin-3 for assessing reduced systolic and diastolic function and had higher prognostic value for mortality. At the same time, galectin-3 was not associated with cardiac function in patients with euglycaemia. This proves that serum galectin-3 is activated specifically by metabolic dysfunction and is a marker of metabolically dependent fibrosis in a cohort of patients with cardiometabolic pathology, and not just hydrodynamic stress, which is measured by NT-proBNP.

At the same time, a study by Ianos RD et al. showed that measuring galectin-3 concentrations in patients with CHF with preserved and moderately reduced ejection fraction can provide a deeper understanding of the severity of heart failure, especially in patients with T2DM, which fully coincides with our statements [12]. Jiang J et

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al also considered galectin-3 was an independent predictor of heart failure with preserved ejection fraction [13].

Khadeja Bi et al. also reveals galectin-3 as a marker for the diagnosis of CHF (at 8 ng/ml, sensitivity 92%, specificity 71%), which also confirms our hypothesis of using serum galectin-3 in CHF risk stratification [2].

The clinical correlations we found between high serum galectin-3 levels and proatherogenic lipid fractions in patients with comorbid T2DM and obesity have also been confirmed in experimental studies. The researches established the role of galectin-3 as an important regulatory factor in myocardial remodelling induced by disturbances in glucose-lipid metabolism [14, 15]. The authors demonstrated that galectin-3 activity promotes fibrosis, apoptosis, and cardiomyocyte hypertrophy by inhibiting the activity of the Akt signalling pathway, thus acting as a key molecular link that converts systemic metabolic disorders into direct myocardial damage and remodelling.

Thus, the study is fully consistent with the results of current scientific advances and provides important clinical confirmation of the fundamental mechanisms identified in experimental and cohort studies in recent years.

Our study expands the current understanding of the role of galectin-3 from a simple marker of fibrosis to a key link integrating inflammation, dyslipidaemia, and CHF progression in T2DM and obesity. The data obtained provide a strong rationale for including galectin-3 in strategies for stratifying cardiometabolic risk.

Conclusions

1. The study confirmed the integrative role of galectin-3 as a potential diagnostic and prognostic marker of lipid metabolism disorders in patients with chronic heart failure of ischaemic origin against the background of concomitant metabolic pathology. The established links between serum galectin-3 and proatherogenic lipid fractions indicate that this biomarker is a key link connecting inflammatory, fibrotic, and metabolic disorders.

2. Patients with chronic heart failure and comorbid metabolic disorders such as type 2 diabetes mellitus and obesity show a significant deterioration in their lipid profile, manifested by an increase in proatherogenic fractions – total cholesterol (by 21.2%), triglycerides (by 97.2%) and low-density lipoprotein cholesterol (by 99.2%) and a decrease in antiatherogenic high-density lipoprotein cholesterol (by 53.4%), as well as the highest concentrations of serum galectin-3 (29.66±1.37 ng/ml vs. 14.54±1.48 ng/ml) were recorded in patients with metabolic syndrome with a combination of chronic heart failure, type 2 diabetes mellitus and obesity, compared to patients without metabolic pathology. This confirms that galectin-3 not only reflects fibrosis induced by heart failure, but is also actively activated by metabolic dysfunction and acts as a key link connecting chronic low-level inflammation, dyslipidaemia and fibrogenesis processes.

3. Correlation analysis confirmed that serum galectin-3 is an integrating biomarker closely associated with dyslipidaemic processes, with the strength of this association depending on the degree of metabolic burden. In patients with chronic heart failure of ischaemic origin against a background of concomitant obesity, galectin-3 showed the strongest direct correlations with proatherogenic fractions, namely triglycerides ($r=0.76$; $p<0.05$) and low-density lipoprotein cholesterol ($r=0.69$; $p<0.05$). In the group with a combination of type 2 diabetes mellitus and obesity, moderate direct correlations were also found with low-density lipoprotein cholesterol ($r=0.56$; $p<0.05$) and triglycerides ($r=0.51$; $p<0.05$), as well as an inverse correlation with antiatherogenic high-density lipoprotein cholesterol ($r=-0.35$; $p<0.05$). At the same time, even in the absence of metabolic pathology, a weaker but statistically significant correlation between galectin-3 and total cholesterol ($r=0.38$; $p<0.05$) and triglycerides ($r=0.43$; $p<0.05$) persists. Thus, serum galectin-3 acts as a key mediator linking inflammatory and profibrotic processes with metabolic dysfunction, while particularly sensitively reflecting the triglyceride-dependent aspect of dyslipidaemia, which is a direct consequence of insulin resistance.

Prospects for further research. Currently, it is extremely important to conduct long-term prospective studies to assess the extent to which

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galectin-3 levels correlate with the risk of acute cardiovascular events (myocardial infarction, stroke) and overall/cardiovascular mortality in metabolically burdened patients.

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Conflict of interest

None

Consent to publication

All procedures related to patient examination and use of the data obtained were carried out in accordance with the principles of biomedical ethics and international standards. Each study participant provided voluntary, informed, and written consent to participate in the study, as well as to the subsequent publication and use of anonymised scientific results. The study was conducted in accordance with the Helsinki Declaration and the recommendations of the Committee on Publication Ethics (COPE). The author confirms that the publication does not contain any personal data that could identify patients.

AI Disclosure

The author used ChatGPT (OpenAI, San Francisco, CA, USA) for language editing of the English text. The authors reviewed and verified all AI-generated content to ensure accuracy and integrity.

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Роль галектину-3 у порушеннях ліпідного обміну у хворих з хронічною серцевою недостатністю ішемічного та супутньою метаболічною патологією

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Анотація. *Хронічна серцева недостатність ішемічного генезу залишається провідною причиною захворюваності та смертності, при цьому її перебіг значно обтяжується супутньою метаболічною патологією (цукровим діабетом 2 типу та ожирінням). Роль галектину-3 у механізмах безпосередньої участі в порушеннях ліпідного обміну в цій вразливій когорті пацієнтів залишається недостатньо вивченою, що обґрунтовує актуальність дослідження. Метою роботи було вивчення ролі галектину-3 як потенційного діагностичного та прогностичного маркера порушень ліпідного обміну у пацієнтів із хронічною серцевою недостатністю ішемічного генезу на тлі супутньої метаболічної патології. У дослідженні було обстежено 225 хворих на хронічну серцеву недостатність при ІХС, яких було розподілено на чотири групи, виходячи з наявності поєднаного перебігу цукрового діабету та ожиріння (n=75), цукрового діабету 2 типу (n=50), ожиріння (n=50), ізольованого перебігу ІХС (n=50) та 30 практично здорових осіб, які увійшли до контрольної групи. Проводилось біохімічне дослідження показників ліпідного обміну, включаючи загальний холестерин, тригліцериди, холестерин ліпопротеїнів високої щільності, холестерин ліпопротеїнів низької щільності, холестерин ліпопротеїнів дуже низької щільності та коефіцієнт атерогенності, а також визначення сироваткового рівня галектину-3 імуноферментним методом. Отримані результати продемонстрували, що концентрація галектину-3 у сироватці крові достовірно зростає пропорційно до ступеня метаболічного обтяження, досягаючи найвищих значень у хворих з поєднанням хронічної серцевої недостатності, цукрового діабету 2 типу та ожиріння, що було більш ніж удвічі вищим порівняно з пацієнтами без супутньої метаболічної патології (p<0,05). У цій же групі виявлено найбільш виражене погіршення ліпідного профілю: холестерин ліпопротеїнів низької щільності збільшився на 99,2 % порівняно з групою без метаболічної патології, а коефіцієнт*

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атерогенності збільшився на 300,9 % (p<0,001). Одночасно зафіксовано значне зниження антиатерогенного холестерину ліпопротеїнів високої щільності. Кореляційний аналіз підтвердив, що сироватковий галектин-3 має тісні зв'язки з дисліпідемічними процесами, причому сила кореляції залежить від коморбідного статусу. Найбільш потужні прямі кореляції з проатерогенними фракціями, такими як тригліцериди і холестерин ліпопротеїнів низької щільності, були встановлені у хворих із супутнім ожирінням. Ці зв'язки вказують, що галектин-3 активно залучений до механізмів дисліпідемії і відображає тригліцерид-залежний аспект порушень, тісно пов'язаний з інсулінорезистентністю та хронічним запаленням. Дослідження також показало, що навіть у пацієнтів без супутньої метаболічної патології зберігається статистично значущий зв'язок галектину-3 із загальним холестерином і тригліцеридами, що підкреслює його роль як маркера фундаментального запалення та фіброзу, незалежного від зовнішніх метаболічних факторів. Таким чином, отримані результати розширюють розуміння ролі галектину-3 як ключового медіатора, що інтегрує запальні, фібротичні та дисліпідемічні процеси, надаючи вагоме обґрунтування для включення галектину-3 у стратегії стратифікації кардіометаболічного ризику та пошуку нових терапевтичних мішеней у пацієнтів із хронічною серцевою недостатністю.

Ключові слова: галектин-3, дисліпідемія, ішемічна хвороба серця, ожиріння, хронічна серцева недостатність, цукровий діабет 2 типу.

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The effect of probiotic supplementation on blood pressure, systemic inflammation and endothelial function in patients with arterial hypertension

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Abstract: *The need for new therapeutic approaches to the treatment of arterial hypertension is due to its increasing prevalence and high mortality rate, which prompts the search for new methods of therapy. Recent scientific data indicate the important role of gut microbiome imbalance, which can lead to disruption of the gut barrier and the development of chronic low-intensity systemic inflammation. This inflammation is a key mechanism in the pathogenesis of arterial hypertension and causes endothelial dysfunction, as evidenced by higher levels of pro-inflammatory cytokines. This highlights new therapeutic perspectives for the correction of gut dysbiosis as a therapeutic strategy with the potential to improve disease control. The aim of this prospective study was to evaluate the effect of dietary probiotic supplementation on blood pressure, systemic inflammation and endothelial function in patients with arterial hypertension through correction of gut dysbiosis. The study involved fifty-five patients who were randomized into two groups: the main group (30 people), which, in addition to standard antihypertensive therapy, received a probiotic that included Saccharomyces boulardii and Lactobacillus, and a comparison group (25 people) receiving only standard therapy. The duration of observation was 3 months. All participants underwent a comprehensive clinical examination with analysis of systolic and diastolic blood pressure, levels of interleukin-6 and interleukin-10, assessment of endothelium-dependent vasodilation of the brachial artery, as well as analysis of the composition of the gut microbiome. The study found that before the intervention, the groups were comparable in terms of basic clinical and demographic indicators, with the exception of a significant difference in the proportion of patients with reduced Roseburia content inulinivorans and Faecalibacterium prausnitzii, which limited the direct comparison of the dynamics of these taxa. After 3 months of observation, patients in the main group achieved a significant decrease in systolic and diastolic blood pressure, as well as the level of pro-inflammatory cytokine interleukin-6, while in the comparison group the levels of inflammatory markers did not change significantly. Microbiome analysis showed that the probiotic supplementation effectively corrected gut dysbiosis, as evidenced by a significant decrease in the ratio of Firmicutes to Bacteroidetes, a decrease in the proportion of Firmicutes, and an increase in the proportion of Bacteroidetes and Lactobacillus. At the same time, comparative analysis did not reveal a statistically significant difference in endothelial function indicators between the groups. The results obtained confirm that dietary probiotic supplementation is an effective adjunct method for correcting gut dysbiosis, which helps improve blood pressure control and reduce systemic inflammation in patients with arterial hypertension, which is important for improving the prognosis of the disease.*

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Keywords: Blood Pressure, Endothelial Function, Gut Microbiome, Systemic Inflammation, Probiotics.

Introduction

Arterial hypertension (AH) is defined as a persistent elevation of office systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg, with diagnosis confirmed by repeated measurements, except in cases of grade 3 hypertension (SBP ≥ 180 mmHg and/or DBP ≥ 110 mmHg), where diagnosis may be established at the first visit. Essential arterial hypertension (AH) is a major global health problem and represents the leading risk factor for cardiovascular diseases, carrying a substantial economic burden. Epidemiological data indicate that AH is associated with high prevalence, significant disability, elevated mortality, and low awareness, particularly in low- and middle-income countries. According to the World Health Organization, approximately 1.28 billion adults worldwide aged 30–79 years have hypertension, two-thirds of whom live in low- and middle-income countries, and about 46% are unaware of their condition. In the United States, high blood pressure was a primary or contributing cause in over 660,000 deaths in 2023, with nearly one-fifth of COVID-19–related deaths occurring in individuals with a history of hypertension. Only 22.5% of adults with hypertension achieve adequate blood pressure control. In Ukraine, 34.8% of adults aged 18–69 years had elevated blood pressure in 2019, with a significant proportion unaware of their diagnosis or not receiving treatment [1-4].

The urgency of developing new therapeutic approaches for AH is driven by its growing prevalence and high mortality, prompting the search for innovative treatment strategies. Disturbances in the gut microbiome (GM) can contribute to systemic inflammation - a key mechanism in the development of AH - and promote endothelial dysfunction [1–3]. This is supported by evidence of elevated pro-inflammatory cytokines in patients with microbiome imbalance [4–5].

Gut dysbiosis triggers molecular pathways leading to increased gut permeability, allowing microbialcomponentssuchaslipopolysaccharides (LPS) to enter the bloodstream and activate chronic inflammation, which may contribute to blood pressure elevation [1-2]. Systemic inflammation further plays a central role in endothelial dysfunction, impairing vascular tone regulation and promoting cardiovascular disorders, including hypertension [2-5].

Recent studies emphasize that the gut microbiota modulates metabolic pathways directly involved in blood pressure regulation. Thus, dysbiosis may represent a critical factor disrupting homeostasis through both microbial and systemic mechanisms, correlating with microbiome alterations in patients with AH [6-8]. These findings highlight new prospects for targeting gut dysbiosis as a therapeutic approach [9-15].

Aim

To assess the impact of dietary probiotic supplementation on blood pressure, systemic inflammation, and endothelial function in patients with arterial hypertension through correction of gut dysbiosis.

Materials and methods

The study was conducted on the basis of the therapeutic department of the Clinical Hospital No. 18 of Kyiv, which is the clinical base of the Department of Internal Medicine No. 1 of the O.O. Bogomolets National Medical University. This work was a prospective study. A clinical examination was conducted, data analysis of previous medical documentation of patients with arterial hypertension and their selection according to the inclusion and exclusion criteria was carried out.

The study involved and examined 100 people aged 40–75 years who provided informed consent to participate. 55 patients with arterial hypertension (the main group) were under observation, who underwent outpatient and/or inpatient treatment and further observation during 2022–2025. The patients included in the study were divided into two randomized groups: the main (group 1, n=30) and the comparison group

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(group 2, n=25). Randomization provided for the distribution of patients taking into account age, gender, severity and duration of hypertension, as well as the presence of comorbidities.

Inclusion criteria were: men and women aged 40–75 years with stage II, grade 1 or 2 essential arterial hypertension, patients not previously treated with antihypertensive therapy, and for women of reproductive age—a negative pregnancy test and signed informed consent.

Exclusion criteria included: stage III essential hypertension, chronic kidney disease stages III–V (eGFR <60 mL/min/1.73 m²), endocrine disorders, office systolic BP <115 mmHg or diastolic BP <55 mmHg, atrial fibrillation or flutter, second- to third-degree AV block on ECG, NYHA class III–IV chronic heart failure, active inflammatory processes (CRP >10 mg/L), history of acute or chronic coronary syndrome, alcoholism, drug addiction, mental disorders, infectious diseases, oncological or hematological diseases, active gastrointestinal or liver diseases, inflammatory bowel diseases (Crohn's disease, ulcerative colitis), IBS, renal artery stenosis, sarcoidosis, urolithiasis, tuberculosis, pregnancy, and lactation.

The study was performed in compliance with bioethical standards in accordance with the Declaration of Helsinki (Helsinki, 2013) and other regulatory documents, which was confirmed by the local bioethics commission (protocol No. 167 dated 11/21/2022).

At the screening visit, all patients with arterial hypertension underwent correction of antihypertensive therapy: patients received an ACE inhibitor(perindopril arginine 5–10 mg) in combination with a calcium channel antagonist (amlodipine 5–10 mg per day).

Fifty-five patients who met the inclusion criteria were selected. According to the assigned treatment, patients were divided into two subgroups using the envelope method:

The main group(group 1, n=30) received combined antihypertensive therapy and was additionally prescribed dietary supplementation. Probiotic (Saccharomyces boulardii - 2.5×10^9 CFU, Lactobacillus acidophilus - 2.5×10^9 CFU, Lactobacillus rhamnosus - 1×10^9 CFU, inulin - 25 mg) at a dose of 2 capsules per day for 3 months (commercial name - Bazhana®, Sopharma). Patients in the comparison group (group 2, n=25) received only basic antihypertensive therapy without probiotics.

The effectiveness of treatment was assessed after 3 months of observation.

All patients in the main group and the comparison group were analyzed for the content of the main types of gut microbiome: Bacteroides, Firmicutes; the proportion of patients with a reduced content of Lactobacillus was determined. spp,(<10^7), Bifidobacterium spp,(<10^9), Prevotella spp.(<10^11), Acinetobacter spp.,(<10^6), Roseburia inulinivorans(<10^10), Faecalibacterium prausnitzii,(<10^8), F/B ratio was estimated. Material for analysis of the main group was collected before the start of antihypertensive therapy to avoid drug effects on the gut microbiome.

The collection and storage of the material was carried out in accordance with the instructions developed by the Diagen laboratory.

Real-time polymerase chain reaction was performed in the Diagen laboratory using a thermal cycler. Rotor-Gene 6000 (Qiagen, Germany).

Endothelial function was assessed by brachial artery ultrasound with assessment of endothelium-dependent (flow-dependent) vasodilation. Brachial artery diameter was measured at rest and after 5-minute occlusion of blood flow using a sphygmomanometer cuff inflated to 250 mm Hg. The percentage increase in artery diameter from baseline was calculated.

Statistical processing of the results was carried out using the EZR software package version 2.8 (Saitama Medical Center, Jichi Medical University, Japan), which is the graphical user interface for the R software package (The R Foundation for Statistics Computing, Austria).

Wilcoxon's W test was used to compare quantitative data within groups, and Fisher's exact test (with Yates' correction) was used for categorical variables. Normality of distribution was assessed using the Shapiro–Wilk test. Normally distributed data are presented as mean ± standard deviation; non-normally

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distributed data as median and interquartile range.

For repeated measurements over time, two-way repeated measures ANOVA was applied, followed by Bonferroni-corrected post hoc comparisons where appropriate. Effect sizes were calculated using Cohen's d for parametric tests and r for non-parametric comparisons.

Results

Table 1 shows the comparative assessment of the observation groups before the intervention.

Baseline characteristics

The groups were comparable in terms of demographic and clinical parameters. Age distribution and gender ratio did not differ significantly between groups. Baseline systolic and diastolic blood pressure, levels of IL-6 and IL-10, and endothelial function (FMD) were also similar.

Most microbiome indicators did not differ significantly at baseline, including the F/B ratio and the proportions of Firmicutes, Bacteroides, Lactobacillus, Bifidobacterium, Prevotella, Acinetobacter and Akkermansia.

Table 1. Comparative evaluation of observation groups before intervention.

Indicator	group 1(n=30)	group 2(n=25)	p
Gender [n(%)]man	15(50)	13(52)	p=0.905
Age, mean ± SD	50.77±7.45	51.68±6.82	p=0.640
Systolic blood pressure, mm Hg.	154 [145-158]	155 [150-159]	p=0.263
Diastolic blood pressure, mm Hg.	93 [90-95]	95 [93-96]	p=0.086.
Interleukin-6, pg /ml	1.99±0.3323	1.992±0.2666	p=0.976
Interleukin-10, pg /ml	3.785±1.519	3.779 ± 1.626	p=0.992
Flow-mediated dilation (FMD) of the brachial artery before and after limb ischemia, %	6 [5-8]	8 [6 - 10]	p=0.068.
F/B ratio	6.22±2.752	6.248±1.939	p=0.968.
Firmicutes spp, %	70 [63-74]	70 [62-74]	p=0.839.
Bacteroides spp, %	10.75 [8.6-15.1]	10.9 [8.9-13.5]	p=0.919.
Proportion of patients with reduced Lactobacillus content spp,(<10^7), %	53.3 [4.9-71.3]	72.0 [52.1-88.2]	p=0.255.
Proportion of patients with reduced Bifidobacterium content spp, (<10^9), %	56.7 [95% CI 38.1-74.3]	56.0 [95% CI 35.6-75.4]	p=0.827.
Proportion of patients with reduced Prevotella levels spp.(<10^11), %	60.0 [95% CI 41.4 - 77.2]	44.0 [95% CI 24.6-64.4]	p=0.367.
Proportion of patients with reduced Acinetobacter levels spp.,(<10^6), %	23.3 [95% CI 9.7-40.6]	16.0 [95% CI 4.1-33.6]	p=0.735.
Proportion of patients with reduced Roseburia content inulinivorans,(<10^10), %	56.7 [95% CI 38.1-74.3]	92.0 [95% CI 77.6-99.4]	p=0.007.
Proportion of patients with reduced Faecalibacterium content prausnitzii,(<10^8),%	53.3 [95% CI 34.9-71.3]	96.0 [95% CI 84.3-100.0]	p<0.001.
Proportion of patients with reduced Akkermansia content muciniphila,(<10^11), %	76.7 [95% CI 59.4-90.3]	80.0 [95% CI 61.4-93.5]	p=0.976.

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However, two taxa showed significant between-group differences: Roseburia inulinivorans and Faecalibacterium prausnitzii, both of which were more frequently reduced in group 2. This baseline imbalance limits the interpretation of subsequent changes in these taxa.

Table 2 shows a comparative assessment of the two groups at the beginning and end of the observation.

Table 2. Comparative assessment of patient groups at the beginning and end of observation

Indicator	group 1(n=30)		p	group 2(n=25)		p
	To	After		To	After	
Systolic blood pressure, mm Hg.	154 [145-158]	123 [120-128]	p<0.001	155 [150-159]	131 [129-135]	p<0.001
Diastolic blood pressure, mm Hg.	93 [90-95]	81 [78-83]	p<0.001	95 [93-96]	84 [83-86]	p<0.001
Interleukin-6, pg /ml	1.9 15 [1.75-2.23]	1.815 [1.69-1.99]	p=0.014	1.96 [1.78-2.18]	2.06 [1.96-2.15]	p=0.200
Interleukin-10, pg /ml	3.785±1.519	3.632±1.535	p<0.001	3.78 ± 1.63	4.16±1.44	p=0.266
Flow-mediated dilation (FMD) of the brachial artery before and after limb ischemia, %	6 [5-8]	10 [9-12]	p<0.001	8 [6 - 10]	11 [9-12]	p<0.001
F/B ratio, %	6.22±2.75	2.3 [1.8-2.8]	p<0.001	6.248±1.94	6.18± 1.89	p=0.041
Firmicutes spp, %	70 [63-74]	55 [47-59]	p<0.001	67.92 ± 8.69	67.08±8.27	p=0.044
Bacteroides spp, %	10.75 [8.6-15.1]	22 [20-27]	p<0.001	10.9 [8.9-13.5]	11 [9-13.2]	p=0.838
Proportion of patients with reduced Lactobacillus content spp,(<10^7), %	53.3 [95% CI 4.9-71.3]	13.3 [95% CI 3.5-28.3]	p=0.034	72.0 [95% CI 52.1-88.2]	68.0 [95% CI 47.8-85.2]	p=0.066
Proportion of patients with reduced Bifidobacterium content spp,(<10^9), %	56.7 [95% CI 38.1-74.3]	36.7 [95% CI 20.0-55.2]	p=0.839	56.0 [95% CI 35.6-75.4]	52.0 [95% CI 31.8-71.9]	p=0.839
Proportion of patients with reduced Prevotella levels spp.(<10^11), %	60.0 [95% CI 41.4 - 77.2]	56.7 [95% CI 38.1-74.3]	p=0.458	44.0 [95% CI 24.6-64.4]	40.0 [95% CI 21.2 - 60.5]	p=0.541
Proportion of patients with reduced Acinetobacter levels spp.,(<10^6), %	23.3 [95% CI 9.7-40.6]	20.0 [95% CI 7.5-36.7]	p=0.003	16.0 [95% CI 4.1-33.6]	12.0 [95% CI 2.2-28.2]	p<0.001
Proportion of patients with reduced Roseburia content inulinivorans, (<10^10), %	56.7 [95% CI 38.1-74.3]	60.0 [95% CI 41.4-77.2]	p=0.458	92.0 [95% CI 77.6-99.4]	92.0 [95% CI 77.6-99.4]	p<0.001
Proportion of patients with reduced Faecalibacterium content prausnitzii, (<10^8), %	53.3 [95% CI 34.9-71.3]	56.7 [95% CI 38.1-74.3]	p=0.720	96.0 [95% CI 84.3-100.0]	96.0 [95% CI 84.3-100.0]	p<0.001
Proportion of patients with reduced Akkermansia content muciniphila,(<10^11),%	76.7 [95% CI 59.4-90.3]	76.7 [95% CI 59.4-90.3]	p=0.006	80.0 [95% CI 61.4-93.5]	80.0 [95% CI 61.4-93.5]	p=0.005

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Dynamics within groups

Group 1 (with intervention)

Patients receiving the intervention showed significant reductions in both SBP and DBP. Levels of IL-6 and IL-10 also decreased significantly.

The intervention resulted in marked shifts in the microbiome: F/B ratio decreased significantly, driven by a reduction in Firmicutes and an increase in Bacteroides; the proportion of patients with Lactobacillus deficiency decreased substantially.

Changes in Bifidobacterium, Prevotella, Roseburia, Faecalibacterium, and Akkermansia were not statistically significant.

Group 2 (no intervention)

Although SBP and DBP also decreased significantly, inflammatory markers IL-6 and IL-10 remained unchanged.

Microbiome changes were minimal. Statistically significant shifts in the F/B ratio and Firmicutes proportion were negligible in magnitude. Bacteroides levels remained stable.

No significant changes were observed in the proportions of patients with reduced Lactobacillus, Bifidobacterium, Prevotella, Roseburia, Faecalibacterium, or Akkermansia.

Table 3 shows comparative data between groups at the end of observation.

Between-group comparison at the end of follow-up

At the end of observation, blood pressure values remained significantly lower in group 1 compared with group 2, for both systolic and diastolic parameters (p<0.001 for both).

Group 1 also demonstrated a significantly lower IL-6 level (p<0.001), whereas IL-10 did not differ between groups.

Endothelial function, assessed by flow-mediated dilation (FMD), showed no significant differences between groups.

Marked distinctions were observed in the gut

Table 3. Comparative data of patient groups at the end of observation

Indicator	group 1(n=30)	group 2(n=25)	p
Systolic blood pressure, mm Hg.	123 [120-128]	131 [129-135]	p<0.001
Diastolic blood pressure, mm Hg.	81 [78-83]	84 [83-86]	p<0.001
Interleukin-6, pg /ml	1.815 [1.69-1.99]	2.06 [1.96-2.15]	p<0.001
Interleukin-10, pg /ml	3.632±1.535	4.162±1.442	p=0.196
Flow-mediated dilation (FMD) of the brachial artery before and after limb ischemia, %	10 [9-12]	11 [9-12]	p=0.255
F/B ratio	2.3 [1.8-2.8]	6.2 [5.6-7]	<0.001
Firmicutes spp, %	53.03±7.289	67.08±8.271	p<0.001
Bacteroides spp, %	22 [20-27]	11 [9-13.2]	p<0.001
Proportion of patients with reduced Lactobacillus content spp,(<10^7), %	13.3 [95% CI 3.5-28.3]	68.0 [95% CI 47.8-85.2]	p<0.001
Proportion of patients with reduced Bifidobacterium content spp,(<10^9), %	36.7 [95% CI 20.0-55.2]	52.0 [95% CI 31.8-71.8]	p=0.388
Proportion of patients with reduced Prevotella levels spp.(<10^11), %	68.0 [95% CI 47.8-85.2]	40.0 [95% CI 21.2 - 60.5]	p=0.341
Proportion of patients with reduced Acinetobacter levels spp.,(<10^6), %	20.0 [95% CI 7.5-36.7]	12.0 [95% CI 2.2-28.2]	p=0.662
Proportion of patients with reduced Akkermansia content muciniphila,(<10^11), %	76.7 [95% CI 59.4-90.3]	80.0 [95% CI 61.4-93.5]	p=0.976

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microbiome profile. Group 1 had a substantially lower F/B ratio and a lower relative abundance of Firmicutes, while the proportion of Bacteroides was significantly higher compared with group 2 (all p<0.001).

Among individual taxa, reduced Lactobacillus levels were considerably more common in group 2 than in group 1. Differences in the prevalence of reduced Bifidobacterium, Prevotella, Acinetobacter, and Akkermansia levels did not reach statistical significance.

Discussion

Summary of findings

The results of our study demonstrate that additional probiotic therapy combined with standard antihypertensive treatment significantly reduced systolic and diastolic blood pressure and decreased systemic inflammation. These effects were accompanied by normalization of the Firmicutes/Bacteroidetes ratio and an increase in Bacteroides spp. No significant changes were observed in endothelial function over the 3-month follow-up.

Interpretation and implications

The results support the role of gut microbiota in the pathophysiology of arterial hypertension via modulation of inflammation and metabolic pathways. The lack of endothelial improvement may reflect the short intervention period, as vascular remodeling often requires longer exposure. Baseline imbalance in Roseburia inulinivorans and Faecalibacterium prausnitzii limits interpretation of changes in these taxa.

Overall, the findings reinforce evidence that probiotic supplementation can enhance antihypertensive therapy, are consistent with data presented in previous publications, and highlight the gut microbiome as a potential therapeutic target [13-15].

The observed decrease in blood pressure aligns with prior clinical trials showing that probiotic supplementation can enhance the efficacy of standard antihypertensive therapy. The reduction in IL-6 and partial normalization of IL-10 levels are consistent with previous reports demonstrating anti-inflammatory effects of probiotics in patients with metabolic or cardiovascular disorders. Changes in the gut microbiome composition, including the Firmicutes/Bacteroidetes ratio and Bacteroides spp., also reflect patterns reported in earlier studies linking dysbiosis with hypertension [16-18]. Further studies with larger samples and longer follow-up are needed to confirm long-term vascular effects.

Conclusions

Dietaryprobioticsupplementationeffectively corrected gut dysbiosis supplementation in patients with AH in combination with standard antihypertensive therapy contributes to a more effective reduction in blood pressure. After 3 months of observation in the main group (group 1), a significant decrease in systolic (p<0.001) and diastolic (p<0.001) blood pressure was achieved, as well as a significant decrease in the level of proinflammatory cytokine IL-6 (p=0.014) compared to the comparison group (group 2), where no such changes were observed.

Probiotic supplementation effectively corrected intestinal dysbiosis in patients in the main group. This is confirmed by a statistically significant decrease in the Firmicutes/ Bacteroidetes ratio (p<0.001), a decrease in the proportion of Firmicutes (p<0.001) and an increase in the proportion of *Bacteroides* spp. (p<0.001). In addition, a significant decrease in the number of patients with reduced Lactobacillus content was noted. spp. (p=0.034).

The results obtained confirm a direct relationship between the state of the gut microbiome and the level of systemic inflammation in patients with AH. Probiotic supplementation can be considered as an effective adjunct to correct gut dysbiosis, which contributes to improved blood pressure control and reduced inflammation, which is important for improving the prognosis of the disease. At the same time, no significant difference in endothelial function indicators between the groups was found at the end of the study (p = 0.255).

Financing

This study did not receive external funding.

Conflict of interests

The author declares the absence of a conflict of interest.

AI Disclosure

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No AI tools were used in the preparation of this manuscript

Consent to publication

The authors received consent to publish this work from all patients. All authors have read and approved the final version of the manuscript.

Ethical approval

The research protocol received approval from institutional Bioethics Committee (protocol №167, dated 11.21.2022)

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Вплив пробіотичної суплементації на артеріальний тиск, системне запалення та ендотеліальну функцію у пацієнтів з есенціальною артеріальною гіпертензією

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Анотація: *Актуальність пошуку нових підходів до лікування есенціальної артеріальної гіпертензії обумовлена її зростаючою поширеністю та високим рівнем смертності, що спонукає до пошуку нових методів терапії. Останні наукові дані вказують на важливу роль дисбалансу кишкового мікробіому, який може призводити до порушення кишкового бар'єру та розвитку хронічного низькоінтенсивного системного запалення. Це запалення є ключовим механізмом у патогенезі артеріальної гіпертензії та викликає ендотеліальну дисфункцію, що підтверджується вищими рівнями прозапальних цитокінів. Цей взаємозв'язок відкриває нові перспективи для корекції кишкового дисбіозу як терапевтичної стратегії, що має потенціал для поліпшення контролю над захворюванням. Метою даного проспективного дослідження було оцінити вплив дієтичної суплементації пробіотиком на показники артеріального тиску, системного запалення та ендотеліальної функції у пацієнтів з есенціальною артеріальною гіпертензією через корекцію кишкового дисбіозу. У дослідженні взяли участь п'ятдесят п'ять пацієнтів, які були рандомізовані на дві групи: основну групу (30 осіб), яка додатково до стандартної антигіпертензивної терапії отримувала пробіотичний комплекс, що включав Saccharomyces boulardii та Lactobacillus, та групу порівняння (25 осіб), що отримувала лише стандартну терапію. Тривалість спостереження становила 3 місяці. Усім учасникам проводилося комплексне клінічне обстеження з аналізом систолічного та діастолічного артеріального тиску, рівнів інтерлейкіну-6 та інтерлейкіну-10, оцінкою ендотелій-залежної вазодилятації плечової артерії, а також аналізом складу кишкового мікробіому. Дослідження встановило, що до початку втручання групи були зіставні за основними клінічними та демографічними показниками, за винятком достовірної різниці у частці пацієнтів зі зниженим вмістом Roseburia inulinivorans та Faecalibacterium prausnitzii, що обмежувало пряме порівняння динаміки цих таксонів. Після 3 місяців спостереження у пацієнтів основної групи досягнуто значущого зниження систолічного і діастолічного артеріального тиску, а також рівня прозапального цитокіну інтерлейкіну-6, тоді як у групі порівняння рівні запальних маркерів суттєво не змінилися. Аналіз мікробіому показав, що пробіотична суплементація ефективно скоригувала кишковий дисбіоз, що підтверджується значним зниженням співвідношення Firmicutes та Bacteroidetes, зменшенням частки Firmicutes та зростанням частки Bacteroidetes*

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і Lactobacillus. Водночас, порівняльний аналіз не виявив статистично значущої різниці у показниках ендотеліальної функції між групами. Отримані результати підтверджують, що дієтична суплементація пробіотиком є ефективним допоміжним методом для корекції кишкового дисбіозу, що сприяє поліпшенню контролю артеріального тиску та зниженню системного запалення у пацієнтів з есенціальною артеріальною гіпертензією, що є важливим для покращення прогнозу перебігу захворювання.

Ключові слова артеріальний тиск, ендотеліальна функція, кишковий мікробіом, системне запалення

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Antibiotic therapy of community-acquired pneumonia in children of different age groups: outcomes of a multidisciplinary team approach (a retrospective analysis)

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Abstract: *Community-acquired pneumonia in children is a common infectious disease associated with a risk of severe complications. Optimisation of antimicrobial therapy is a key task, particularly with the involvement of a clinical pharmacist. The aim of this study was to evaluate the effectiveness of a multidisciplinary team, with a focus on the role of the clinical pharmacist in rationalising antimicrobial therapy for paediatric community-acquired pneumonia. A retrospective analysis of 90 cases of community-acquired pneumonia treatment in children was conducted at a clinic where a multidisciplinary team operates within the infection control unit. The analysis included the frequency of antibiotic prescriptions (considering the AWaRe classification), duration of therapy, and routes of administration of antimicrobials. Statistical analysis was performed using the χ^2 and t-test. The most frequently prescribed agents were cefotaxime (55.1%) and macrolides (24.4%). In the older age group, antibiotic combinations were more commonly used, which was associated with a significantly higher days of treatment burden ($p<0.005$). Reserve group antibiotics were not used. In 36.7% of cases, antibiotics were administered orally. The involvement of a multidisciplinary team, particularly a clinical pharmacist, contributes to improving the quality of antimicrobial therapy, minimising the unjustified use of broad-spectrum antibiotics, and ensuring adherence to the AWaRe principles and WHO recommendations.*

Keywords: Community-Acquired Pneumonia, Antimicrobial Stewardship, Pharmacists, Humans, Child.

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Introduction

The incidence of community-acquired pneumonia (CAP) remains high [1]. In children, CAP is one of the leading causes of mortality [2,3], particularly in those under 5 years of age [4], accounting for 20% of deaths in this group [5]. Approximately 14.5% of children with CAP require admission to the intensive care unit [6].

The most common pathogens of CAP in children are viruses; therefore, not every patient with non-severe CAP without risk factors requires antibiotic treatment. In such cases, a "watchful waiting" approach without antibiotics is recommended. This strategy helps to reduce adverse effects, treatment costs, and the spread of antimicrobial resistance [1]. However, a considerable proportion of pediatric CAP cases have a bacterial etiology, or bacterial superinfection may develop, in which case antibiotic therapy remains the cornerstone of etiological treatment.

It is well established that *S. pneumoniae*, the leading causative agent of CAP [7], is also the major contributor to years of life lost associated with or driven by antimicrobial resistance [8]. Therefore, timely and adequate antibacterial therapy in children with CAP is of utmost importance. On the other hand, aggressive antibiotic therapy may cause adverse reactions and carries the risk of promoting antimicrobial resistance.

To optimise antimicrobial therapy in healthcare facilities, infection control units are established, within which multidisciplinary teams operate. According to the Order of the Ministry of Health of Ukraine No. 1614 dated August 2, 2021, these teams must include a clinical pharmacist, who serves as the coordinator of the antimicrobial stewardship program [9]. The role of the clinical pharmacist in antimicrobial management has been widely discussed [10,11]. Pharmacist recommendations have been shown to reduce the duration of antimicrobial therapy for pneumonia [12–14]. Pharmacist involvement has also contributed to reducing the use of broad-spectrum antimicrobials [15]. Antimicrobial stewardship in the management of children with CAP includes educational programs, monitoring and reporting of antibiotic use and resistance, periodic audits with feedback, and pre-authorization procedures [16].

Aim

The aim of the research was to assess the impact of a multidisciplinary team (paediatricians, paediatric infectious disease specialists, and clinical pharmacists) on optimising antimicrobial therapy for paediatric community-acquired pneumonia.

Materials and Methods

The study was conducted at the Non-Commercial Enterprise "Kyiv City Children's Clinical Hospital No. 2," where in 2022 an infection control unit was established and local treatment protocols for infectious diseases were developed, including a local protocol for the management of community-acquired pneumonia in accordance with the clinical guideline "Community-acquired pneumonia in children" [17], WHO recommendations [18], and the national standard of care "Rational use of antibacterial and antifungal medicines for therapeutic and prophylactic purposes" [19].

A retrospective analysis was conducted on the use of antimicrobial agents in children with CAP who received inpatient treatment between January 1, 2025, and March 31, 2025. In total, 90 children (46 girls and 44 boys) aged 7 months to 17 years (mean age 8.36 ± 5.15 years) were treated for community-acquired pneumonia. Among them, 33 children were under 5 years of age (18 girls and 15 boys), and 57 were older than 5 years (28 girls and 29 boys).

Table 1. Demographic characteristics of the study population by age and sex

Age of children	Girls	Boys	Overall
≤5 years	18	15	33
>5 years	28	29	57
Total	46	44	90

Statistical analysis was performed using Microsoft Excel 365. Quantitative variables were described using the mean (M) and standard deviation (SD). The χ^2 (chi-square) test was used to compare frequencies, and the Student's

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t-test was applied to assess the significance of differences between mean values. Differences were considered statistically significant at $p < 0.05$. To evaluate antimicrobial burden, the days of therapy (DOT) metric was used.

Results

In total, 127 antimicrobial prescriptions were made for 90 patients. Most frequently (Fig. 1), children were empirically prescribed the third-generation intravenous cephalosporin cefotaxime (55.1%), often in combination with oral macrolides, clarithromycin (16.5%) or azithromycin (7.9%). Aminopenicillins, mostly in combination with β-lactamase inhibitors, were used less frequently (ampicillin/sulbactam in 7.9%, amoxicillin/clavulanate in 5.5%, and amoxicillin in 3.9%). Only three children (2.4%) older than 8 years received doxycycline, and one infant (0.8%) received cefpodoxime.

Combination therapy (two antimicrobial agents, mostly cefotaxime with clarithromycin, azithromycin, or doxycycline) was observed in 27 patients (47.4%) in the older age group and 5 patients (15.1%) in the younger age group, with the difference being statistically significant ($p < 0.005$). Consequently, antimicrobial burden, measured as days of therapy (DOT), was significantly higher in older children (10.44 ± 4.56 days vs. 8.03 ± 3.23 days; $p < 0.005$).

According to the data presented in Table 2, younger children more frequently received ampicillin/sulbactam (19.5% vs. 2.3%; $p < 0.05$), whereas older children were significantly more often prescribed cefotaxime (61.6% vs. 41.5%; $p < 0.05$). Azithromycin and doxycycline were prescribed exclusively to older children.

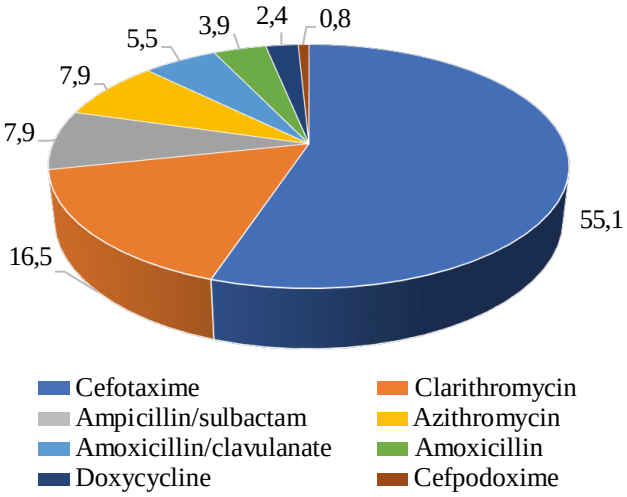

Figure 1. Proportion of antimicrobial agents prescribed to children with community-acquired pneumonia

Table 3 shows the features of the use of antimicrobial agents according to the AWaRe classification. No drugs from the Reserve group were used at all.

In older children, Watch group antibiotics were predominantly used (90.7%), whereas in younger children, Access group antibiotics (both protected and unprotected aminopenicillins) were used in 41.5% of cases, with the difference being statistically significant ($p < 0.001$).

Table 2. Use of antimicrobial agents in children of different age groups

Antimicrobial agent	Age of children					
	≤5 years		>5 years		Overall	
	Abs.	%	Abs.	%	Abs.	%
Amoxicillin	4	9.8	1	1.2	5	3.9
Amoxicillin/clavulanate	5	12.2	2	2.3	7	5.5
Ampicillin/sulbactam	8	19.5*	2	2.3	10	7.9
Doxycycline	0	0.0	3	3.5	3	2.4
Azithromycin	0	0.0	10	11.6	10	7.9
Clarithromycin	6	14.6	15	17.5	21	16.5
Cefotaxime	17	41.5	53	61.6*	70	55.1
Cefpodoxime	1	2.4	0	0.0	1	0.8
Total	**41**	**100.0**	**86**	**100.0**	**127**	**100.0**

An asterisk (*) indicates a significant difference ($p<0.05$)

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Table 3. Use of antimicrobial agents in children of different age groups according to the AWaRe classification

Groups of antimicrobial agents according to AWaRe classification	Age of children					
	≤5 years		>5 years		Overall	
	Abs.	%	Abs.	%	Abs.	%
Access group	17	41.5*	8	9.3	25	19.7
Watch group	24	58.5	78	90.7*	102	80.3
Reserve group	0	0.0	0	0.0	0	0.0
Total	**41**	**100.0**	**86**	**100.0**	**127**	**100.0**

An asterisk (*) indicates a significant difference ($p<0.05$)

Table 4. Route of administration of antimicrobial agents in children of different age groups

Route of administration of antimicrobial agents	Age of children					
	≤5 years		>5 years		Overall	
	Abs.	%	Abs.	%	Abs.	%
Parenteral	163	61.5	381	64.0	544	63.3
Oral	102	38.5	214	36.0	316	36.7
Total	**265**	**100.0**	**595**	**100.0**	**860**	**100.0**

No significant differences were observed in the route of administration of antimicrobial agents between age groups. In two-thirds of cases, drugs were administered intravenously, while in the remaining cases they were given orally.

The duration of antimicrobial therapy for community-acquired pneumonia in older patients was on average 6.89 ± 1.74 days, and in younger patients 6.58 ± 1.57 days.

Thus, the presence of a multidisciplinary team in the clinic contributed to the fact that, according to our 3-month retrospective audit, Reserve group antimicrobials were not used in the treatment of children with CAP.

Beta-lactam antibiotics of third-generation cephalosporins, protected and unprotected aminopenicillins were predominantly used, consistent with the main causative pathogen (*S. pneumoniae*). In cases with suspected atypical pneumonia (mainly in older children), macrolides (clarithromycin or azithromycin) or the tetracycline antibiotic doxycycline were prescribed in combination with beta-lactams.

Discussion

The results of other researchers indicate that mycoplasma pneumonia is detected in 7.4% of children with CAP, more frequently in older children with a mean age of 8.8 years [20]. It should be noted that macrolide resistance of *Mycoplasma* remains high. However, *M. pneumoniae* still demonstrates good *in vitro* susceptibility to second-line antibiotics such as tetracyclines, which makes them an effective treatment option for patients with initial treatment failure when macrolides are used [21].

The low consumption of Access group antibiotics in Ukraine is a widespread problem [22]. The activities of a multidisciplinary team help overcome barriers in physicians' acceptance of pharmacists' recommendations for optimising antimicrobial therapy, particularly in minimising the use of Reserve group antibiotics [23].

The success of therapy in children with community-acquired pneumonia, along with the minimal antimicrobial burden that reduces the risks of adverse drug reactions, drug-drug interactions, and the development of antibiotic resistance, was largely ensured by the activities of the multidisciplinary team. In particular, the clinical pharmacist was involved in the development of local protocols, the pre-authorization procedure, and the monitoring of antimicrobial prescriptions. According to other

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researchers, pharmacist-initiated interventions contributed to reducing antimicrobial use and preventing adverse drug reactions, with a relatively high level of physician acceptance [24]. The pharmacist participates in antibiotic selection and proposes dosing regimens for paediatric pneumonia [25,26]. Other studies indicate that clinicians generally respond positively to pharmacists' recommendations for CAP treatment, especially regarding the switch from intravenous to oral antibiotic administration, while being less receptive to restrictions on antibiotic use [27]. Evidence also shows that caregivers of children with pneumonia accept pharmacists' recommendations for optimising antimicrobial therapy [10]. Prolonged antimicrobial treatment remains a common practice [28]. This retrospective analysis has several limitations, namely a relatively small sample size and the absence of an assessment of the effectiveness of such antimicrobial stewardship interventions, specifically, a prospective audit with feedback. Future research should focus on evaluating the impact of prospective pharmaceutical consultations on the duration of antimicrobial therapy, the number of days of antibiotic use, and related outcomes.

Conclusions

The analysis of medical records conducted within this retrospective study demonstrated the effectiveness of a multidisciplinary team, including a clinical pharmacist, in the management of children with community-acquired pneumonia. All patients received antimicrobial therapy in accordance with current standards; reserve group antibiotics were not used; therapy was not associated with dose-dependent adverse effects; the average duration of antimicrobial treatment was approximately 7 days; and in one-third of cases, antibiotics were administered orally. These findings highlight the important role of the clinical pharmacist in rationalising antibiotic therapy and improving the quality of medical care for children with CAP.

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Conflict of interests

This publication does not cause any conflict between the authors, has not been and will not be the subject of commercial interest or remuneration in any form.

AI Disclosure

The authors used ChatGPT for language editing of the English text. The authors reviewed and verified all AI-generated content to ensure accuracy and integrity.

Consent to publication

All authors have read the text of the article and gave consent to its publication.

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Антибіотикотерапія негоспітальної пневмонії у дітей різних вікових груп: результати діяльності мультидисциплінарної команди (ретроспективний аналіз)

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Анотація: *негоспітальна пневмонія у дітей є поширеним інфекційним захворюванням із ризиком розвитку тяжких ускладнень. Оптимізація антимікробної терапії є ключовим завданням, зокрема із залученням клінічного фармацевта. Метою цього дослідження було оцінити ефективність роботи мультидисциплінарної команди, зокрема участь клінічного фармацевта, у раціоналізації антимікробної терапії негоспітальної пневмонії у дітей. У дослідженні проведено ретроспективний аналіз 90 випадків лікування негоспітальної пневмонії у дітей у клініці, в якій функціонує мультидисциплінарна команда на базі відділення інфекційного контролю. Аналізували частоту призначень антибіотиків, в т.ч. із урахуванням класифікації AWaRe, тривалість терапії, шляхи введення антимікробних препаратів. Статистичну обробку здійснено з використанням χ^2 та t-критерію. Найчастіше призначались цефотаксим (55,1%) та макроліди (24,4%). У старшій віковій групі частіше застосовували комбінації антибіотиків, що супроводжувалось достовірно вищим навантаженням кількості днів терапії ($p<0,005$). Препарати групи резерву не використовувались. У 36,7% випадків антибіотики призначались перорально. Участь мультидисциплінарної команди, зокрема клінічного фармацевта, сприяє підвищенню якості антимікробної терапії, мінімізації необґрунтованого використання антибіотиків широкого спектра, дотриманню принципів AWaRe та рекомендацій ВООЗ.*

Ключові слова: негоспітальна пневмонія, адміністрування антимікробних препаратів, фармацевти, люди, дитина

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Клінічний випадок туберкульозного менінгоенцефаліту у дитини

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Анотація: *Туберкульозний менінгоенцефаліт залишається актуальною медико-соціальною проблемою через високу смертність, складність діагностики, та зростання числа випадків серед дітей. Мета дослідження: Підвищити обізнаність та настороженість медичних працівників щодо можливості виникнення туберкульозного менінгоенцефаліту у дітей на основі демонстрації клінічного випадку. Матеріали і методи. Ми провели емпіричне, описове дослідження клінічного випадку захворювання на туберкульозний менінгоенцефаліту у дитини 1,5 років в період проходження стаціонарного лікування в Київській міській дитячій клінічній інфекційній лікарні (КНП «КМДКІЛ») міста Києва. Дослідження виконано відповідно до принципів Гельсінської декларації. Протокол дослідження ухвалено біоетичною комісією лікарні (протокол №3 від 24.09.2025р). Результати та їх обговорення: Дитина 1,5 років, надійшла до стаціонару на 7-й день хвороби зі скаргами на підвищення температури до 38,5°С, в'ялість, нудоту. При огляді дитини рубчик БЦЖ був відсутній. На 3-й день стаціонарного лікування стан з негативною динамікою. Спостерігались лихоманка, виражена в'ялість, повторна блювота. Дитина не ходить, не сидить, обмежені руки в лівих кінцівках. На рентгенограмі ОГК виявлено лівобічну пневмонію. Стан дитини в динаміці погіршувався. За даними огляду, лабораторних та інструментальних обстежень діагностовано менінгоенцефаліт, набряк головного мозку, кому, судомний синдром, лівобічний геміпарез, двобічне ураження легень. На МРТ виявлені ознаки енцефаліту в базальних ядрах, коліні мозолистого тіла та медіальних відділах правої скроневої долі. Методом ПЛР (молекулярно-генетичним тестом GeneXpert MTB/RIF) з ліквору виділені Mycobacterium tuberculosis GeneXpert MTB + RIF – . Встановлено діагноз: туберкульоз нервової системи, менінгоенцефаліт. Об'єктивний стан при надходженні до ВАІТ вкрай тяжкий за рахунок неврологічної симптоматики на фоні специфічного ураження ЦНС, проявів набряку головного мозку, інтоксикаційного синдрому. Загальний стан дитини стрімко погіршувався. Парез кишківника, анурія без відповіді на діуретики, анемія та тромбоцитопенія, декомпенсований метаболічний ацидоз- корегується, ДВЗ-синдром. Свідомість - кома ІІІ ст. За шкалою FOUR = 0б. Дифузна м'язова гіпотонія, арефлексія. Зіниці розширені D=S, фотореакція відсутня. Температура тіла 35,6^0 С. Виражені периферичні набряки. АТ 71/30 мм.рт.ст. ЧСС 94уд/хв. Тони серця приглушені. Не зважаючи на проведене лікування, випадок завершився летально. Висновки. Настороженість щодо можливості виникнення туберкульозного менінгоенцефаліту у дітей має важливе значення в діагностиці інфекційних хвороб.*

Ключові слова: туберкульозний менінгоенцефаліт, діагностика, діти.

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Вступ

Туберкульоз (ТБ) залишається однією з головних інфекційних проблем охорони здоров'я у світі. За даними Всесвітньої організації охорони здоров'я (ВООЗ), у 2022 році більше 10 мільйонів людей захворіли на активний туберкульоз, що відповідає рівню захворюваності близько 133 випадків на 100 000 населення з особливою концентрацією випадків у регіонах Південно-Східної Азії, Африки та Тихоокеанського регіону [1-3]. Крім того, надзвичайно поширеною є латентна інфекція, за даними літератури, реєструється близько у 1/4 населення світу [4].

В Україні туберкульоз також є нагальною медичною та соціальною проблемою. За даними Міністерства охорони здоров'я України (МОЗ) 2023 році зареєстровано 19 851 випадок активного туберкульозу, з них 639 серед дітей до 14 років та 196 серед підлітків 15–17 років [5].

В динаміці рівень захворюваності на ТБ знизився порівняно з попередніми роками — наприклад, за період з 2018 по 2022 роки — але водночас спостерігаються й тривожні тенденції: у 2021 році серед дітей до 14 років зафіксовано зростання захворюваності на приблизно 25,4 % у порівнянні з 2020 роком [6].

ТБ може проявлятися не лише у вигляді первинного легеневого ураження, але також викликає численні позалегеневі ускладнення. Серед найбільш значущих -дисемінований туберкульоз (наприклад, міліарний ТБ), ураження кісток, суглобів, нирок, лімфатичних вузлів, мозку, перикарда, статевих органів тощо, залежно від локалізації інфекції, що може призвести до хронічних запалень, функціональних порушень, інвалідизації [7,8]. Можливий розвиток лікарської стійкості (мультирезистентних, полірезистентних форми), що значно ускладнює лікування та погіршує прогноз [9].

Туберкульозний менінгіт (часто з залученням енцефаліту або менінгоенцефаліту) — одна з найважчих форм позалегеневого туберкульозу, особливо у дітей. Вона характеризуэться інфікуванням мозкових оболонок мікобактерією з розвитком серозного менінгіту та ураженням основи головного мозку.

За даними літератури, найвищий ризик розвитку туберкульозного менінгіту у дітей віком до 4 років. В 2019 році близько 24 000 дітей віком до 15 років у світі захворіли на туберкульозний менінгіт, з них більшість — діти молодше 5 років [10]. Смертність серед дітей становить близько 19 %, а серед тих, хто вижив неврологічні наслідки розвиваються у більш ніж 50 % випадків [11].

Мета

Підвищити обізнаність та настороженість медичних працівників щодо можливості виникнення туберкульозного менінгоенцефаліту у дітей на основі демонстрації клінічного випадку.

Матеріали і методи

Ми провели емпіричне, описове дослідження клінічного випадку захворювання на туберкульозний менінгоенцефаліту у дитини 1,5 років в період проходження стаціонарного лікування в Київській міській дитячій клінічній інфекційній лікарні (КНП «КМДКІЛ») міста Києва. Дослідження виконано відповідно до принципів Гельсінської декларації. Протокол дослідження ухвалено біоетичною комісією лікарні (протокол №3 від 24.09.2025р). Батьками була надана інформована згода.

Опис випадку

Дитина 1,5 років, надійшла до стаціонару на 7-й день хвороби зі скаргами на підвищення температури до 38,5°С, в'ялість, нудоту.

З анамнезу життя відомо, що дитина від 8 вагітності, 8 пологів, вага при народженні 2кг. Зі слів батьків, в пологовому будинку отримала щеплення БЦЖ, проте при огляді дитини рубчик БЦЖ був відсутній. Хворіла на ГРВІ, бронхіти. Проживає з батьками та іншими дітьми в підвальному приміщенні.

Зі слів батьків захворіла, коли вперше підвищилась температура тіла, епізодично виникало блювання. Дитина була оглянута лікарем ЕМД, стан був оцінений як прорізування зубів, призначено симптоматичне лікування. Через 4 дні спостерігалось зниження рухової активності, дитина не ставала на ніжки, перестала сидіти та втратила раніше набуті навички, відмічалось зниження тонусу в кінцівках. На 7-й день хвороби госпіталізована в дитячу лікарню м. Києва в стані середньої

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тяжкості. Діагноз при надходженні ГРВІ, ацетонемічний синдром.

На 3-й день стаціонарного лікування стан з негативною динамікою. Спостерігались лихоманка, виражена в'ялість, повторна блювота. Дитина не ходить, не сидить, обмежені руки в лівих кінцівках. Була проведена рентгенографія органів грудної клітки (ОГК). Результат наведений на рисунку 1.

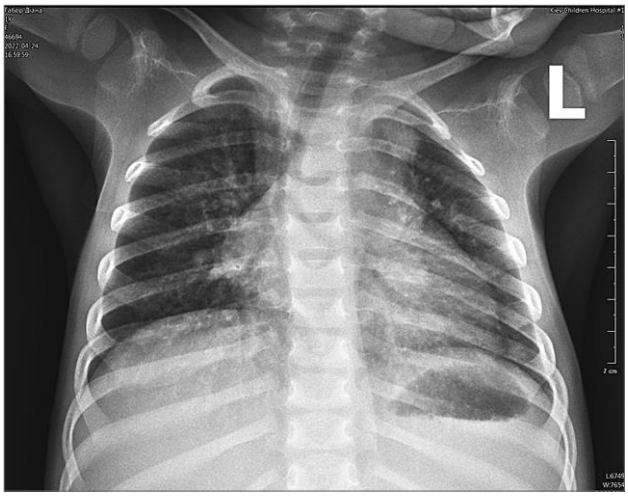

Рисунок 1. Клінічний випадок.
Рентгенограма ОГК у дитини 1,5 років

В задньо-передній проекції відмічаються фокуси інфільтрації в проекції верхівки та навколо кореня лівої легені (рис.1). Легеневий малюнок помірно посилений. Корені частково перекриті тінню середостіння. Контури серця, діафрагми чіткі. Синуси вільні. Заключення: Лівобічна пневмонія. Рентен-контроль після антибактеріальної терапії. При відсутності динаміки - дообстеження для виключення специфічного процесу.

Дитина була оглянута неврологом, спеціаліст відзначив ознаки лівобічного геміпарезу з загальною симптоматикою, що потребує диференціації з гострим порушенням мозкового кровообігу, перебігом нейроінфекції. Рекомендовано провести МРТ головного мозку та консультація нейрохірурга.

Того ж дня проведено МРТ. За результатом є ознаки енцефаліту в базальних ядрах, коліні мозолистого тіла, медіальних відділах правої скроневої долі, під питанням ділянки гострої ішемії; ознаки локального лептоменінгіту, вентрикулоділятація.

Нейрохірург припустив наявність енцефаліту та призначив люмбальну пункцію. За результатами дослідження спинномозкової рідини (СМР): цитоз 156 в 1 мкл, переважно за рахунок нейтрофілів, білок 0,35 г/л. Заключення: у дитини має місце нейроінфекція - менінгоенцефаліт.

Враховуючи аналіз СМР, проведена корекція антибактеріальної терапії, призначений цефтріаксон та ванкоміцин, противірусна терапія ацикловіром до отримання результатів вірусологічного дослідження.

В динаміці спостереження стан дитини з негативною динамікою, продовжує лихоманити, не реагує на огляд, погляд не фіксує, відмічається косоокість, посмикування лівими кінцівками, позитивні менінгеальні симптоми, спостерігаються тонічні судомні напади. За Шкалою ком Глазго 11 балів. Повторна люмбальна пункція-цитоз 176 х 10х6/л (N-58%,L-42%),білок -0,63г/л, цукор 2,06 ммоль/л.

Отримані негативні результати вірусологічного дослідження СМР на HSV 1½, CMV, EBV, ентеровіруси. Ацикловір відмінено.

Через два дні проведений консиліум, враховуючи соціальний статус родини, перебіг клінічного процесу з боку ЦНС та легень (кома Іст, тонічні судоми, відсутність достовірних даних за БЦЖ у дитини, доцільно провести сімейну діагностику на збудника туберкульозу. Заключення консиліуму: Нейроінфекція. Менінгоенцефаліт. Набряк головного мозку. Кома Іст. Судомний синдром. Лівобічний геміпарез. Двобічне ураження легень.

За результатом люмбальної пункції: ліквор прозорий, частими краплями. Методом ПЛР (молекулярно-генетичним тестом GeneXpert MTB/RIF з ліквору виділена Mycobacterium tuberculosis GeneXpert MTB + RIF –.

Встановлений діагноз: Туберкульоз нервової системи. Менінгоенцефаліт (G05.0). Набряк головного мозку. Кома I ст. Судомний синдром. Лівобічний геміпарез. Двобічне ураження легень.

Для подальшого лікування дитина була переведена в ВАІТ КНП "КМДКІЛ" у вкрай тяжкому стані зі скаргами, зі слів батьків, на

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порушення свідомості, підвищення температури тіла та судоми.

Об'єктивний стан при надходженні до ВАІТ: Загальний стан вкрай тяжкий за рахунок неврологічної симптоматики на фоні специфічного ураження ЦНС, проявів набряку головного мозку, інтоксикаційного синдрому. Свідомість - кома 1 ст. За ШКГ (Е2V3М4) = 9б. Положення пасивне, реагує на больові подразники. Дифузна м'язова гіпотонія. Менінгеальні симптоми виражені. Дитина фебрильно лихоманить. Обличчя симетричне. Зіниці звужені D=S, фотореакція збережена. Судом на момент огляду немає. Годується через назогастральний зонд. Т 38,0 С. Дихання самостійне, ЧД 34 уд/хв, SpO_2 99%. Аускультативно: дихання проводиться у всі відділи легень, дещо ослаблене зліва в нижніх та середніх відділах, хрипи не вислуховуються. ЧСС 170/ хв , тони серця ритмічні. АТ 128/76 мм.рт.ст. Гепатоспленомегалія (печінка +2,5 см, селезінка +1см). Лімфоаденопатія.

Консультація дитячого невролога: Стан вкрай важкий за рахунок загальномозкової симптоматики. ЧМН: очі при нахилі голови в крайніх відведеннях, що викликано симптомом "ляльковых очей"(відхилення ока в протилежному напрямку у відповідь на повороти голови). Зіниці - мідріаз, фотореакція відсутня, рогівковий рефлекс відсутній з обох сторін. Периостальні та сухожилкові рефлекси відсутні. Черевні, підошовні відсутні - арефлексія. М'язовий тонус - виражена м'язова гіпотонія. Шкіра холодна на дотик. Температура тіла 35,9°С; Діагноз: Кома ІІІ ст. Туберкульозний менінгоенцефаліт. Множинні вогнищеві ураження кори та підкіркових структур обох гемісфер. Набряк головного мозку. Судомний синдром.

На 3-й день перебування у ВАІТ незважаючи на адекватну терапію, стан прогресивно погіршувався за рахунок патологічної неврологічної симптоматики на фоні множинних вогнищевих уражень ураження кори та підкіркових структур обох гемісфер туберкульозної етіології, пізніше за рахунок приєднання та прогресування синдрому поліорганної недостатності.

Загальний стан дитини критичний, з негативною динамікою. Парез кишківника, анурія без відповіді на діуретики, анемія та тромбоцитопенія, декомпенсований метаболічний ацидоз- корегується, ДВЗ-синдром. Свідомість - кома ІІІ ст. За шкалою FOUR = 0б. Дифузна м'язова гіпотонія, арефлексія. Зіниці розширені D = S, фотореакція відсутня. Температура тіла 35,6^0 С. Виражені периферичні набряки. АТ 71/30 мм.рт.ст. ЧСС 94 уд/ хв. Тони серця приглушені.

О 23:00 асистолія, розпочаті реанімаційні заходи, в 23:45 зафіксовано біологічну смерть.

Лікування включало проведення оксигенотерапії, ШВЛ, медикаментозну седацію, антибіотикотерапію, протигрибкові засоби, глюкокортикостероїди, симпатоміметичну, протисудомну, імунокорегуючу (імуноглобулін людини нормальний), орієнтовану інфузійну, замісну, ситуаційну та посиндромну терапії. Специфічне лікування проводилось відповідно до Наказ МОЗ України від 19.01.2023 р. №102 «Про затвердження стандартів медичної допомоги «Туберкульоз» [12].

Діагноз заключний клінічний:

Основний: А17.0 - Туберкульозний менінгоенцефаліт. Ускладнення:Сепсис. Септичний шок. СПОН: ДН ІІІ ст; НК ІІІ ст; гостра ниркова недостатність; ДВЗ – синдром; Парез кишківника; кома ІІІ ст; набряк головного мозку. Судомний синдром. Анемія. Тромбоцитопенія.

Діагноз патологоанатомічний:

Попередній: Туберкульозний менінгоенцефаліт. Множинне вогнищеве ураження кори та підкоркових структур обох гемісфер головного мозку. Ускладнення основного: Набряк- набухання головного мозку. Асцит. Гідроторакс. Парез кишківника. Ішемія ниркової кори. Причина смерті: Поліорганна недостатність, ураження підкіркових структур головного мозку, туберкульозний менінгоенцефаліт.

Обговорення

Робота присвячена демонстрації летального клінічного випадку туберкульозного менінгоенцефаліту у дитини 1,5 років, що вказує на тяжкість ранньої діагностики та підкреслює потребу в мультидисциплінарному підході.

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Наша робота співвідноситься з дослідженням Colosimo M та співавторів (2022), які представили летальний випадок туберкульозного менінгіту у дитини 2 років, яка не мала БЦЖ та проживала в незадовільних економічних та соціальних умовах [13]. Клінічна картина та результати лабораторних обстежень описаного нами пацієнта здебільшого корелювали з результатами описаного випадку італійськими вченими, хоча описана авторами дитина не мала жодних легеневих проявів. Відкладена постановка остаточного діагнозу була вирішальною в обох клінічних випадках, у зв'язку з чим невідкладний початок лікування не дав позитивних результатів.

Sharifi, G та співавтори (2024) представили випадок успішного лікування туберкульозного менінгіту у 11-місячного пацієнта. Дитина була госпіталізована з приводу прогресуючої слабкості кінцівок та втрати раніше здобутих рухових навичок. Попередньо пацієнту діагностували гідроцефалію через можливий гострий бактеріальний менінгіт на КТ та МРТ. При фізикальному огляді спостерігалося випинання тім'ячка, ригідність м'язів шиї, параліч VI пари черепних нервів та спастичний квадрипарез. Аналіз спинномозкової рідини та ПЛР підтвердили туберкульозний менінгіт. Через 5-6 днів після початку прийому протитуберкульозних препаратів було відзначено зниження температури, а через гідроцефалію було встановлено вентрикулоперитонеальний шунт. Поступово тонус тулуба та кінцівок, а також рухова функція та емоційна реакція покращилися. В 15-місячному віці після проведених маніпуляцій пацієнт може ходити без сторонньої допомоги, а гідроцефалія при контрольних дослідженнях не спостерігається [14].

Пізня діагностика може призвести до дуже серйозних наслідків, включаючи підвищений ризик смерті, неврологічні ускладнення або довгострокові наслідки. Ключовим компонентом в покращенні стану пацієнтів з ТБ є своєчасний початок специфічного лікування, проте це потребує підвищення обізнаності та прискорення призначення та виконання діагностичних методів, особливо в районах з високою поширеністю захворювання та у пацієнтів з підозрілою клінічною картиною [15].

Висновки

Настороженість щодо можливості виникнення туберкульозного менінгоенцефаліту має важливе значення в діагностиці інфекційних хвороб у дітей. Динамічне спостереження, мультидисциплінарний підхід та застосування широкого спектру лабораторно-інструментальних та лікувальних засобів може бути корисним в своєчасному наданні допомоги та уникненні діагностичних помилок.

Фінансування

Дане дослідження не отримало зовнішнього фінансування.

Конфлікт інтересів

Автори засвідчують відсутність конфлікту інтересів.

Згода на публікацію

Батьки надали згоду на використання результатів обстеження та публікацію. Всі автори ознайомлені з текстом рукопису та надали згоду на його публікацію.

Використання ШІ:

Під час підготовки цього рукопису ШІ-інструменти не використовувалися.

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Clinical case of tuberculous meningoencephalitis in a child

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Abstract: *Tuberculous meningoencephalitis remains an urgent medical and social problem due to high mortality, dificulty in diagnosis, and an increase in the number of cases among children. Aim of the study was to increase awareness and alertness of medical workers regarding the possibility of tuberculous meningoencephalitis in children based on the demonstration of a clinical case. Materials and methods. We conducted an empirical, descriptive study of a clinical case of tuberculous meningoencephalitis in a 1.5-year-old child during inpatient treatment at the Kyiv City Children's*

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Clinical Infectious Diseases Hospital. The study was performed in accordance with the principles of the Declaration of Helsinki. The study protocol was approved by the hospital's bioethical committee (protocol №3 dated 24.09.2025). Results and their discussion: A 1.5-year-old child was admitted to the hospital on the 7th day of illness with complaints of fever up to 38.5°C, lethargy, and nausea. When examining the child, the BCG scar was absent. On the 3rd day of inpatient treatment, the condition showed negative dynamics. Fever, severe lethargy, repeated vomiting were observed. The child does not walk, does not sit, and the hands in the left limbs are limited. Left-sided pneumonia was detected on the X-ray. The child's condition deteriorated in dynamics. According to the examination, laboratory and instrumental examinations, meningoencephalitis, cerebral edema, coma, convulsive syndrome, left-sided hemiparesis, bilateral lung damage were diagnosed. MRI revealed signs of encephalitis in the basal nuclei, the knee of the corpus callosum and the medial parts of the right temporal lobe. Mycobacterium tuberculosis (G+R-) was isolated from the cerebrospinal fluid by PCR, and a diagnosis of nervous system tuberculosis and meningoencephalitis was established. The objective condition upon admission to the intensive care unit is extremely severe due to neurological symptoms on the background of specific CNS damage, manifestations of cerebral edema, intoxication syndrome. The child's general condition rapidly deteriorated. Intestinal paresis, anuria without response to diuretics, anemia and thrombocytopenia, decompensated metabolic acidosis - corrected, DIC syndrome. Consciousness - coma of the III degree. On the FOUR scale = 0b. Diffuse muscular hypotension, areflexia. Pupils are dilated D = S, no photoreaction. Body temperature 35,6° C. Severe peripheral edema. Blood pressure 71/30 mm Hg. Heart rate 94 beats / min. Heart sounds are muffied. Despite the treatment, the case ended fatally. Conclusions. Vigilance regarding the possibility of tuberculous meningoencephalitis in children is important in the diagnosis of infectious diseases.

Keywords: Children, Tuberculous Meningoencephalitis, Tuberculosis, BCG, Pneumonia, Diagnostics.

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Гігієнічна оцінка ризику для людини при вживанні овочів контамінованих фунгіцидами на основі дифеноконазолу

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Анотація: *Одним із ключових напрямків підвищення врожайності сільськогосподарських культур є використання хімічних засобів захисту рослин, зокрема пестицидів. Враховуючи зростання їх застосування через інтенсивні технології вирощування, дослідження стійкості пестицидів у сільськогосподарських культурах має велике значення для збереження якості та безпеки продукції. Неконтрольоване використання пестицидів, може негативно впливати на здоров'я, зокрема при їх застосуванні для обробки сільськогосподарської продукції. Метою нашої роботи була гігієнічна оцінка ризику для людини при споживанні овочів, контамінованих фунгіцидом на основі дифеноконазолу. Матеріали та методи дослідження включали визначення вмісту сполуки хімічного класу триазолів – дифеноконазолу в овочевих культурах (томатах, огірках, моркві, картоплі, капусті) в різних ґрунтово-кліматичних зонах України. Оцінено стійкість фунгіциду в різних овочевих культурах, розраховано показники його періоду напівруйнування (τ_{50}) та майже повного руйнування (τ_{95}). Оцінка небезпечності пестицидів здійснювалася за інтегральним показником небезпечності при вживанні контамінованих пестицидами продуктів, класифікованим за чотирма класами від малонебезпечних до надзвичайно небезпечних. Статистична обробка результатів проводилася з використанням програмних пакетів MedStat v.5.2 (Copyright © 2003-2019), Microsoft® Excel® для Microsoft 365 MSO (версія 2305, збірка 16.0.16501.20074) та Python 3.11. τ_{50} дифеноконазолу в досліджуваних сільськогосподарських культурах в загальному складав 9,51±0,67 доби. Необхідно зазначити, що τ_{50} був достовірно найменшим в картоплі 5,9±0,55 діб (95% ДІ 4,5-7,31), порівняно із іншими овочевими культурами. Порівняння отриманих результатів з літературними даними з інших країн показало, що періоди напіврозпаду дифеноконазолу в овочевих культурах є співставними і знаходяться в допустимих інтервалах. Розраховані параметри стійкості (τ_{50}) дали змогу віднести дифеноконазол до ІІІ класу небезпечності в усіх досліджуваних культурах (ДСанПіН 8.8.1.002-98). При оцінці інтегрального показника небезпечності при вживанні продуктів (ІПНВП) дифеноконазолу на організм людини було встановлено, що при вживанні контамінованої сільськогосподарської продукції досліджуваний фунгіцид належав до 3 класу небезпечності. Отримані результати повинні бути враховані при розгляді можливості розширення використання фунгіцидів на основі дифеноконазолу для забезпечення безпеки людини та ефективності застосування на різних рослинах.*

Ключові слова: сільськогосподарські культури, забруднення навколишнього середовища, залишки пестицидів, пестициди, санітарні обстеження, напівруйнування.

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Вступ

Одним із ключових напрямків підвищення врожайності сільськогосподарських культур, а також збереження якості та кількості продукції є використання хімічних засобів захисту рослин. Застосування пестицидів щороку значно зростає через активне впровадження інтенсивних технологій вирощування сільськогосподарських культур [1,2]. Попри певні недоліки, цей метод залишатиметься найбільш дієвим інструментом для збереження врожаю сільськогосподарських культур через свою високу ефективність, економічну вигідність [3]. Оскільки пестициди є біологічно активними речовинами, їх неправильне використання може мати шкідливий вплив на здоров'я, особливо при їх застосуванні для захисту сільськогосподарської продукції, яка вживається в сирому вигляді і може бути контамінована пестицидами [4].

Мета

Гігієнічна оцінка ризику для людини при вживанні овочів контамінованих фунгіцидами на основі дифеноконазолу.

Матеріали та методи дослідження

Досліджено пестицидні формуляції (Циделі Топ, Скор, Протект Фунгус, Серкадіс Плюс, Скор, Кіер) на основі сполуки хімічного класу триазолів (дифеноконазол). Під час польових досліджень у різних ґрунтово-кліматичних зонах України визначили реальний вміст досліджуваної сполуки в овочевих культурах (томатах, огірках, моркві, картоплі, капусті). Параметри стійкості досліджуваних фунгіцидів у сільськогосподарських культурах за ґрунтово-кліматичних умов України були визначені на основі аналізу результатів отриманих в натурних експериментах даних, проведених у різних районах країни. В ході дослідження відбирали проби плодів овочевих культур починаючи з дня після останньої обробки та з фіксованими інтервалами, 3-7 разів протягом вегетаційного сезону до моменту збирання врожаю. Для порівняння також відбирали контрольні проби до початку обробки культур, в яких досліджувані діючі речовини не були виявлені [5]. Визначення вмісту дифеноконазолу в плодах овочевих культур проводили методам офіційно затвердженими методиками із застосуванням газоріднної хроматографії (ГРХ) №785-2007, №1195-2012, №1536-2018, №1654-2020.

Згідно з отриманими результатами, були розраховані показники стійкості дифеноконазолу (період напівруйнування (τ_{50}) та майже повного руйнування (τ_{95})) в вище перерахованих овочевих культурах. Отримані дані математичного моделювання дозволили спрогнозувати персистентість дифеноконазолу в овочевих культурах.

Для класифікації речовин за стабільністю у рослинах було використано ДСанПіН 8.8.1.002-98 (Держстандарт (1998)). Згідно з цією класифікацією, речовини поділяються на 4 класи в залежності від їх стабільності в рослинах: 1 – високостійкі (τ_{50} більше 30 діб), 2 – стійкі (τ_{50} від 15 до 30 діб), 3 – помірно стійкі (τ_{50} від 5 до 14 діб), 4 – мало стійкі (τ_{50} менше 5 діб). Результати власних досліджень були оцінені згідно з цією класифікацією для визначення стабільності пестицидів у рослинах.

Для оцінки ризику несприятливого впливу дифеноконазолу на здоров’я людини при споживанні овочевої продукції була використана методика, що враховує допустиму добову дозу (ДДД), період напівруйнування (τ_{50}) в рослинах та середньодобове споживання продукту [6]. Інтегральний показник небезпечності при вживанні контамінованих пестицидами продуктів (ІПНВП) оцінюється за шкалою: 4 клас (малонебезпечні) – 3-5 балів, 3 клас (помірно небезпечні) – 6-8 балів, 2 клас (небезпечні) – 9-11 балів, 1 клас (надзвичайно небезпечні) – більше 11 балів [7,8] .

Статистична обробка результатів була виконана за допомогою пакету MedStat v.5.2 (Copyright © 2003-2019), Microsoft® Excel® для Microsoft 365 MSO (версія 2305, збірка 16.0.16501.20074) та Python 3.11. У Python використовували бібліотеки Numpy, Pandas, Statsmodels.api, scikit_posthocs, scipy.stats, а також веб-інтерактивне обчислювальне середовище Jupyter Notebook 7.0.8. Нормальність розподілу в досліджуваних групах оцінювали за допомогою тесту Шапіро-Вілка. Обробку даних було здійснено за допомогою методів варіаційної статистики з розрахунком середнього арифметичного значення, дисперсії,

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середнього квадратичного відхилення та похибки. У всіх групах було встановлено нормальний розподіл даних (p>0,05), тому для порівняння було використано критерій Ст'юдента.

Результати

Результати, отримані в ході натурних досліджень таблиці 1 та використання методу математичного моделювання дозволили розрахувати параметри стійкості досліджуваних сполук у вегетуючих сільськогосподарських культурах (τ_{50}). При розрахунку середнього періоду напіврозпаду дифеноконазолу в досліджуваних сільськогосподарських культурах було встановлено цей показник в досліджуваних овочевих культурах (в загальному) на рівні 9,51±0,67 доби (95% ДІ 8,13-10,89), проте необхідно зазначити, що τ_{50} був достовірно найменшим в картоплі 5,9±0,55 діб (95% ДІ 4,5-7,31) порівняно із іншими овочевими культурами (таблиця 2, рис 1). Між іншими комбінаціями культур, даної відмінності не було виявлено (p=0,056-0,508 за критерієм Ст'юдента).

Для комплексної оцінки потенційної небезпеки впливу дифеноконазолу на організм людини при споживанні забруднених сільськогосподарських продуктів (томати, огірки, морква, картопля, капуста) за шкалою з чотирьох рівнів ми аналізували показники допустимої добової дози (ДДД), середньодобового споживання продукту та періоду напіврозпаду (τ_{50}) в рослинах (табл. 3) [2].

Оцінені значення (в балах) сумували для визначення загального рівня небезпеки при потраплянні в організм людини дифеноконазолу з харчовими продуктами. Було встановлено, що за стійкістю дифеноконазол у сільськогосподарських культурах (томатах, огірках, моркві, картоплі, капусті) відповідно до ДСанПіН 8.8.1.002-98 віднесено до III класу небезпечності (помірно стійкий). При оцінці інтегрального показника небезпечності при вживанні продуктів (ІПНВП) дифеноконазолу на організм людини було встановлено, що при вживанні контамінованої сільськогосподарської продукції досліджуваний фунгіцид належав до 3 класу небезпечності.

Обговорення

Отримані результати поведінки дифеноконазолу в овочевих культурах порівняли з результатами, отриманими в інших країнах світу [9-14]. Та було встановлено, що розраховані нами значення періодів напіврозпаду, а саме діапазони 95% довірчого

Таблиця 1. Показники деградації дифеноконазолу в овочевих культурах

культура	Препарат	Показники швидкості руйнації M±m				Кінетичне рівняння	R^2
		*τ_{50}, доба	τ_{50}, доба	τ_{95}, доба	τ_{95}, доба		
томати	Циделі Топ	10,56±2,2	10,79±0,87	45,92±9,85	46,94±3,81	$y = 0{,}0339e^{-0{,}085x}$	0,98
	Скор	10,22±1,84		44,44±8,02		$y = 2{,}1218e^{-0{,}102x}$	0,96
	Протект Фунгус	11,56±0,42		50,46±1,84		$y = 0{,}1576e^{-0{,}06x}$	0,94
огірки	Циделі Топ	8,13±0,66	8,13±0,66	35,36±2,88	35,36±2,88	$y = 0{,}0812e^{-0{,}087x}$	0,89
морква	Циделі Топ	16,06±1,18	12,21±1,88	69,85±5,15	53,12±8,1	$y = 1{,}6162e^{-0{,}078x}$	0,94
	Серкадіс Плюс	8,37±1,22		36,39±5,31		$y = 2{,}1218e^{-0{,}102x}$	0,96
картопля	Скор	7,11±1,51	7,11±1,51	30,89±0,91	30,89±0,91	$y = 0{,}1081e^{-0{,}098x}$	0,97
капуста	Серкадіс Плюс	4,70±0,07	6,76±0,92	50,46±1,84	29,42±4,03	$y = 2{,}1218e^{-0{,}102x}$	0,96
	Кіер	8,83±0,17		38,41±0,76		$y = 2{,}1218e^{-0{,}102x}$	0,96

Примітки: t табличне становить 2,2 при p=0,05 і df=3; *M* – середнє арифметичне значення; *m* – похибка середнього арифметичного; τ_{50} – період напіврозпаду; τ_{95} – період розпаду 95 % вихідної кількості речовини; розходження не достовірно; * – розходження не достовірні за критерієм Стьюдента (t) при p>0,05; R^2 – Коефіцієнт детермінації.

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Таблиця 2. Порівняння поведінки дифеноконазолу в овочевих культурах (незалежні вибірки, двостороння критична область)

Досліджувані культури		Овочеві	Томати	Огірки	Морква	Картопля	Капуста
Період напіврозпаду		**τ_{50}**					
Капуста	τ_{50}	0,340	0,056	0,365	0,133	0,002*	–
Картопля		<0,001*	0,001*	0,045**	0,018*	–	
Морква		0,115	0,461	0,188	–		
Огірки		0,508	0,128	–			
Томати		0,320	–				
Овочеві		–					
Достовірність розходжень (p)							

Встановлено статистично достовірну відмінність між середнім значенням періоду напіврозпаду дифеноконазолу в досліджуваних овочевих культурах (ANOVA-Велча: F-статистика=7,378 (F_{crit}=3,730); p=0,007)

Примітки: «*» – встановлено достовірну відмінність за критерієм Ст'юдента; «**» – при виконанні пост-хок тестів (Гамеса-Хоуелла та Тамхане) період напіврозпаду дифеноконазолу в огірках достовірно не відмінний від того, що спостерігався в картоплі (p=0,214-0,233, відповідно), на цей факт буде звернуто особливу увагу в майбутніх дослідженнях.

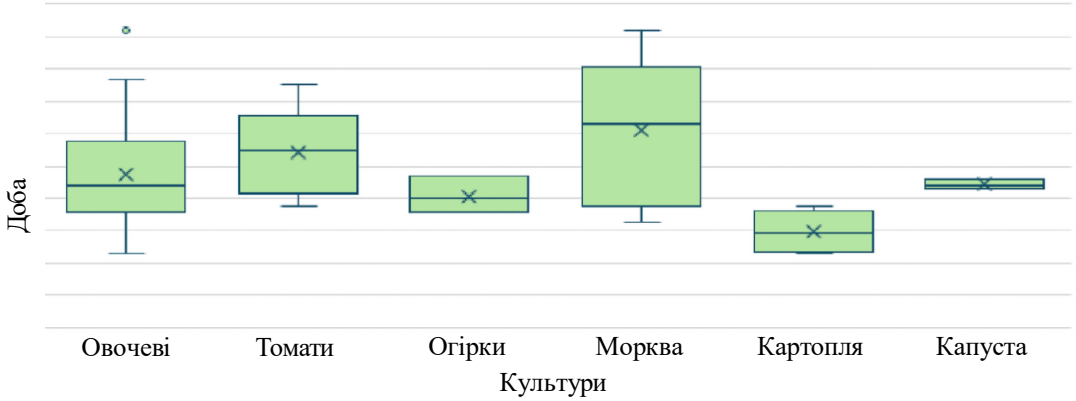

Рис. 1. Розподіл періоду напівруйнування (τ_{50}) із досліджуваних культур

Таблиця 3. Оцінки ризику несприятливого впливу дифеноконазолу на здоров'я людини при споживанні овочевої продукції, вирощеної при їх застосуванні

Культура	Середнє споживання продукту, г/добу	τ_{50} в рослинах, доба1	ДДД, мг/кг	ІПНВП	
				значення	клас
томати	68,5 / 1 бал	10,79±0,87 / 3 бали	0,002	7 балів	3
огірки	68,5 / 1 бал	8,13±0,66 / 3 бали		7 балів	3
морква	24,7 / 1 бал	12,21±1,88 / 3 бали		7 балів	3
картопля	260,3 / 3 бали	7,11±1,51 / 2 бали	3 бали	8 балів	3
капуста	76,7 / 1 бал	6,76±0,92 / 2 бали		6 балів	3
Всього	498,7 / 7 балів	9,51±067 / 3 бали	0,002 / 3 бали	13 балів	1

Примітки: 1. ДДД – допустима добова доза, мг/кг; 2. ІПНВП – інтегральний показник небезпечності при вживанні продуктів; τ_{50} – період напіврозпаду

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інтервалу практично не відрізняються від літературних (95% ДІ 8,77-12,82; 5,28-10,99; 7,38-17,05; 4,5-7,31; 8,08-9,59 діб для томатів, огірків, моркви, картоплі та капусти, відповідно). За даними літератури τ_{50} дифеноконазолу складає в: томатах – 7,0-9,9 доби, огірках – 3,15-9,62 доби, моркві – 7,8-10,5 доби, капусті – 2,09-7,8 діб, що співпадає із нашими результатами (при порівнянні максимальних та мінімальних значень цих діапазонів не було виявлено статистичної відмінності: p=0,286-0,556 (тест Манна-Уітні)).

Висновки

1. Встановлено, що дифеноконазол відноситься до помірно стійких засобів у сільськогосподарських рослинах (ІІІ клас небезпечності), що визначає його ефективність для використання на різних культурах.
2. Згідно з інтегральним показником небезпечності при споживанні контамінованих продуктів (ІПНВП), дифеноконазол належить до 3 класу небезпечності (помірно небезпечні), що пов'язано з його відносно низькою допустимою добовою дозою та широким спектром застосування на сільськогосподарських культурах.
3. Отримані результати повинні бути враховані при розгляді можливості розширення використання фунгіцидів на основі дифеноконазолу для забезпечення безпеки людини та ефективності застосування на різних рослинах.

Фінансування

Фінансової підтримки від державної, громадської або комерційної організації ця стаття не отримала.

Конфлікт інтересів

Автори заявляють про відсутність потенційних та явних конфліктів інтересів, пов'язаних з рукописом.

Згода на публікацію

Всі автори ознайомлені з текстом рукопису та надали згоду на його публікацію.

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Під час підготовки цього рукопису ШІ-інструменти не використовувалися.

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Hygienic risk assessment for humans from consuming vegetables contaminated with difenoconazole-based fungicides

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Abstract: *One of the key directions for increasing agricultural crop yields is the use of chemical plant protection products, particularly pesticides. Considering the growing use of these products due to intensive cultivation technologies, the study of pesticide persistence in agricultural crops is of great importance for maintaining product quality and safety. Uncontrolled use of these substances may negatively affect human health, especially when employed for treating agricultural products. The aim of our study was to carry out a hygienic risk assessment for humans consuming vegetables contaminated with a difenoconazole-based fungicide. Materials and methods of the study included determining the content of the triazole-class compound, difenoconazole, in vegetable crops (tomatoes,*

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cucumbers, carrots, potatoes, cabbage) in various soil and climatic zones of Ukraine. The persistence of the fungicide in different vegetable crops was evaluated, and the values of its half-life period (τ_{50}) and near-total degradation period (τ_{95}) were calculated. The assessment of pesticide hazards was carried out using an integral hazard index in consumption of pesticide-contaminated products, classified into four categories ranging from low hazardous to extremely hazardous. Statistical processing of the results was performed using the software packages MedStat v.5.2 (Copyright © 2003-2019), Microsoft® Excel® for Microsoft 365 MSO (version 2305, build 16.0.16501.20074), and Python 3.11. The half-life (τ_{50}) of difenoconazole in the studied agricultural crops was 9.51±0.67 days on average. It should be noted that the τ_{50} was significantly the shortest in potatoes, with a value of 5.9±0.55 days (95% CI 4.5-7.31), compared to other vegetable crops. A comparison of the obtained results with published data from other countries showed that the half-life periods of difenoconazole in vegetable crops are comparable and fall within acceptable intervals. The calculated stability parameters (τ_{50}) allowed difenoconazole to be classified as belonging to Hazard Class III in all the studied crops (SSanN&R 8.8.1.002-98). When assessing the integral hazard index in consumption of pesticide-contaminated products (IHIPC) of difenoconazole on human health, it was found that when consuming contaminated agricultural products, the studied fungicide belonged to hazard class III. The obtained results should be taken into account when considering the possibility of expanding the use of difenoconazole-based fungicides to ensure human safety and the effectiveness of application on various plants.

Keywords: Agricultural Crops, Environmental Pollution, Half-life, Pesticide Residues, Pesticides, Sanitary Surveys.

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The role and evaluation of parental medical activity in the prevention of chronic gastrointestinal diseases in children

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Abstract. *Chronic gastrointestinal diseases in children represent a significant medical and social issue characterized by long-lasting conditions, periodic flare-ups, and a substantial decline in the quality of life. These conditions not only impact physical health but also interfere with educational performance, physical activity, and emotional well-being, ultimately affecting the child's overall development. The management and outcome of these diseases heavily rely on the involvement of parents, including their ability to seek timely medical care, ensure adherence to prescribed diets and pharmacological treatments, maintain health records, and organize psychological support for their child. In this context, the role of parental medical activity is of crucial importance in preventing complications, managing symptoms, and improving the child's overall quality of life. The purpose of this study was to evaluate the level of medical involvement among parents of children with chronic gastrointestinal disorders, identify factors influencing this involvement, and assess its significance in the prevention, treatment, and enhancement of the child's quality of life. To achieve this, a cross-sectional survey was conducted involving 80 children aged 6 to 17 years, all registered with a dispensary for chronic gastrointestinal conditions, including gastritis, peptic ulcer disease, and irritable bowel syndrome. The survey included 47 questions divided into seven thematic areas: socio-demographic information, the course of the disease, awareness and interaction with healthcare services, prevention, psycho-emotional status, social support, and school or kindergarten adaptation. The responses were evaluated using a 1-3 point scale, with the total score used to categorize parental medical activity levels as low, moderate, good, above average, or high. The results indicated that 10% of parents had low activity levels, 22.5% demonstrated moderate involvement, 36.2% showed good activity, 21.3% had above-average activity, and 10% exhibited high engagement. In total, 67.5% of parents displayed a suficient level of medical activity, while 32.5% showed low or moderate involvement. The areas where parents excelled included adherence to medical prescriptions (72.5%) and informing educational institutions about the child's condition (65%). However, the most concerning aspects were the regular maintenance of medical records, which only 22.5% of parents managed effectively, and participation in psychological or social programs, which was less than 15%. These findings suggest that the psychosocial component of care remains undervalued by many families. Additionally, parental activity varied significantly depending on the educational and socio-economic status of the family. The study concluded that parental involvement in medical care plays a vital role in the prevention and treatment of chronic gastrointestinal diseases in children.*

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This involvement directly affects the child's health outcomes, psychosocial development, and overall quality of life. Future initiatives should focus on enhancing parental awareness, improving family education on medical and psychosocial care, and increasing support for families with lower socio-economic status to ensure equitable and effective management of chronic gastrointestinal conditions in children.

Keywords: Child; Chronic Disease; Family Support; Gastrointestinal Tract; Quality of Life.

Introduction

Chronic gastrointestinal (GI) diseases in children are one of the important medical and social problems that have a significant impact on the physical, emotional, and social well-being of children [1,2,3]. They are often accompanied by a prolonged course and periodic exacerbations, which significantly reduce the quality of life and can lead to the development of secondary disorders, such as growth disorders, decreased physical activity, and psychological disorders. Chronic pain, abdominal discomfort, or other manifestations of the disease create increased anxiety and emotional tension, contributing to the development of psychological disorders such as depression or adjustment disorders [4,5,6,7,8,9].

One of the main factors determining the effectiveness of treatment and prevention of complications of such diseases is the level of parental involvement in the medical care of the child [10,11,12]. Parents play a key role in timely visits to medical institutions, adherence to diet, following medical recommendations, keeping health diaries, and organising psycho-emotional support [13,14]. Their activity affects not only the treatment process but also the psychological state of the child, which, in turn, can influence the course of the disease and its prognosis. Insufficient parental involvement in these aspects can lead to delays in diagnosis, inadequate treatment, increased frequency of disease exacerbations, and reduced adherence to therapy [15,16,17].

Aim

To assess the level of medical activity of parents of children with chronic gastrointestinal diseases, to study the factors influencing this level, and to determine its significance for the prevention, treatment, and improvement of the quality of life of children.

Materials and methods

To assess the level of medical activity of parents of children with chronic gastrointestinal diseases, a sample of 80 children aged 6 to 17 years was formed, who were registered at a specialised outpatient clinic with diagnoses of chronic gastrointestinal diseases, such as gastritis, peptic ulcer disease, irritable bowel syndrome. All diagnoses were made on the basis of clinical data, laboratory test results, and instrumental examination methods, which confirmed the presence of chronic gastrointestinal diseases in accordance with international standards and recommendations. Diagnoses were verified by reviewing patient medical records, consulting with gastroenterologists, and additional confirmation of the diagnosis using modern diagnostic techniques (endoscopy, ultrasound, blood tests for inflammation markers, testing for Helicobacter pylori, etc.). All patients had officially confirmed diagnoses recorded in their medical records at the time of the study.

The main tool for data collection was a questionnaire consisting of 47 questions, which were divided into 7 main sections:

1. Socio-demographic data - questions concerning parents' education, their professional activities and socio-economic status.
2. Course of the disease - questions concerning the duration of the disease, frequency of exacerbations, and changes in treatment approach.
3. Parental awareness and interaction with medicine - assessment of parents' knowledge of the disease, their attitude to medical consultations and treatment.
4. Prevention - questions about adherence to diet, regularity of medical examinations, and physical activity of children.

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5. Psycho-emotional state - assessment of the child's level of anxiety and stress, as well as the parents' reaction to these symptoms.
6. Social support and participation - parents' participation in charitable and social programmes, their interaction with other parents.
7. School/kindergarten adaptation - questions regarding teachers' awareness of the child's condition and the availability of individual learning conditions.

Each question in the questionnaire had three possible answers, which were rated on a scale of 1 to 3 points. According to this scale: 1 point - low activity/unsatisfactory condition; 2 points - average activity/conditional condition; 3 points - high activity/satisfactory condition. The overall result was calculated using the formula: Overall result = (N1 × 1) + (N2 × 2) + (N3 × 3), where N1, N2, and N3 are the number of answers that received 1, 2, and 3 points, respectively. The level of medical activity of parents was determined depending on the points received, where: 47-65 points - low level of activity; 66-84 points - moderate level; 85-103 points - good level; 104-122 points - above average level; 123-141 points - high level of activity.

Statistica and Microsoft Excel software were used to process the data obtained. Variational statistical analysis was used to assess the level of medical activity of parents, using percentage distributions and descriptive statistics (mean values ± standard deviation). The level of statistical significance was determined according to the standard criterion $p<0.05$.

Results

The study assessed the level of medical activity of parents of children with chronic gastrointestinal tract (GIT) diseases. Overall, among the 80 parents surveyed, the distribution by level of activity was as follows:

– A low level of activity (47-65 points) was recorded in 8 (10%) parents.
– Moderate activity (66-84 points) was demonstrated by 18 (22.5%) parents.
– Good activity (85-103 points) was demonstrated by 29 (36.2%) parents.
– Above-average activity levels (104-122 points) were observed in 17 (21.3%) parents.
– High activity levels (123-141 points) were found in 8 (10%) parents.

About 67.5% of parents showed a high or good level of involvement in the treatment and care of their children, which indicates their significant activity in medical support. However, 32.5% of parents demonstrated a low and moderate level of activity, indicating a need to improve the participation of these families in the treatment and prevention process.

According to the results, there are several key problem areas that require attention. Medical record keeping: only 22.5% of parents regularly monitored their child's well-being, nutrition, and other aspects of health. This may indicate insufficient attention to the importance of this tool in managing chronic diseases, although keeping medical records is critical for timely therapy adjustments. Participation in psychological or social programmes, as less than 15% of parents participated in such programmes or sought psycho-emotional support for their child. This highlights a lack of attention to the psychosocial aspects of treatment, which is an important component of comprehensive care for children with chronic gastrointestinal diseases.

The best results were observed in areas such as adherence to medical prescriptions, as 72.5% of parents reported that they followed all recommendations from medical professionals, indicating a high level of responsibility and awareness of the importance of medication control for their child's condition. 65% of parents regularly inform educational institutions about their child's chronic disease, which is an important aspect in ensuring appropriate conditions for children's education and social adaptation.

The results of the study show significant variability in the level of medical activity of parents, determined by both positive and negative aspects of their involvement. At the same time, the high level of compliance with medical recommendations and informing school staff indicates that most parents understand the importance of medical control and support

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at various levels. However, given the existing problems in other aspects of care, it is necessary to develop support programmes aimed at increasing parents' awareness and involvement in the medical process, in particular through involvement in medical record-keeping and psycho-emotional support programmes.

The level of parental medical activity is a key factor determining the effectiveness of treatment and prevention of chronic gastrointestinal tract (GIT) diseases in children. More than two-thirds of the parents surveyed demonstrate a sufficient or high level of activity, indicating an adequate understanding of the importance of medical care and monitoring of their child's condition. However, a significant proportion of parents (32.5%) have a low or moderate level of involvement, indicating a need for further measures to increase the activity of these families.

One of the most problematic aspects is the maintenance of medical records. Only 22.5% of parents reported that they regularly keep health diaries and other important records, which is a prerequisite for effective monitoring of their child's condition. Keeping medical records is an important tool for the timely detection of changes in health status and the adjustment of therapeutic measures. This indicator shows that parents aren't really motivated or aware of how important this is. So, we need to roll out extra educational programmes for parents to make them more aware of how important it is to keep medical records.

Psycho-emotional support for children is another important area where there is a significant gap between the high level of parental involvement in physical treatment and insufficient attention to the child's psychological state. Less than 15% of parents participated in psychological or social programmes, which may indicate an underestimation of the importance of psycho-emotional support in the context of chronic diseases. Given that such diseases can be accompanied by stress, anxiety, and social isolation, the role of psycho-emotional support cannot be underestimated. Children with chronic diseases often face emotional difficulties, which can worsen their overall well-being and even lead to the development of depression or other mental disorders. In this regard, it is important to raise parents' awareness of the need to provide psychological support to their children and to encourage families to participate in relevant programmes.

The highest results were recorded in areas such as compliance with medical recommendations (72.5% of parents comply with all medical prescriptions) and informing teachers about the child's condition (65% of parents). This indicates a high level of awareness among parents of the need for medication control and the importance of interacting with educational institutions to ensure favourable conditions for the child. A high level of awareness among teachers about the child's condition allows for an individual approach to learning, which in turn contributes to better socialisation and adaptation of children to the school environment. However, even these aspects require further attention, as not all parents are fully prepared to openly discuss medical issues with teachers, which may be due to various social, psychological, or cultural barriers.

Nevertheless, despite the significant number of highly active parents, the problem of social isolation of some families remains. About 32.5% of parents do not participate in charitable or social programmes, which may indicate a lack of support from the community or medical institutions. This points to the need to develop a support system that includes both medical and social components. Psychosocial support for families, in particular through the creation of support groups or online resources, could significantly improve the situation and reduce the level of social isolation.

Attention should also be paid to the problem of heterogeneity in the level of activity among parents. Factors that may influence this level include education, social status, access to medical resources, and information. Parents with higher levels of education and better access to medical information tend to be more medically active, confirming the importance of providing access to medical knowledge and support to all segments of the population. This factor is key to developing programmes aimed at increasing medical awareness in different social groups.

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The study results highlight the importance of a comprehensive approach to the treatment and prevention of chronic gastrointestinal diseases in children, where parental involvement is a key component. To achieve the best results, it is necessary not only to improve medical support but also to focus on psychological and social support for children and their families. Given the results obtained, it is important to continue developing educational programmes for parents that will increase their involvement in the treatment of children, as well as to implement initiatives to improve access to information and medical resources for all segments of the population.

Conclusions

1. Parental medical activity is a key factor in the prevention and treatment of chronic gastrointestinal diseases in children, particularly in the context of COVID-19.

2. A high level of parental activity promotes compliance with medical prescriptions and better social functioning of children, while a lack of attention to medical record keeping and psycho-emotional support can worsen the course of the disease.

3. To improve the effectiveness of treatment, it is important to develop educational programmes for parents, particularly regarding medical record keeping and participation in psychological support programmes.

4. Increasing the level of parental involvement in medical care has a direct impact on the child's quality of life and the effectiveness of treatment, so it is necessary to strengthen information support for families with low socioeconomic status.

Ethical Approval

The study was conducted in accordance with the ethical standards set forth in the Declaration of Helsinki (2013) and relevant international requirements for biomedical research. All study participants signed an informed consent form for participation in the study and processing of personal data. The study was conducted within the framework of the research project ‘Improvement of methods for the diagnosis, treatment and prevention of socially significant childhood diseases’ (state registration number 0125U000113), with a completion date of 2025-2027.

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Conflict of interest

There is no conflict of interest in this article. No rewards received.

Consent to publication

All authors of the article are acquainted with the final version of the manuscript and have no objections to its publication. The article does not use personal data and information about patients.

AI Disclosure

AI tools were not used in preparing this manuscript.

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Роль і оцінка медичної діяльності батьків у профілактиці хронічних захворювань шлунково-кишкового тракту у дітей

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Анотація. *Хронічні захворювання шлунково-кишкового тракту у дітей є значною медичною та соціальною проблемою, що характеризується тривалим перебігом, періодичними загостреннями та істотним погіршенням якості життя. Ці захворювання не тільки впливають на фізичне здоров'я, але й заважають навчанню, фізичній активності та емоційному благополуччю, що в кінцевому підсумку позначається на загальному розвитку дитини. Лікування та результати цих захворювань значною мірою залежать від залучення батьків, зокрема від їхньої здатності своєчасно звертатися за медичною допомогою, забезпечувати дотримання призначених дієт і фармакологічних методів лікування, вести медичні записи та організовувати психологічну підтримку для своєї дитини. У цьому контексті роль батьківської медичної активності має вирішальне значення для запобігання ускладнень, лікування симптомів та поліпшення загальної якості життя дитини. Метою цього дослідження було оцінити рівень медичної активності батьків дітей із хронічними шлунково-кишковими розладами, визначити фактори, що впливають на цю активність, та оцінити її значення для профілактики, лікування та поліпшення якості життя дитини. Для цього було проведено перехресне опитування 80 дітей віком від 6 до 17 років, які були зареєстровані в амбулаторії з приводу хронічних шлунково-кишкових захворювань, включаючи гастрит, виразкову хворобу та синдром подразненого кишечника. Опитування включало 47 питань, розділених на сім тематичних областей: соціально-демографічна інформація, перебіг захворювання, обізнаність та взаємодія з медичними службами, профілактика, психоемоційний стан, соціальна підтримка та адаптація в школі або дитячому садку. Відповіді оцінювалися за 1-3-бальною шкалою, а загальний бал використовувався для класифікації рівня медичної активності батьків як низький, помірний, хороший, вище середнього або високий. Результати показали, що 10% батьків продемонстрували низький рівень активності, 22,5% — помірну залученість, 36,2% — добру активність, 21,3% — активність вище середнього, а 10% — високий рівень залученості. Загалом 67,5% батьків продемонстрували достатній рівень медичної активності, а 32,5% — низьку або помірну залученість. Серед областей, в яких батьки продемонстрували високі результати, були дотримання медичних призначень (72,5%) та інформування навчальних закладів про стан дитини (65%). Однак найбільш турбуючими аспектами були регулярне ведення медичних записів, з яким ефективно справлялися лише 22,5% батьків, та участь у психологічних або соціальних програмах, яка становила менше 15%. Ці результати свідчать про те, що психосоціальний компонент догляду залишається недооціненим багатьма сім'ями. Крім того, активність батьків значно варіювалася залежно від освітнього та соціально-економічного статусу сім'ї. У дослідженні зроблено висновок, що участь батьків у медичному догляді відіграє важливу роль у профілактиці та лікуванні хронічних захворювань шлунково-кишкового тракту у дітей. Ця участь безпосередньо впливає на стан здоров'я дитини, її психосоціальний розвиток та загальну якість життя. Майбутні ініціативи повинні бути спрямовані на підвищення обізнаності батьків, поліпшення освіти сім'ї з питань медичної та психосоціальної допомоги, а також збільшення підтримки сімей з нижчим соціально-економічним статусом для забезпечення справедливого та ефективного лікування хронічних захворювань шлунково-кишкового тракту у дітей.*

Ключові слова: Дитина; Хронічне захворювання; Підтримка сім'ї; Шлунково-кишковий тракт; Якість життя

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Assessment of the correlation between Pharyngeal Airways and Palatal Index in different skeletal growth patterns

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Abstract: *In the discipline of orthodontics, a person's face structure can be ascertained through the specific characteristics and anatomical correlations of the palate depth, width, and airway dimensions, which aid in the identification of malocclusions. A greater awareness of the relationship between upper airway structure and sleep disordered breathing, as well as the relationship between this condition and craniofacial morphology in general, has led to a gradual increase in interest in upper and lower airway dimensions over the past few decades. The study comprised 30 participants, with a mean age of 17.5 years. Skeletal classes I, II, and III were assigned to the participants based on their ANB (A point, nasion, B point) angle (N = 10). The study models were used to calculate the palatal height, palatal breadth, and palatal height index using Korkhaus analysis. McNamara Airway Analysis was used to measure the upper and lower pharyngeal airway dimensions based on the lateral cephalogram. The ANOVA test was used to calculate the findings. For the palatal index and airway dimensions, there was a statistically significant difference observed in all three groups of malocclusions (class I, II, and III). The subjects with skeletal class II malocclusion showed the highest mean palatal index values (P=0.03). For the upper airway, class I had the greatest mean value (P=0.041), while class III had the highest mean value (P=0.026) for the lower airway. It was concluded that subjects with the class II skeletal pattern have a high palate and reduced upper and lower airways when compared with class I and class III skeletal patterns, which showed larger upper and lower airways, respectively.*

Keywords: Orthodontics, Diagnosis, Malocclusion, Orthodontic appliances, Dental Arch.

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Introduction

In the discipline of orthodontics, a person's face structure can be ascertained through the specific characteristics and anatomical correlations of the palate depth, width, and airway dimensions, which aid in the identification of malocclusions. Since sleep-disordered breathing has been linked to upper airway shape [1] and has been linked to general craniofacial morphology, interest in upper and lower airway dimensions has gradually grown over the past few decades. The palate has been the subject of numerous research, some of which traced the palate's transverse, median, and sagittal shapes at various developmental stages in dental casts to look into changes in the palate's growth [2]. Certain conditions, such as Treacher-Collin syndrome, Apert's syndrome, Turner's syndrome, etc., might have a high or narrow palate [3]. The development of craniofacial form and occlusal patterns depends on a number of factors. The effects of upper airway obstruction on dental development and craniofacial growth require a thorough examination. Clinical trials have linked mouth breathing to the development of skeletal and dental abnormalities [4, 5]. In orthodontics, changes to the upper airway must always be evaluated clinically before starting therapy, in addition to using cone beam computed tomography (CBCT) or lateral cephalograms. Since cephalometry converts three-dimensional traits into two-dimensional ones, the information it provides is scant.

However, because CBCT creates projections on many planes and shows dimensional structures in 3D, it offers a wealth of diagnostic information that enables us to measure the volume of different structures. Breathing becomes even more difficult when there is obstruction of the upper airways, which can also result in malocclusion, jaw deformity, and craniofacial abnormalities. Furthermore, research has demonstrated that aberrant craniofacial development can result in a lifetime of health issues, including chronic mouth breathing, sleep apnea, respiratory impairment, airway obstruction, and sleep disorders [6]. In the craniofacial hierarchy, the craniofacial form and function may be ranked highest. Therefore, it is important to carefully regulate the shape and function of the craniofacial region, especially in the early phases of growth and development, using orthodontic and orthopedic therapy. First developed by Korkhaus [4], the palatal height index is derived from the combination of palatal width and palatal depth. The McNamara airway analysis is used to determine the upper and lower pharyngeal airway measures [7]. There appears to be variation in the shape of palatal vaults in each skeletal pattern, thus further research is necessary to thoroughly investigate airway and palatal morphology for improved treatment-plan formulation. There is also a connection between craniofacial development and airway development.

Thus, in class I, II, and III skeletal morphologies, our study's goal is to link palatal index index with pharyngeal airway.

Materials and methods

The Department of Orthodontics and Propaedeutics of Orthopaedic Dentistry at Bogomolets National Medical Universityin Kyiv, Ukraine, conducted the research of this study. Thirty individuals were randomly chosen from among the patients who came to the department for orthodontic treatment in order to get lateral cephalograms and dental plaster models. Using the G*Power program 3.1.9.2 (Erdfelder, Faul, & Buchner, Germany), the sample size was determined. The ANB (A point, nasion, B point) angle and wits appraisal were used to categorize the participants into three groups, Class I, II, and III, according to the type of sagittal relationship. Patients with class I skeletal bases and ANB values between 0° and 2° made up Group I. Patients in Group II included those with class II skeletal bases and ANB levels higher than 2°. Finally, group III patients had class III skeletal bases with ANB lesser than 0°. The individuals' eyes were reflected in a mirror five feet in front of them, and their teeth were in centric occlusion with the Frankfort horizontal plane parallel to the ground, as this was the normal head posture used to acquire the lateral cephalograms. To keep the head from spinning during exposure, ear rods and nasal support were used to stabilize the position. Using a 2H pencil, all cephalogram tracings were completed by hand on clear acetate

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sheets. For each patient, the McNamara airway analysis was used to record the upper and lower airway dimensions [7].

From a point on the back of the soft palate outline to the nearest point on the posterior pharyngeal wall, the upper pharyngeal breadth is measured. Because the region just next to the posterior nasal aperture is crucial for assessing upper respiratory patency, this measurement is performed on the anterior half of the soft palate outline. A two-dimensional depiction of a three-dimensional structure is the nasopharynx head film outline (Figure 1). The location on the posterior pharyngeal wall closest to the junction of the inferior border of the mandible and the posterior border of the tongue is where the lower pharyngeal width is measured (Figure 1) [8].

Alginate impression material (Hydrogum 5, Zhermack) was used to create the impressions required to make the study models, which are built of Type 3 Gypsum. Using a divider and scale, each subject's palatal index was independently determined on the study models for the Korkhaus analysis. The width measured the separation at the cervical line between the maxillary first permanent molars. The height was the shortest path between the plane defined by the other reference points and the midline where the hard and soft palates converge [4].

The palatal height Index was calculated using the following formula (Figure 2): Palatal height index = palatal height/palatal width × 100.

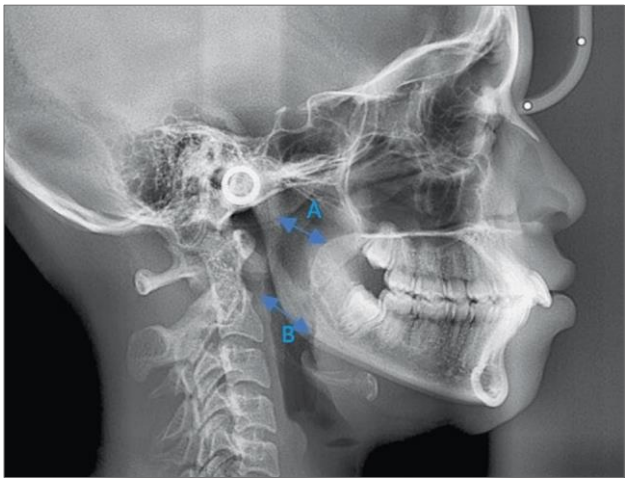

Figure 1: Measurement of the upper airway (A) and lower airway (B) on a lateral cephalogram

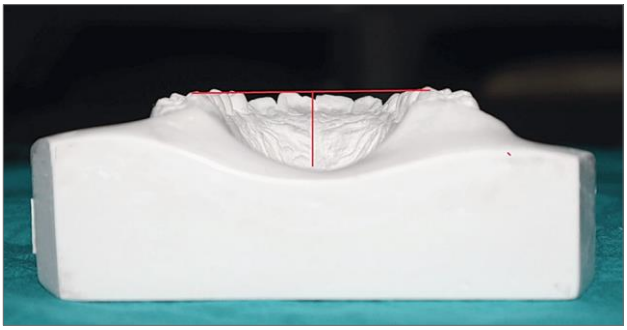

Figure 2: Study model showing palatal height and width

Statistical analysis:

IBM SPSS software for Windows, version 21 was used for data analysis. The palatal index, lower airway, and upper airway differences between the three classes were ascertained using the ANOVA test. The standard deviation and mean of the palatal index, upper airway, and lower airway in classes I, II, and III were calculated using descriptive statistics.

Results

Tables 1-3 display the descriptive data and an ANOVA test comparison of the palatal index with the upper and lower airways. The palatal index mean and standard deviations for each of the three classes are shown in Table 1, along with the findings of the ANOVA test, which indicates that there is a statistically significant difference in the palatal index between the three classes, with class II having the highest mean value (47.20). Table 2 indicates that class I had the highest mean upper airway (11.90) out of the three classes. The ANOVA test's p-value of 0.04 suggests that there is a statistically significant difference between the three groups. According to Table 3, class III had the greatest mean lower airway (12.90), and there was a statistically significant difference in lower airway across the three classes (p-value = 0.026).

Discussion

Environmental influences, eating habits, and ethnicity have all been found to affect palate dimensions. Each race or racial group has a unique cranium and facial structure. Individuals from other nations and cultures may also vary from one another in terms of their characteristics and facial features [8]. The palate morphology is a crucial sign of the anatomical structure that can

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Table 1: The Anova-test for palatal index

Class	N	Mean	Standard deviation	F-value	P-value
Class I	10	43.720	1.726		0.03*
Class II	10	47.200	5.788	1.777	
Class III	10	43.040	6.065		

Table 2: The Anova-test for upper airway

Class	N	Mean	Standard deviation	F-value	P-value
Class I	10	11.90	3.315		0.041*
Class II	10	11.80	2.486	0.174	
Class III	10	11.10	2.751		

Table 3: The Anova-test for lower airway

Class	N	Mean	Standard deviation	F-value	P-value
Class I	10	10.20	2.860		
Class II	10	10.00	2.789	2.562	0.026*
Class III	10	12.90	3.843		

alter the skeletal pattern because the craniofacial complex also comprises the face [9]. For this reason, knowledge of the morphometrics of the hard palate is clearly useful in several dental specialties, such as orthognathic surgery and orthodontics [10,11]. Our study attempted to correlate palatal depth with pharyngeal airway in class I, II, and III malocclusions because airway and craniofacial development are associated. The ANOVA test was used in this investigation to compute and compare the mean and standard deviations of the palatal index for each of the three classes. According to the results, there is a statistically significant difference in the palatal index across the three classes, with class II having the highest mean value. This implies that the palatal index was greater in individuals with class II malocclusion than in ordinary participants. This may be due to the fact that class II malocclusion has a broad range of arch-form aberrations and a varied etiology, which may include thumb sucking habits. High palatal vaults are primarily caused by thumb sucking [12]. Research by Linder A [13], Gwynne-Evans [14], and Klein [15] revealed this. They discovered that those who mouth breathe, had adenoid hypertrophy, or habitually sucked their thumbs had higher palatal heights. In those cases, a class II malocclusion was also evident. According to our study, there was a statistically significant difference between the three classes, with the mean upper airway being the highest in class I patients out of all three. According to Balter's theory [16], class II malocclusions are caused by the tongue being positioned backward. An blockage of the respiratory function in the pharynx region causes incorrect deglutition and mouth breathing. Thus, when compared to other malocclusions, the mean value of the class I malocclusion was larger. This was in line with a research that Jain et al. [17] did. Similar findings were found in another study by Flores-Blancas et al. [18]: nasopharyngeal linear anteroposterior widths are wider in brachyfacial individuals with class I malocclusion than in mesofacial and dolichofacial individuals. In this study, class III patients had the highest mean lower airway, and there was a statistically

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significant difference in lower airway between the three classes. This implies that compared to skeletal class I and II samples, all lower pharyngeal airway features showed significantly greater values in skeletal class III malocclusion samples. This may indicate a forward tongue position, which is linked to skeletal class III malocclusion. These discoveries corroborate the findings of McNamara [7], who suggested that an increase in the lower pharyngeal airway size more than 15 mm indicates a forward-placed tongue. This was as similar as a study done by Jain et al. [18] who also found the same results. These results indicate a close link between the pharynx and dentofacial structures, and suggest that the pharyngeal structures and dentofacial pattern will interact. This stimulates interest in orthodontics. Therefore, it is important to recognize the clinical significance of the pharyngeal airway, particularly in adolescents whose maxillary and mandibular growth and development are critical. This information is also necessary for the diagnosis of the developing class III malocclusion brought on by the tongue's forward orientation. The tongue's forward position may be caused by visceral interferences, such as an enlarged tongue, expanded lymphoid tissue, or respiratory embarrassment. Another scenario is that small upper and lower pharyngeal airways can aid in the early detection of class II malocclusion and the more effective use of growth modification tools to address the malocclusion. In order to detect and prevent the emergence of malocclusion at the proper time, a qualified physician may be able to use this information to test patients for probable respiratory disorders at an early stage and to initiate suitable medication at the relevant time [19]. Cephalometric films were found by Malkoc et al. to be extremely dependable and repeatable for pharyngeal airway dimension estimation [20]. Since the study was carried out on a general population, these conclusions can be extended to different populations. Even said, one potential drawback of the current study could be its smaller sample size. In order to link the pharyngeal airway with the palate depth in all skeletal configurations with greater sample sizes, more research is necessary.

Conclusion

When comparing class II malocclusion participants to class I and class III subjects, the palatal index of the latter group showed the greatest mean value. Class I malocclusions had the highest mean value for the upper airway when compared to class II and class III malocclusions. Furthermore, class III malocclusions had the highest mean value for the lower airway when compared to class I and class II malocclusions.

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Conflict of interest

The authors declare no conflict of interest.

Consent of Publication

The author gives her permission for publication

AI Disclosure

The authors used ChatGPT (OpenAI, San Francisco, CA, USA) for language editing of the English text. The authors reviewed and verified all AI-generated content to ensure accuracy and integrity.

Ethical approval

"All human studies were approved by the institutional ethics committee and conducted in accordance with the Declaration of Helsinki (2013).»

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Оцінка кореляції між глотковими дихальними шляхами та піднебінним індексом при різних моделях росту скелета

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Анотація: *В ортодонтії структуру обличчя людини можна визначити за специфічними характеристиками та анатомічними кореляціями глибини, ширини та розмірів піднебіння, що допомагає у виявленні аномалій прикусу. Більш глибоке усвідомлення зв'язку між структурою верхніх дихальних шляхів та порушеннями дихання під час сну, а також зв'язку між цим станом та краніофаціальною морфологією загалом призвело до поступового зростання інтересу до розмірів верхніх та нижніх дихальних шляхів протягом останніх кількох десятиліть.У дослідженні взяли участь 30 учасників, середній вік яких становив 17,5 років. Учасникам були призначені скелетні класи I, II та III на основі їхнього кута ANB (точка A, назіон, точка B) (N = 10). Моделі дослідження використовувалися для розрахунку висоти піднебіння, ширини піднебіння та індексу висоти піднебіння за допомогою аналізу Коркхауса. Для вимірювання розмірів верхніх та нижніх глоткових дихальних шляхів на основі латеральної цефалограми використовувався аналіз дихальних шляхів Макнамари. Для розрахунку результатів використовувався тест ANOVA. Щодо піднебінного індексу та розмірів дихальних шляхів, спостерігалася статистично значуща різниця у всіх трьох групах аномалій прикусу (клас I, II та III). У суб'єктів зі скелетним аномалією II класу спостерігалися найвищі середні значення піднебінного індексу (P=0,03). Для верхніх дихальних шляхів клас I мав найбільше середнє значення (P=0,041), тоді як клас III мав найвище середнє значення (P=0,026) для нижніх дихальних шляхів. Було зроблено висновок, що суб'єкти зі скелетним типом II класу мають високе піднебіння та зменшені верхні та нижні дихальні шляхи порівняно зі скелетними типами класу I та класу III, які показали більші верхні та нижні дихальні шляхи відповідно.*

Ключові слова: ортодонтія, діагноз, патологія прикусу, ортодонтичні апарати, зубна дуга.

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Explanatory language in dental informed consent communication

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Abstract: *Informed consent is a legal and ethical cornerstone of dental care, yet its effectiveness depends not only on content but also on clarity of communication. While existing research extensively covers the ethical and legal aspects, less attention has been given to the linguistic strategies that shape patient comprehension. This study examines the use of code glosses, i.e. in-text clarifications of technical terms, in 50 informed consent forms (ICFs) used in U.S. dental practices. Using Hyland's metadiscourse model and the Text Inspector tool, glosses were identified, categorized, and analyzed across different sections of the forms. Results show that Explanation glosses dominate (45.9%), with Implication and Exemplification glosses each at 19.7%. Most glosses appear in Procedure (30%) and Diagnosis (28%) sections, while fewer are found in Risk (22%) and Consent statements (10%). These findings highlight areas where patients may receive insuficient support to understand complex or abstract information, particularly when it comes to making truly informed choices. Glosses improve readability by unpacking specialized language and reducing cognitive load, especially under conditions of stress or limited health literacy. Despite their benefits, certain gloss types, such as analogies or conditionally phrased advisories, remain underused, possibly due to legal caution or a preference for standardized phrasing. The study underscores that code glosses are essential communicative tools, not mere stylistic additions. Greater integration of patient-friendly language and multimodal strategies is recommended to strengthen informed consent practices and promote clearer, more equitable healthcare communication.*

Keywords: Dental Care, Health Communication, Informed Consent, Patient-Centered Care, Patient Education, Terminology.

Introduction

Informed consent is a cornerstone of ethical and legal dental practice, ensuring that patients make voluntary and informed decisions about their treatment. The concept of informed consent involves a process where patients voluntarily agree to treatment after being informed about its advantages, risks, alternatives, and potential consequences. In dentistry, as well as in healthcare more broadly, informed consent is not only an ethical obligation but also a legal requirement. It protects patient autonomy, promotes transparency in the patient-provider relationship, and serves as a safeguard against potential legal disputes. The failure to obtain proper informed consent may lead to legal liability for negligence or battery, even if the clinical outcome is successful. Moreover,

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informed consent functions as both a procedural and communicative act, requiring not just the presentation of information, but its meaningful exchange and patient comprehension.

Informed consent has been a subject of extensive research across multiple disciplines, including medicine [1 – 3], law [4 – 6], nursing [7 – 9], bioethics [10 – 12], sociology [13 – 15], and psychology [16 – 18]. By 2003, over 4,000 empirical studies had been published on the topic, reflecting its critical role in modern healthcare ethics and communication [10]. However, despite this extensive literature, there remains a significant gap in exploring the discursive and linguistic dimensions of consent forms as communicative instruments. Recent studies have highlighted the challenges posed by complex language in consent documents, which can hinder participant comprehension and undermine the consent process [3; 9; 10]. For instance, a 2017 computational linguistic analysis revealed that many consent form templates use language exceeding the recommended reading level, potentially impeding participant understanding [19]. Other research emphasizes the need for clearer language and more inclusive communication strategies to ensure truly informed consent [20; 21; 22]. Kazembe D. M. et al. identified long and complex consent forms as major barriers to participant understanding, recommending efforts to simplify language, use demonstrations, and allow repeated explanations to improve comprehension [20]. Santel F. at al emphasized that technical language and ambiguity in consent forms negatively impact participant understanding and compliance [21]. Goldshmitt M. et al reviewed digitalization of informed consent, highlighting AI-driven chatbots and large language models like ChatGPT to simplify consent materials, provide personalized explanations, and improve patient comprehension and engagement [23]. These findings as well as extensive existing literature underscore the importance of addressing linguistic and cultural barriers to enhance the effectiveness of informed consent as a communicative act.

Building on these concerns, evidence from dental settings further illustrates how inadequate communication can compromise the consent process [24; 25]. A substantial number of dental practices fail to provide sufficient verbal explanations alongside written forms, heightening the risk of misunderstanding or misinterpretation. The use of specialized medical terminology, for example, prosthodontics or periodontitis, can be particularly problematic for individuals without a healthcare background [26]. This challenge is further intensified by systemic constraints: clinicians' time with patients is increasingly restricted by regulatory requirements, documentation and billing tasks, administrative responsibilities, and broader market pressures, all of which reduce opportunities to deliver thorough explanations as mentioned by Bala S. and co-authors [27]. Whether informed consent forms are presented on paper or through digital platforms, patients often face comparable challenges in navigating lengthy and complex text. Online formats may improve accessibility and standardization, but they do not automatically resolve issues of readability, jargon, or cognitive overload [28; 29]. Indeed, electronic forms may even introduce new barriers, such as limited digital literacy, distractions from multitasking, or difficulties in engaging with static text on screens [30]. Conversely, some studies suggest that interactive digital consent systems, those incorporating visuals, videos, or adaptive explanations, can enhance comprehension and recall when compared with traditional written documents [31]. Nevertheless, the core difficulty remains: patients must still struggle through highly technical content, often at moments of heightened anxiety, regardless of the medium.

Compounding this issue, emotional factors often affect patients' ability to process complex information. High levels of anxiety or distress can impair cognitive functioning, leading patients to feel overwhelmed or disengaged [32]. These emotional states not only reduce information retention but can also distort patients' perceptions of risks and benefits, ultimately impairing their capacity for informed decision-making [22; 33, 34]. Individuals experiencing anxiety often struggle to fully comprehend and retain the information

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provided by healthcare professionals, which further complicates their ability to process essential medical details [35]. Thus, beyond linguistic complexity, both emotional and contextual factors play a critical role in shaping the efficacy of informed consent, particularly in high-stress clinical environments.

In response to these challenges, researchers and practitioners have turned to linguistic strategies aimed at enhancing clarity and supporting informed decision-making. One such strategy is the use of code glosses – brief, in-text explanations that clarify technical or specialized terms [36]. Recognized in discourse analysis as one of key elements of metadiscourse, code glosses serve both textual and interpersonal functions [37; 38]. They help readers navigate dense medical language by providing definitions, reformulations, or illustrative examples, thereby making unfamiliar content more accessible. In the context of informed consent forms, code glosses can significantly improve comprehension and promote patient autonomy by reducing the cognitive load associated with complex terminology.

Within medical and dental discourse, particularly in legally binding documents such as consent forms, code glosses function as textual signposts, guiding the reader's attention to essential terms while fostering clarity and transparency. In their recent studies, Hyland K. and co-authers emphasize their dual role in enhancing understanding and fulfilling ethical obligations regarding patient information disclosure [39 – 41]. By incorporating glosses, healthcare providers can better accommodate patients with diverse levels of health literacy, ensuring that critical procedural information, risks, and alternatives are comprehensible. Furthermore, the use of code glosses has been linked to reduced cognitive overload, which is especially important in emotionally charged settings such as hospitals [19; 42]. Contemporary linguistic research also advocates for multimodal glossing, combining textual explanations with visual aids or analogies to support comprehension, particularly for low-literacy or multilingual populations [43 – 45]. This evolving approach positions code glosses not as superficial clarifications, but as essential communicative tools that enhance equity, inclusion, and ethical patient care.

Aim

The purpose of this study is to examine the integration and distribution of code glosses in dentistry informed consent forms (ICFs), with a particular focus on their role in enhancing textual clarity, reducing miscommunication, and promoting patient autonomy. Grounded in both practical and academic concerns, this research emphasizes the alignment of gloss usage with patient-centered care principles, as well as legal and ethical standards of transparency. Specifically, the study aims to analyze how code glosses are employed across various sections of informed consent documents, categorize them by linguistic and functional types, and evaluate their effectiveness in supporting patient understanding of medical and procedural terminology. The research also seeks to identify usage patterns across different dental specialties, contributing to the development of more accessible, ethically sound, and communicatively effective consent practices in dental care.

Materials and methods

This study adopts adescriptiveandexploratory approach, aiming to examine metadiscourse features as they naturally occur in written texts. The identification and categorization of metadiscourse elements, particularly code glosses, is grounded in Hyland's metadiscourse model [36].

The data set comprises a corpus of 50 original ICFs for dental treatment and procedures used within the U.S. healthcare system by providers authorized to deliver oral and dental services. The forms were retrieved using the Google search engine, with documents sourced from reputable platforms including Open Dental Software, the American Dental Association (ADA) dental records reference, and Delta Dental Incorporation.

To analyze metadiscourse markers, the texts were processed using *Text Inspector*, a professional web-based linguistic analysis tool. This platform identifies fourteen categories of metadiscourse markers based on the classification system developed by Bax S. et al [46, which

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expand upon Hyland's original taxonomy [36]. The results of the metadiscourse analysis, generated by *Text Inspector*, were visually represented in bar charts (Fig. 1), enabling quantitative insights into distribution patterns.

Within each ICF, code glosses were identified and systematically categorized. Their percentage distribution was calculated to detect usage patterns across different sections of the forms. Furthermore, the glosses were assessed in terms of clarity, relevance, and accessibility, particularly in linguistically dense sections such as *Procedure descriptions* and *Risk disclosures*. This multi-level analysis provided a comprehensive understanding of the role glosses play in enhancing patient comprehension within this type of medical documentation.

Results and Discussion

The analysis of a corpus comprising 50 randomly selected dentistry ICFs revealed coverage across a broad spectrum of dental procedures. Surgical and anesthesia-related interventions accounted for the largest proportion (40%), followed by orthopedic and orthodontic treatments (25%); therapeutic procedures (20%) and cosmetic dentistry (15%) were found to represent the smaller shares.

Each ICF was systematically analyzed for the presence of code glosses, metadiscursive devices that clarify or elaborate on specialized terminology and procedural details. These markers were categorized into five functional types, based on K. Hyland's taxonomy [36] and recent discourse-analytic frameworks:

1. Explanation (*e.g., 'that is', 'in other words'*): defines or rephrases technical dental terms (*e.g., 'apicoectomy, that is, surgical removal of a root tip of the tooth'*).
2. Implication (*e.g., 'this means', 'therefore'*): emphasizes outcomes or significance (*e.g., 'Local anesthesia will be used; this means you may feel pressure but no pain'*).
3. Specification (*e.g., 'specifically', 'particularly'*): narrows general instructions to precise situations (*e.g., 'Avoid hard foods, specifically nuts or raw vegetables'*).
4. Exemplification (*e.g., 'for example', 'such as'*): offers tangible examples (*e.g., 'Risks include bleeding, such as prolonged oozing from the extraction site'*).

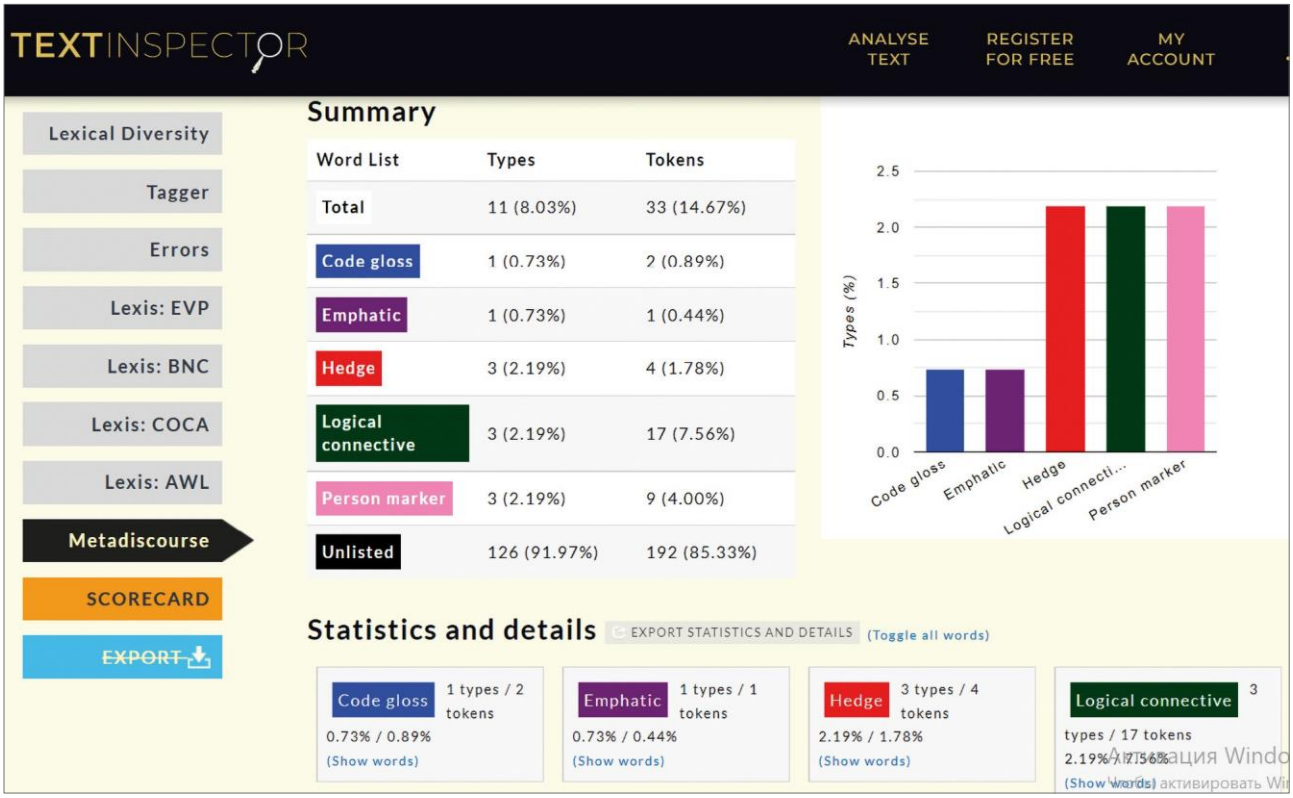

Fig. 1. Results of the Metadiscourse Analysis via Text Inspector

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5. Others: encompasses less conventional or hybrid glosses, including analogies and metaphors, which often serve to make abstract concepts more relatable (*e.g., 'The implant fuses with the bone like a natural tooth root'*).

Applying Hyland's classification sheds light on how code glosses bridge technical and patient-friendly language, reinforcing ethical and legal standards for comprehensibility in ICFs. Words such as *that is, for example, this means, specifically*, etc. function as metadiscursive signaling expressions that precede explanations, clarifications, or elaborations. Rather than contributing directly to the propositional content, they guide readers through the text by indicating how to interpret the surrounding information. Operating at both the textual and interpersonal levels, these pragmatic markers, typically categorized as adverbial phrases, enhance cohesion, support reader comprehension, and facilitate logical flow within informed consent forms.

The above functional categorization can offer a nuanced understanding of how glossing strategies support patient comprehension and contribute to more transparent and ethically responsible communication in dental consent practices. The distribution of gloss types across the analyzed corpus further emphasizes this communicative role.

The distribution of gloss types across the analyzed corpus highlights their distinct communicative functions (Fig. 2).

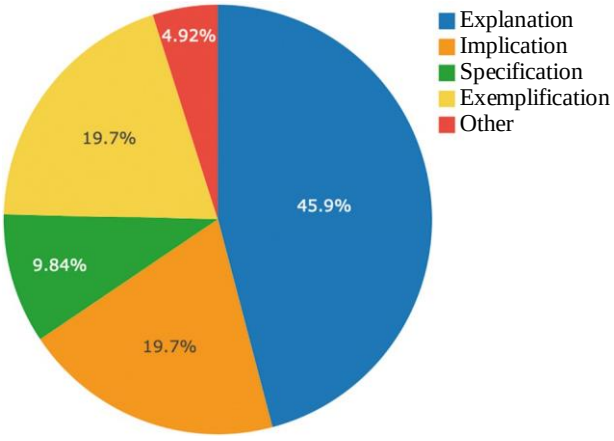

Fig. 2. Distribution of Code Gloss Types by Communicative Function in Dental Informed Consent Forms

Explanation glosses were by far the most prevalent, comprising 45.9% of all cases and signaling a strong emphasis on the direct clarification of dental terminology, e. g.:

Osteomyelitis (a bone infection) may begin. [59]

A crown, bridge, veneer (cosmetic cover), natural crown, a dental restoration or my natural tooth may break or crack because of the root canal treatment. [60]

Local anesthesia (injection) with oral premedication (pills before treatment). Informed consent and permission form – extractions. [61]

Implication and Exemplification glosses each accounted for 19.7%, approximately half the frequency of Explanations, underscoring their importance in contextualizing procedures and illustrating potential outcomes to aid interpretation. Within dental informed consent forms, implications serve as interpretive bridges between medical facts and patient understanding. They translate clinical risks into what these may mean for a patient's oral health, treatment, or daily life, thereby guiding readers toward clear conclusions, for example:

There is a high risk of damage to the restoration which may mean loss of porcelain or fracture. [62]

This may require transferring it to _____, where there isn't enough bone support (usually for placing dental implants). [63]

Failure to have a permanent restoration placed within 6 weeks following root canal treatment may result in leakage of the temporary restoration and reinfection of the root canals (requiring retreatment of the root canal) or fracture of the tooth (often requiring extraction). [60]

Exemplification glosses stand out because they anchor abstract, technical, or vague risks into familiar, concrete experiences. Unlike explanation glosses, which rephrase or define a term, specification glosses, which narrow general statements to precise situations, or implication glosses, which stress consequences, exemplification relies on vivid, patient-friendly examples that reduce abstraction and aid recall. In the context of medical settings, where patients

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are often confronted with dense medical or legal terminology, exemplification serves as a quite appropriate strategy for scaffolding comprehension [47 – 48]. For example:

Materials such as biodentine can help where nerve near nerve exposure is found (IC for Root Canal Treatment). [60]

Very sticky food, including some types of gum, sticky candies such as caramels, some licorices, very hard substances, etc., can cause loosening or dislodgment of the sealant. [64]

By offering concrete illustrations, clinicians make technical concepts tangible and relatable [36, 49].

Exemplification also aligns with findings in health communication research, which shows that patients process and retain information more effectively when it is presented through specific, everyday examples rather than abstract generalities [50 – 51]. For instance, the U.S. National Institutes of Health (NIH, 2017) recommends that risk communication should "include concrete examples that illustrate how a risk might be experienced in real life", as this improves patient understanding and decision-making [52]. Similarly, Spence P. et al demonstrate that the use of exemplars in medical risk communication enhances not only comprehension but also trust, as patients perceive the information as more transparent and accessible [53]. Informed consent in dentistry often involves discussing abstract risks such as '*possible complications*', '*failure of treatment*', or '*post-operative discomfort*'. Without exemplification, such terms may remain too vague for patients to grasp their practical implications. However, by embedding glosses like '*post-operative discomfort, such as swelling or tenderness when chewing*', practitioners bridge the cognitive gap between professional terminology and patient experience. This strategy reduces uncertainty, mitigates anxiety, and supports ethical principles of autonomy by ensuring patients can make genuinely informed choices [54 – 55]. Taken together, Exemplification glosses are not merely stylistic devices but evidence-based communicative tools that make complex medical information concrete, memorable, and actionable for patients, thereby enhancing the quality of informed consent.

Specification glosses were less frequent, comprising 9.84% of the total. While still valuable, their more limited use may reflect the nature of informed consent documents, which often prioritize general explanations over situational details. Because these texts are typically designed for broad applicability across patients and scenarios, there may be fewer opportunities, or less perceived necessity, for narrowing general instructions to specific cases. For example:

Even though in the majority of the cases (whitening, bleaching, bonding and veneering teeth) there is usually no appreciable sensitivity, this type of treatment may cause teeth to become sensitive. [59]

I understand that the process of fabricating and fitting removable prosthetic appliances (partial dentures and/or complete artificial dentures) includes risks and possible failures. [65]

Other glosses, including analogies, hybrid glosses, or conditionally phrased advisories, comprised only 4.92% of the total. Here are some examples:

Hybrid gloss: *Crowns and bridges are not as strong as natural teeth and extra care is needed to avoid undue trauma to them such as wearing mouth-guards during sports.* [65]

Analogue: *Occasionally, the canals are calcified or blocked, preventing sealing of the root end. Similarly, instruments tips occasionally break of f within the canal preventing sealing of the root end.* [60]

Conditionally phrased advisories: *If you do not follow post-operative instructions, healing may be delayed.* [59]

The analogies include concrete comparison (e. g. crowns vs natural teeth) to help patients understand limitations in familiar terms; the advisories, often use modal verbs lie *may, might, could*, or conditional phrases like *if, in case, depending on* to indicate conditionality and tend to blend description of what *could* happen with what *might* make those risks more likely (pre-disposing factors, patient behavior, etc.). The advisories typically point out potential risks,

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side effects, or procedural outcomes without overpromising or creating legal liability and emphasize the role of patient compliance in recovery outcomes: they are a cautious way to clarify uncertainties while still informing the patient.

The relatively low frequency of these residual glosses may be attributed to the inherently cautious and standardized nature of medical-legal documents like ICFs. While such glosses can be rhetorically powerful and helpful in making abstract concepts more relatable (e.g., comparing an implant to a natural tooth root), they may also introduce ambiguity or unintended interpretations.

As a result, healthcare professionals and legal advisors may limit their use to avoid miscommunication or legal liability. Furthermore, the use of figurative or non-literal language is less common in technical writing, which often prioritizes precision, neutrality, and clarity over creativity or personalization. Consequently, these glosses tend to appear only in cases where a more accessible or empathetic explanation is considered essential to patient understanding.

In addition to functional classification, each gloss was mapped to the specific section of the consent form in which it appeared, including *Description of the procedure/treatment*, *Diagnosis or condition information*, *Risks and potential complications*, and *Voluntary consent statements*. The percentage distribution of gloss types was calculated to identify dominant patterns and potential areas of linguistic complexity or patient misunderstanding. The analysis revealed that the highest proportion of glosses (30%) appeared in the section describing the procedure or treatment, followed closely by 28% in the section providing diagnosis or information about the condition requiring treatment. Glosses related to possible risks and complications accounted for 22%, while only 10% were found in the patient's voluntary consent section. These findings suggest that the most conceptually and linguistically dense sections, particularly those explaining procedures and diagnoses, may benefit from enhanced clarity and additional support to facilitate patient comprehension.

The observed distribution indicates prioritized a focused effort to ensure terminological clarity and enhance patient understanding in consent form sections that involve greater conceptual or procedural complexity. The predominance of explanation glosses reflects purposeful linguistic adjustments aimed at supporting informed decision-making in high-stakes dental contexts, where miscommunication may compromise patient autonomy or adherence. These results point to the need for targeted improvements in patient-healthcare provider communication, including practitioner training in the consistent and effective use of metadiscursive clarification strategies.

Gloss usage within informed consent documents demonstrates a clear strategy to improve comprehension and reduce ambiguity. The frequent inclusion of explanation glosses shows an intent to make technical dental language more accessible by rephrasing or unpacking key terms. This is especially critical in sections detailing procedures and diagnoses, where accurate understanding is essential. The comparable presence of implication and exemplification glosses further enhances interpretability by providing contextual cues and concrete examples that aid patient processing of complex information.

The lower frequency of specification and other glosses may indicate areas where consent form designers rely less on nuanced clarification, potentially because the content is more straightforward, or due to space constraints. However, these underused gloss types could offer additional support, particularly for patients with lower health literacy levels.

From a clinical communication perspective, the strategic placement of glosses within complex sections of the form points to an awareness, whether conscious or intuitive, of where patients are most likely to struggle. These findings align with existing research highlighting the importance of clarity and plain language in legal and medical documentation [30, 56 – 58].

However, the overall effectiveness of glosses also depends on their clarity, tone, and relevance. A gloss that is too technical or too vague may do little to aid comprehension. This reinforces

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the need for patient-centered design principles, where consent forms are co-developed or tested with actual patients, ensuring that linguistic strategies such as glossing serve their intended purpose: enhancing understanding, not merely expanding content.

Limitations

While this study provides valuable insights into the role of code glosses in enhancing the readability and communicative clarity of dental ICFs, several limitations should be acknowledged. First, the sample size was limited to a specific set of consent forms from dental clinics and academic institutions, which may not fully represent the diversity of ICFs used across regions, specializations, or healthcare systems. The generalizability of the findings may therefore be constrained by institutional or cultural variations in document design and language use.

Second, the study focused exclusively on the linguistic features of the written consent forms and did not include patient feedback or comprehension assessments. As a result, while the functional categorization of glosses provides a useful framework for assessing potential clarity, it does not offer conclusive evidence about their effectiveness in practice. Moreover, individual differences in health literacy, language proficiency, and prior dental knowledge may significantly mediate how patients interpret and benefit from these clarifying strategies.

Third, the study did not assess visual or multimodal elements that may accompany or support textual content in ICFs such as diagrams, icons, or formatting features, which can also play a critical role in shaping understanding.

Future research should aim to address these limitations by incorporating mixed-methods approaches, combining textual analysis with patient surveys, interviews, or comprehension testing. Investigating how different patient groups (e.g., varying in literacy level, language background, or age) interpret glosses would offer critical insights into tailoring consent materials for inclusivity and equity. Exploring the integration of digital or multimedia consent formats (e.g., interactive forms with embedded glosses, audio explanations, or visuals) presents a promising avenue for future innovation in consent communication.

Conclusion. This study shows that code glosses are vital for enhancing patient comprehension and safeguarding ethical principles of autonomy and informed decision-making. Nearly half (45.9%) of glosses served to explain technical terms, underscoring the central role of definitional clarity in dental communication. Their frequent use in procedure (30%) and diagnostic (28%) descriptions highlights clinicians' awareness of patient needs in complex areas, while their relative absence in risk and consent sections raises concern about patients' ability to make fully informed choices.

Clear and patient-centered communication is fundamental to ethically robust informed consent. For Ukrainian healthcare, where rebuilding trust and ensuring transparency are especially important in the context of war-related stress and ongoing reform, strengthening informed consent practices is a pressing priority. Improving how risks, benefits, and patient rights are communicated can help ensure that consent is not only a formality but a genuine expression of understanding and autonomy. Expanding these practices, supported by patient feedback and cross-cultural analysis, will contribute to more ethically sound and legally resilient healthcare delivery.

Financing

This study had not obtained external funding.

Conflicts of interest

Authors have no conflict of interest to declare.

AI disclosure

The authors declare that no AI tools were used in the generation of content, data analysis, or drafting of this article.

Consent to publication

All authors agreed to publish this manuscript. All authors have read and approved the final version of the manuscript.

Ethical Considerations

This study involved a text-based linguistic analysis of publicly available informed consent documents and did not include any human participants or personal data. Therefore, ethical approval was not required. The study complies with the principles of the Declaration of Helsinki

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(2013 version) regarding ethical standards in biomedical research involving human subjects, particularly in its emphasis on transparency and informed decision-making.

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Software: Anastasiia Pysarenko;

Validation: Viktoriia Kostenko;

Formal Analysis: Viktoriia Kostenko, Anastasiia Pysarenko;

Investigation: Anastasiia Pysarenko, Viktoriia Kostenko;

Resources: Anastasiia Pysarenko, Viktoriia Kostenko

Data Curation: Viktoriia Kostenko;

Writing – Original Draft: Anastasiia Pysarenko;

Writing – Review & Editing: Viktoriia Kostenko;

Visualization: Anastasiia Pysarenko;

Supervision: Viktoriia Kostenko;

Project Administration: Viktoriia Kostenko;

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Пояснювальні стратегії у процесі отримання інформованої згоди в стоматологічній практиці

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Анотація: *Успішне отримання інформованої згоди на лікування залежить не лише від змісту документа, а й від чіткості, доступності та ефективності комунікації між лікарем і пацієнтом. Попри значну увагу до етичних і правових аспектів інформованої згоди, лінгвістичні чинники, що впливають на розуміння пацієнтами наданої інформації, залишаються недостатньо вивченими. Метою дослідження є аналіз використання внутрішньотекстових роз'яснень складних медичних термінів (code glosses) у формулярах інформованої згоди, що застосовуються у стоматологічних клініках США. У вибірку увійшли 50 документів. Аналіз здійснено на основі моделі метадискурсу Кена Гайленда із використанням інструменту Text Inspector для ідентифікації та класифікації типів роз'яснень і визначення їх функціонального навантаження в різних структурних розділах текстів. Результати показали, що найбільш поширеними є роз'яснення типу пояснення (explanation), що складають 45,9%, тоді як вказівка на наслідки (implication) та приклад (exemplification) становлять по 19,7% кожен. Більшість роз'яснень зафіксовано у розділах «Опис процедури» (30%) та «Діагноз» (28%), рідше – у розділах «Ризики, пов'язані з процедурою» (22%) та «Добровільна згода» (10%). Ці дані свідчать про нерівномірність лінгвістичної підтримки в текстах інформованої згоди, що потенційно ускладнює розуміннядля пацієнтів з низьким рівнеммедичноїграмотності. Внутрішньотекстові роз'яснення відіграють важливу роль у зниженні когнітивного навантаження та забезпеченні доступностіінформації,особливодлявразливихгрупнаселення.Натомістьдеякітипироз'яснень, зокрема аналогії або умовні формулювання, використовуються вкрай рідко, імовірно через юридичні чи стилістичні обмеження. Дослідження підтверджує, що лінгвістичні стратегії, спрямовані на роз'яснення спеціалізованої інформації, є не другорядними стилістичними засобами, а ключовими елементами пацієнт-орієнтованої комунікації. Рекомендується ширше впроваджувати зрозумілу, адаптовану до потреб пацієнта мову, а також мультимодальні інструменти для підвищення ефективності інформованої згоди.*

Ключові слова: стоматологічна допомога, комунікація в охороні здоров'я, інформована згода, пацієнт-орієнтована допомога, навчання пацієнтів, термінологія.

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Prevalence and intensity of dental caries in adolescents with juvenile idiopathic arthritis

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Abstract: *One of the central problems of modern dentistry is the analysis of the impact of juvenile idiopathic arthritis (JIA) - the most widespread heterogeneous rheumatic disease in pediatrics on a child's dental health. The prevalence of JIA in Ukraine is 0,37 cases per 1000 children under 17 years of age with a tendency to increase. JIA is a collective term that combines various forms of arthritis of unknown etiology, which debut in children under 16 and lasts for more than 6 weeks. The central idea in JIA management is that treatment, timeliness, and adequacy determine the disease's prognosis and the child's further development. The primary principles in the treatment of JIA manifestations remain the principles of basic therapy of the disease, necessarily with the use of disease-modifying antirheumatic drugs. Taking into account the negative dynamics of the incidence of JIA and scientific data about the impact of the disease on the condition of hard dental tissues, conducting research in this area is of particular scientific interest to us. This study aims to determine the prevalence and intensity of the carious process in adolescents suffering from JIA, taking into account the subtypes of rheumatological disease and the possible negative impact of basic drug therapy. As part of the study, a dental examination of 80 adolescent children suffering from JIA was conducted. The control group consisted of 20 healthy adolescents. By the study design, the study participants were divided primarily by the presence of JIA; the second division was based on the presence of a specific subtype of JIA in the study participants: groups with polyarticular rheumatoid factor positive (RF+) (n=29), oligoarticular (n=24), enthesitis-associated (n=12), polyarticular RF- (n=10), undifferentiated (n=5) variants of JIA and a control group (n=20). Another division of the study participants took place according to the basic medical support: groups of patients taking methotrexate at a dose of less than or equal to 15 mg (n=43) and greater than 15 mg (n=18), a group of patients receiving adalimumab (n=20) and a control group (n=20). An examination of the oral cavity, recording of the dental formula and determination of the prevalence and intensity of the carious process in the studied groups depending on the presence of JIA, basic medical support and subtype of the disease were performed. Statistical analysis of the data was performed using the STATISTICA 10.0 program. It was noted that patients with JIA have a 1,6-fold higher intensity of dental caries compared to children without JIA (p= 0,004). Analysis of the structure of the DMF+df index allows us to state that patients with JIA have carious lesions of permanent teeth on average 2 times more often compared to the control group (p= 0,004). Analysis of the effect of basic drug therapy on the caries intensity in general and separately on each*

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structural component of the DMF+df index showed that patients taking methotrexate at a dose of less than or equal to 15 mg have an average caries intensity of 1,25 times higher compared to patients who take adalimumab, and a 2-fold higher intensity of the carious process compared to children without general somatic pathology (p = 0,0096 and p = 0,0008, respectively). The study also showed that patients taking methotrexate at a dose of less than or equal to 15 mg have an average of 3 times higher frequency of carious lesions of permanent teeth (p = 0,0016). The analysis of the influence of the JIA subtype on the intensity of the carious process showed that patients with RF-negative polyarticular and oligoarticular variants of JIA have, on average, twice the intensity of caries compared to the control group (p = 0,0032 and p = 0,0065, respectively). In contrast, the JIA subtype does not affect the structure of caries incidence in adolescents.

Keywords: Adolescent, Dental Caries, Prevalence, Arthritis, Juvenile.

Introduction

Juvenile idiopathic arthritis (JIA) is “arthritis of unknown etiology that begins before the age of 16 and lasts at least 6 weeks and other known conditions are excluded” [1,2]. According to official statistics, the prevalence of JIA in Ukraine is 0,37 cases per 1000 people and there is a fairly pronounced tendency for its increase [3].

According to scientific research, JIA is considered the main rheumatological disease of childhood that leads to short-term and long-term disability [4]. The central place in the problem of JIA is occupied by the issue of treatment, the timeliness and adequacy of which determines the prognosis of the disease and, probably, the further life of the child [5].

The main goal of JIA treatment is to achieve clinical remission [6]. The main goal of treatment is to control the activity of JIA [7]. Until the time goal is achieved, drug therapy should be changed at least every 3 months [6].

The primary treatment for JIA manifestations today remains the principles of basic therapy of the disease, which include disease-modifying antirheumatic drugs [8].

The main dilemma of JIA treatment is that, on the one hand, the lack of drug support for patients with this disease leads to impaired growth and development of the child's body (Garner AJ et al.) [9], and on the other hand, the use of disease-modifying antirheumatic drugs, as the authors indicate, can cause serious side effects [10].

Analysis of the results of scientific studies related to the investigation of caries in patients with JIA showed rather ambiguous results. Thus, Pylypyuk O.Yu. in her PhD thesis states that children with JIA have 2-3 times higher intensity of caries compared with healthy individuals. She also notes that patients with JIA demonstrate a tendency to the prevalence of decompensated forms of caries in the structure of dental morbidity as opposed to compensated ones in the control group [11].

Similar results were obtained by Welbury, R. et al. Thus, they emphasized the increase in the frequency of caries in all age groups of children with JIA compared to children in the control group [12].

Savioli, C. et al., studying this problem in Brazil, also noted a difference in the DMF index in children with JIA, that correlates with the tendencies cited above [13].

At the same time, Gil E. et al., analyzing the prevalence of caries in children with JIA living in Norway, compared to the control group, did not find any differences in the prevalence of this dental disease. At the same time, they did not reject the hypothesis of the presence of potential correlations between the indicators characterizing JIA and the activity of caries [14]. Taking into account the negative dynamics of the incidence of JIA, the lack and certain controversy of data in the literature on the impact of the disease on the condition of hard dental tissues (Walton A.G. et al.) [15], conducting research in this area is of particular scientific interest to us.

Aim

To determine the prevalence and intensity of caries in adolescents with JIA, taking into account the subtypes of the rheumatological

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disease and the possible negative impact of basic drug therapy.

Materials and methods

The study, which was conducted at the Department of Cardiorheumatology of the State Institution "Institute of Child and Adolescent Health Care, AMS of Ukraine", involved 80 children aged 10 to 17 years with a diagnosis of JIA, verified by a pediatric rheumatologist. Patients received treatment according to the guidelines of medical care for children in the specialty "Pediatric Cardiorheumatology". The control group consisted of 20 adolescents aged 10 to 17 years without concomitant general somatic pathology. Before being involved in the study, informed consents were signed by the participants and their parents or caregivers. The research protocol was developed in accordance with The Declaration of Helsinki (2013) principles and was approved by the Ethics and Bioethics Commission of Kharkiv National Medical University on October 12, 2022 (protocol № 2). All participants in the experiment underwent a basic dental examination and a dental formula record. To determine the intensity of the carious process during the period of alternating occlusion, the index DMF+df, permanent- DMF (where d- decayed temporary tooth, f- filled temporary tooth, D- carious lesion of a permanent tooth, F- filled permanent tooth, M- missed permanent tooth) was used. Prevalence of caries in children with JIA and the control group was calculated as the percentage of people with carious, filled and extracted teeth from the total number of respondents in the group.

According to the study design, the distribution of participants occurred three times. Firstly, patients were divided according to the presence (n = 80) or absence (n = 20) of JIA. Within the next division, 4 groups were created according to the basic therapy of JIA: patients with JIA receiving methotrexate (MTX) at a dosage of less than or equal to 15 mg (n = 43), patients with JIA receiving MTX at a dosage of more than 15 mg (n = 18), patients with JIA receiving MTX and adalimumab (n = 19) and the control group (n = 20). The third distribution was based on the presence of a certain subtype of JIA in the patient: patients with polyarthritis rheumatoid factor positive (RF+) (n = 29), polyarthritis RF- (n = 10), enthesitis-related (n = 12), undifferentiated (n = 5), oligoarthritis (n = 24) variants of JIA and the control group (n = 20). In each of the distributions, the groups were comparable in age and sex.

Statistical analysis was performed using the STATISTICA 10.0 program. Shapiro-Wilk normality test (W test) was used to analyze the distribution of quantitative characteristics in each group. For samples with non-normal distribution, the values of the median (Me), upper and lower quartiles Me (Lq; Uq) were indicated. Taking into account a non-normal distribution of data, the Mann-Whitney U-test (UMV) was used to test the significance of the differences in the mean values of independent groups in the case of pairwise comparisons, and with three or more comparisons, the Kruskal-Wallis H-test with posterior comparisons by UMV was used. To assess the statistical significance of the differences in relative indicators Pearson's chi-square test was used taking into account the fact that when the expected phenomenon took a value from 5 to 9, the Yates correction was used. When comparing relative indicators, the Fisher exact test was used. A $p<0,05$ value was considered statistically significant; for multiple comparisons of quantitative characteristics, the Holm-Bonferroni and Benjamini-Hochberg methods were used.

Results

Analyzing the prevalence of caries in this study, we found that in the group of children with JIA out of 80 adolescents, only 6 people did not have signs of carious lesions of the teeth (92,5%), and in the control group, among the 20 examined, only two did not have carious disease (90%). Thus, both groups demonstrate quite similar indicators, which may be interpreted as a high prevalence of caries. The Fisher exact test ($p = 0,659$) indicates the impossibility of rejecting the null hypothesis, i.e., there is no statistically significant difference in the prevalence of caries between the JIA and control groups in this study.

Having analyzed the intensity of the caries process in the group of children with JIA, we found that the median value is 4,0 with an

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interquartile range from 2,0 to 6,0. The intensity of caries in the control group was 2,5 (1,0;4,0), respectively. Further analysis of the data set using UMV showed a statistically significant difference in the data obtained (p = 0,004), and therefore we can state that patients with JIA in this study had an average of 1,6 times higher intensity of the carious process compared to children without somatic pathology (Table 1). Analysis of the structure of the intensity of the carious process in the above groups did not reveal statistically significant differences in the components "d", "f", "F", and "M", however, the intensity of carious lesions of permanent teeth was 2 times higher in the group of adolescents with JIA compared to those somatically healthy with p = 0,004 (Table 2). In general, we see that adolescents of both groups have carious lesions and dental fillings mainly in permanent teeth, and therefore it is necessary to carry out effective prevention of diseases of the hard tissues of permanent teeth.

As a next step, the impact of basic JIA therapy on the intensity of the caries was assessed. Kruskal-Wallis test was performed (H (3, N = 100) = 14,45, p = 0,002) to indicate the presence of significant differences between the compared groups. Then pairwise comparisons were made between groups using a posterior UMV with a level of statistical significance adjusted according to the Holm-Bonferroni method. It was found that patients receiving MTX at a dosage of less than or equal to 15 mg had a 1,25-fold higher intensity of the carious process compared to patients receiving adalimumab, and a 2-fold higher intensity of the carious process compared to the control group, and the above differences are statistically significant (Table 3). The analysis of the structure of the DMF+df index depending on the type of basic medication did not reveal statistically significant differences in the components "d", "f", "F", "M", however, the Kruskal-Wallis test (H (3, N=100)= 13,51, p= 0,004) showed the presence of significant differences in the component of carious lesions of permanent teeth. A series of posterior pairwise comparisons with the level of statistical significance adjusted according to the Holm-Bonferroni method allows us to conclude that in this study, patients receiving MTX at a dosage of less than or equal to 15 mg were three times more likely than children in the control group to have carious lesions of permanent teeth (p=0,0016) (Table 4).

As the next step, the analysis of the influence of JIA subtypes on the intensity of caries was performed. The Kruskal-Wallis test showed the result H (5, N=100) = 11,03, p = 0,049, which indicates the presence of significant differences in the compared groups. A series of pairwise posterior comparisons using UMV with the level of statistical significance adjusted according to the Benjamini-Hochberg method allows us to state that patients with RF-negative polyarticular and oligoarticular variants of JIA have on average twice the intensity of the caries process compared to that in healthy children of the control group (Table 5). The analysis of the DMF+df index did not reveal statistically significant differences between the groups, which allows us to conclude

Table 1. Prevalence and intensity of the carious process in children with JIA and the control group

	Patients with JIA (n=80)	**Controls (n=20)**	**p**
Prevalence of caries	92,5 %	90 %	p= 0,659
Intensity of caries	4,0 (2,0;6,0)	2,5 (1,0;4,0)	p UMV=0,004

Table 2. Structure of caries intensity in adolescents with JIA and controls

	d	**f**	**D**	**F**	**M**
Patients with JIA (n=80)	0 (0;0)	0 (0;0)	2 (1;4)	0 (0;2)	0 (0;0)
Controls (n=20)	0 (0;0)	0 (0;0)	1(0;1)	0 (0;2)	0 (0;0)
p UMV	0,42	0,96	0,004	0,66	0,80

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Table 3. Intensity of the carious process in JIA patients dependent on medication

	JIA patients, taking MTX ≤15 mg (n=43)	JIA patients, taking MTX >15 mg (n=18)	JIA patients, taking MTX+adalimumab (n=19)	Controls (n=20)
Caries intensity	5,0 (3,0;8,0)	4,0 (2,0;6,0)	4,0 (2,0;5,0)	2,5 (1,0;4,0)

$p_{MTX \leq 15mg - MTX >15mg} = 0,198$; $p_{MTX \leq 15mg - adalimumab} = 0,0096$*;
$p_{MTX \leq 15mg - controls} = 0,0008$*; $p_{MTX >15mg - adalimumab} = 0,256$;
$p_{MTX>15mg - controls} = 0,049$; $_{adalimumab - controls} = 0,243$
* – statistically significant p value corrected using Holm-Bonferroni method

Table 4. Structure of caries intensity in adolescents with JIA dependent on medication

	d	f	D	F	M
JIA patients, taking MTX ≤15 mg (n=43)	0 (0;0)	0 (0;0)	3(1;5)	1 (0;2)	0 (0;0)
JIA patients, taking MTX >15 mg (n=18)	0 (0;0)	0 (0;0)	2(1;4)	1 (0;2)	0 (0;0)
JIA patients, taking MTX+adalimumab (n=19)	0 (0;1)	0 (0;0)	1(0;3)	0 (0;1)	0 (0;0)
Controls (n=20)	0 (0;0)	0 (0;0)	1(0;1)	0 (0;2)	0 (0;0)
Kruskal-Wallis test	H (3, N=100) = 2,17, p= 0,54	H (3, N=100) = 0,58, p= 0,89	H (3, N=100) = 13,51, p= 0,004	H (3, N=100) = 1,77, p= 0,62	H (3, N=100) = 1,68, p= 0,64

$p_{MTX \leq 15mg - MTX >15mg} = 0,50$; $p_{MTX \leq 15mg - adalimumab} = 0,025$;
$p_{MTX \leq 15mg - controls} = 0,0016$*; $_{pMTX >15mg - adalimumab} = 0,118$;
$p_{MTX>15mg - controls} = 0,126$; $p_{adalimumab - controls} = 0,204$
*– statistically significant p value corrected using Holm-Bonferroni method

Table 5. Intensity of the carious process in JIA patients dependent on disease subtype

	JIA polyarthritis RF+ (n=29)	JIA polyarthritis RF- (n=10)	JIA enthesitis-related (n=12)	JIA undifferentiated (n=5)	JIA oligoarthritis (n=24)	Controls (n=20)
Caries intensity	4,0 (2,0;6,0)	5,0 (4,0;5,0)	5,0 (3,0;7,5)	5,0 (4,0;5,0)	5,0 (3,0;6,5)	2,5 (1,0;4,0)

$p_{poly RF+ - poly RF-} = 0,26$; $p_{poly RF+ - enth-rel} = 0,31$; $p_{poly RF+ - undif} = 0,44$;
$p_{poly RF+ - oligo} = 0,24$; $p_{poly RF+ - controls} = 0,16$; $p_{poly RF- - enth-rel} = 0,59$;
$p_{poly RF- undif} = 0,95$; $p_{poly RF- - oligo} = 0,60$; $p_{poly RF- - controls} = 0,0032$*;
$p_{enth-rel - undif} = 0,95$; $p_{enth-rel - oligo} = 0,76$; $p_{enth-rel - controls} = 0,02$;
$p_{undif - oligo} = 1,0$; $_{undif - controls} = 0,08$; $p_{oligo - controls} = 0,0065$*
*– statistically significant p value corrected using Benjamini-Hochberg method

that the JIA subtype has no influence on the structure of caries intensity in adolescents in this research (Table 6).

The results obtained in this research correlate with those reported by Gil E. et al. [14], and we also did not find a statistically significant difference in the prevalence of caries between children with JIA and those without comorbidity. Also, our analysis allows us to distinguish the disease subtype and its basic medical support

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Table 6. Structure of caries intensity in adolescents with JIA dependent on disease subtype

	d	f	D	F	M
JIA polyarthritis RF+ (n=29)	0 (0;0)	0 (0;0)	2,0 (1,0;4,0)	1,0 (0;1,0)	0 (0;0)
JIA polyarthritis RF- (n=10)	0 (0;0)	0 (0;0)	3,0 (2,0;4,0)	0 (0;1,0)	0 (0;0)
JIA enthesitis-related (n=12)	0 (0;0,5)	0 (0;0,5)	2,0 (0;5,0)	2,0 (0;2,0)	0 (0;0)
JIA undifferentiated (n=5)	0 (0;0)	0 (0;0)	1,0 (1,0;2,0)	3,0 (0;3,0)	0 (0;0)
JIA oligoarthritis (n=24)	0 (0;1,5)	0 (0;0,5)	2,5 (0;3,0)	0 (0;1,0)	0 (0;0)
Controls (n=20)	0 (0;0)	0 (0;0)	1(0;1)	0 (0;2)	0 (0;0)
Kruskal- Wallis test	H (5, N=100) = 10,23, p= 0,07	H (5, N=100) = 3,57, p= 0,61	H (5, N=100) = 10,72, p= 0,06	H (5, N=100) = 6,39, p= 0,27	H (5, N=100) = 2,6, p= 0,75

as specific factors that influence the course of caries. Also, our results correlate with those obtained by a Ukrainian researcher [11] in the context of the presence of differences in the intensity of caries between the studied groups, which in our opinion, can serve as a basis for the development and implementation of a rational program for the prevention of dental diseases in adolescents with JIA.

We believe that further large-scale multicenter clinical studies aimed at studying the impact of juvenile idiopathic arthritis on the condition of dental hard tissues are warranted. Such studies, in particular, using a larger sample of patients and standardized assessment methods, will allow us to more objectively confirm our conclusions and expand our scientific understanding of the relationship between systemic rheumatic diseases and dental health.

Conclusions

The data obtained during the study indicate that the basic therapy and the subtype of JIA have an impact on the caries intensity and the structure of the DMF+df index in the caries of permanent teeth component.

We see further prospects for the study in conducting multicenter prospective studies that will be concerned with the search for correlations between JIA-specific disease factors and caries disease, which will contribute to increasing the effectiveness of prevention programs and providing high-quality dental care to this group of patients.

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Conflict of interest

The authors declare that there is no conflict of interest.

Consent to publish

Komarov D.O. and Savelieva N.M. have reviewed the manuscript and agree to publish it.

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Поширеність та інтенсивність каріозного процесу у дітей підліткового віку, які хворіють на ювенільний ідіопатичний артрит

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Анотація: *однією з центральних проблем сучасної стоматології є вивчення впливу на стоматологічне здоров'я дитини ювенільного ідіопатичного артриту (ЮІА) – найбільш поширеного гетерогенного хронічного ревматичного захворювання у педіатрії. Поширеність ЮІА в Україні становить 0,37 випадки на 1000 дітей віком до 17 років з тенденцією до зростання. ЮІА – збірне поняття, що об'єднує різні форми артритів невідомої етіології, які дебютують у дітей до 16 років і тривають понад 6 тижнів. Центральне місце у проблемі ЮІА займають питання лікування, від своєчасності та адекватності якого залежить прогноз захворювання і, напевне, подальша доля дитини. Первинним у лікуванні проявів ЮІА залишаються принципи базисної терапії захворювання неодмінно із застосуванням хворобомодифікуючих протиревматичних препаратів. Зважаючи на негативну динаміку захворюваності на ЮІА та обмаль даних в літературі щодо впливу захворювання на стан твердих тканин зубів, проведення досліджень в цьому напрямку представляє для нас особливий науковий інтерес. Метою даного дослідження є визначенняпоширеностітаінтенсивностікаріозногопроцесувдітейпідліткового віку, які хворіють на ЮІА з урахуванням субтипів ревматологічного захворювання та можливого негативного впливу медикаментозної базової терапії. В рамках виконання дослідження проведене стоматологічне обстеження 80 дітей підліткового віку, які хворіють на ЮІА. Група контролю складалась з 20 соматично здорових підлітків. Згідно з дизайном дослідження було проведено розподіл учасників дослідження в першу чергу за наявністю у них ЮІА; другий розподіл базувався на наявності у учасників дослідження певного субтипу ЮІА: групи пацієнтів з поліартикулярним позитивним за ревматоїдним фактором (РФ+) (n=29), олігоартікулярним(n=24), ентезит-асоційованим (n=12), поліартикулярним РФ- (n=10), недиференційованим (n=5), варіантами ЮІА та група контролю (n=20). Ще один розподіл учасників дослідження відбувся відповідно до базового медикаментозного супроводу: групи пацієнтів, які приймають метотрексат у дозуванні менше чи рівному 15 мг (n=43) та більшому за 15 мг (n=18), група пацієнтів, яка прходить лікування адалімумабом (n=20), та контрольна група (n=20); Було проведено: огляд ротової порожнини, запис зубної формули, визначення показників поширеності та інтенсивності каріозного процесу в досліджуваних групах в залежності від наявності ЮІА, базового медикаментозного супроводу та субтипу захворювання. Статистична обробка масиву отриманих даних проведена з використанням програми STATISTICA 10.0. Визначено, що пацієнти з ЮІА мають у 1,6 разів вищу інтенсивність каріозного процесу в порівнянні з дітьми без ЮІА (p= 0,004). Аналіз структури індексу КПВ+кп дозволяє стверджувати, що пацієнти з ЮІА мають каріозні ураження постійних зубів в середньому в 2 рази частіше в порівнянні з контрольною групою (p=0,004). Аналіз впливу базової медикаментозної терапії на показник інтенсивності карієсу та окремо на кожен структурний компонент індексу КПВ+кп показав, що пацієнти, які отримують метотрексат у дозуванні менше чи рівному 15 мг мають інтенсивність карієсу в середньому в 1, 25 разів вищу в порівнянні із пацієнтами, які отримують адалімумаб, і у 2 рази більшу інтенсивність каріозного процесу в порівнянні з дітьми без загальносоматичної патології (p=0,0096 та p=0,0008 відповідно). В дослідженні також продемонстровано, що пацієнти, які отримують метотрексат у дозуванні менше чи рівному 15 мг, мають в середньому в 3 рази більшу частоту каріозного ураження постійних зубів (p=0,0016). Проведений аналіз впливу субтипу ЮІА на показник інтенсивності каріозного процесу показав, що пацієнти з РФ-негативним поліартикулярним та олігоартикулярним варіантами ЮІА мають в середньому у два рази більшу інтенсивність карієсу в порівнянні з групою контролю (p=0,0032 та p=0,0065 відповідно), в той же час субтип ЮІА жодним чином не впливає на структуру захворюваності на карієс у дітей підліткового віку.*

Ключові слова: підлітки, зубний карієс, поширеність, артрит ювенільний.

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Temporary Anchorage Devices usage stability in modern orthodontics: systematic review

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Abstract: *In orthodontic treatment, TADs have mostly been utilized for anchorage when patient compliance is lacking. Various failure rates have been reported in modern orthodontic literature. An accurate assessment of the TADs stability rate and potential risk factors for the mechanically-retained TADs was the aim of our research. Up to December 2017, MEDLINE, Scopus, and the Cochrane Library were used for electronic database searches. Reference lists were examined and further searching for ongoing and unpublished data was done. Hand searches of pertinent journals and grey literature were also conducted. We gathered English-language published prospective cohort studies (PCSs) and randomised controlled trials (RCTs) that detailed the failure rate of miniscrews, which are less than 2 mm in diameter, when used as an orthodontic anchoring. In this study, data extraction, risk of bias evaluation, and blind and duplicate study selection were done. Using the random-effects model, failure rates and pertinent risk variables for miniscrews were determined, along with the accompanying 95 percent confidence intervals (CIs). The* I^2 *and* Chi^2 *tests were used to evaluate the heterogeneity among the studies. The Newcastle-Ottawa Scale and the Cochrane Risk of Bias were used to determine the risk of bias. The robustness of the meta-analysis results was tested by using subgroup and sensitivity analyses. This study comprised 30 prospective clinical trials as well as 16 randomized clinical trials. Because there was insuficient statistical data to calculate the impact sizes, five studies were excluded from the meta-analysis. In a random-effect model, 3250 miniscrews approximately amongst 41 trials were combined. Miniscrews showed an overall failure rate of 13.5% (95% CI 11.5%–15.9%). Analysis of division groups revealed that smoking and the kind of gingivae had statistically significant effects on the rate of miniscrew failure, while the diameter, length, and design of the miniscrews, patient age, and place of insertion had non-significant effects. Conclusion: TADs have an acceptably low failure rate. Because of the high degree of heterogeneity and imbalanced groups in the included research, care should be taken when interpreting the results. To validate the results of this review, significant sample sizes from high-quality randomized clinical trials are needed.*

Keywords: Orthodontic Anchorage Procedures, Orthodontic Tooth Movement, Malocclusion, Orthodontic Appliances, Orthodontic Preventive, Orthodontic, Interseptive.

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Introduction

Orthodontists utilize orthodontic skeletal anchoring devices for a variety of therapeutic purposes. These consist of anchoring reinforcement, incisor and molar intrusion, molar protraction, molar distalization, and cross bite correction [1–7]. The modern form of orthodontic skeleton anchoring devices gained popularity with Konami's 1997 publication [8]. In general, orthodontic skeletal anchorage devices fall into two categories: osteo-integrated implants such as mid-palatal implants [9] and on-plants [10], as well as mechanically maintained devices including: titanium mini-plates [11,12], zygomatic wires, and mini-screws [13, 14]. Because miniscrews are biocompatible, easy to assemble and remove, affordable, and able to withstand orthodontic stresses, their usage in orthodontic therapy has expanded [15, 16]. A significant amount of research has been done on mechanically held miniscrews; from a small number of publications in the 1980s to over 5000 papers by the end of 2017, there was a great deal of interest in skeletal anchorage. Regretfully, very few published clinical trials make up the great majority of these publications, which are biomedical science trials and clinical case studies. In order to be successful, orthodontic force should ideally keep miniscrews immobile. Because the stability of the miniscrews rely on the Threads are manually linked into the bone tissues rather than osseointegration, they may be able to withstand orthodontic loads, which has become a concern. Miniscrews' success is influenced by a number of factors, some of which are linked to the patient, some of which are related to the design, and clinical elements. Because of the difference in buccal plate thickness, adolescents have a higher failure rate than adults, which is correlated with age [17]. Other patient-related factors that lower the survival probability of mini-screws include smoking and poor dental hygiene [18–20]. Additional patient-related characteristics include the mucosa type (keratinized versus non-keratinized) and the place of insertion. Miniscrews have generally been shown to have a fair success rate when put through keratinized gingivae and in the maxillary area [17, 19, 21]. When it comes to miniscrew design parameters, it has already been established that miniscrews with a diameter of 1.1 to 1.6 mm provide the highest success rate [22]. Additionally, miniscrews longer than 5 to 8 mm are more stable than shorter ones [19, 22]. Asepsis and sterilization, loading process [23], implantation torque [24, 25], insertion angle [26], and the clinician's experience have all been linked factors connected to clinicians that could have a major impact on miniscrew survival rate. The usefulness of various skeletal anchorage devices for anchorage provision in comparison to traditional techniques has been examined in recent reviews [7, 27, 28]. Nevertheless, the results of these assessments did not address mechanically held miniscrews, the most often utilized skeletal anchorage device. The aim of this study was to perform a systematic review and meta-analysis of controlled and non-controlled prospective clinical trials in order to update our understanding of miniscrews in orthodontic clinical practice, particularly with regard to their stability and associated risk factors. This is because of specific clinical parameters determination that impact clinical success has become increasingly important in nowadays practice.

Methods

No specific grant from a public, private, or nonprofit organization was given for this review. The Cochrane Guidelines for Systematic Reviews [30] and the preferred reporting items for systematic review and meta-analysis [29] were followed in the planning and reporting of this systematic review.

Inclusion criteria

The PICO format was used to define the primary research question (Table 1). English-language publications of prospective cohort studies (PCSs) and randomized clinical trials (RCTs) involving humans until December 2017 were included in this systematic review. Regarding the commencement date, there was no constraint in the search method. Comparators were not required because the objective of this research was to compile failure rates of the miniscrews. This study excludes case reports, case series, reviews, investigations on miniscrews in vitro, animal studies, and miniscrews having

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Table 1. PICO format.

Population	Participants receiving orthodontic treatment who need miniscrews (less than 2 mm) being inserted and are not limited in terms of the patients' presenting age, gender, or type of orthodontic appliance.
Intervention and comparators Any kind of orthodontic procedure that required miniscrew insertion	
Outcome	The primary result was the early loss of the miniscrews within the specified study time, as evidenced by movement, infection, inflammation, or other reasons.Confounders and risk factors linked to miniscrew failure were secondary outcomes.

a diameter larger than 2 mm. Two inquiries for more information were made to the author in cases where the study design was not obvious. The study was disregarded if the author did not respond.

Search strategy

Free text terms and a regulated lexicon were applied to the distribution of completed, ongoing, and unfinished research. If necessary, the original search was followed to update the vocabulary and identify all the research that would be taken into consideration for this evaluation. Up until December 1st, 2017, those databases were searched: the Cochrane Library of Systematic Reviews, PubMed, and Access MEDLINE. Until December 2017, additional bibliographic databases, such as Google Scholar, were also looked for unreported and continuing data. These databases included the clinical trial registration, PhD theses, doctoral theses and the ISRCTN register, and grey literature in Europe. Up to December 2017, a manual search of pertinent orthodontic journals was also conducted. In order to find any more pertinent literature and, if available, to add restricted vocabulary and open access text terms, references of the included papers and any pertinent systematic reviews related to the subject were examined. The two review authors' agreement was evaluated using the Cohen kappa statistic.

Data collection and selection of studies

Software for handling endnote citations was used for removing duplicate researches. After reviewing the names and abstracts of the papers, the most pertinent ones were found. Two reviewers evaluated the potential papers' full texts (K.K. and P.B.) to determine their eligibility. Only products that came with an open access text in English were decided to be included due to the possible challenges associated with translating several articles into the English language. To prevent bias in the search methodology, this exclusion criterion was, however, used after the initial search and a third reviewer (Z.Z.) resolved any potential conflicts between the two reviewers (K.K., P.B.) as they used a modified data extraction form that Papadopoulos and his associates developed [7] to capture research characteristics and results blindly and independently. For every study, the following details were provided: the study's year of publication, its setting, its design, the number and varieties of miniscrews utilized, the success criteria, the failure rate, and the methods employed to deal with failures.

Assessment of risk bias

A method created by the Cochrane group was used to assess the bias risk of RCTs [30]. The following criteria were used to assess each included study for bias: creating randomised sequences; hiding allocations; masking outcome analysts; providing insufficient outcome data; selectively reporting; and other possible causes of bias. Every randomized controlled trial (RCT) was allocated a total risk of bias, which can be categorized as low, high, or unclear depending on whether more than one critical domain exhibited high, low, or unclear risk. The Newcastle–Ottawa Scale (NOS) was used to evaluate PCSs for bias risk [31]. The research in the following three areas is evaluated by the NOS: 1. choice; 2. equivalent; 3. result. If there was a conflict between both writers, a mutually agreed upon decision was reached through conversation. Once more, the potential disputes resolved by a third reviewer were evaluated using the Cohen kappa statistic to gauge the level of agreement between the two review writers. The pooled estimate,

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subgroup, and divided studies were planned in advance and predetermined (a priori), as were the length, diameter, age group, jaw, study type (cohort or RCT), and size of the sample (100 TADs and more) were used to investigate miniscrews impact. Additionally, we intended to investigate the impact on the pooled estimate of self-drilling miniscrews, non-self-drilling miniscrews, and miniscrew designs that need a pilot hole to be pre-drilled before insertion. It was intended to employ subgroup analysis in at least five different studies.

Assessment of publication bias

The asymmetry of the funnel plot was visually examined in order to evaluate publication bias. Additionally, two statistical techniques—Egger's method [35] and Begg/Mazumdar's method [34]—were applied to generate significance tests in order to identify publication bias.

Results

Study characteristics: combining electronic and manual searches yielded 8636 hits. Following the exclusion of duplicate research, 7915 papers were found to have not met the inclusion criteria based on the abstract and title (Figure 1). After the whole texts of the high-quality studies were obtained, rest of them were disqualified. This was due to the fact that they were not pertinent to the review issue or were laboratory studies, retrospective studies, or systematic reviews.

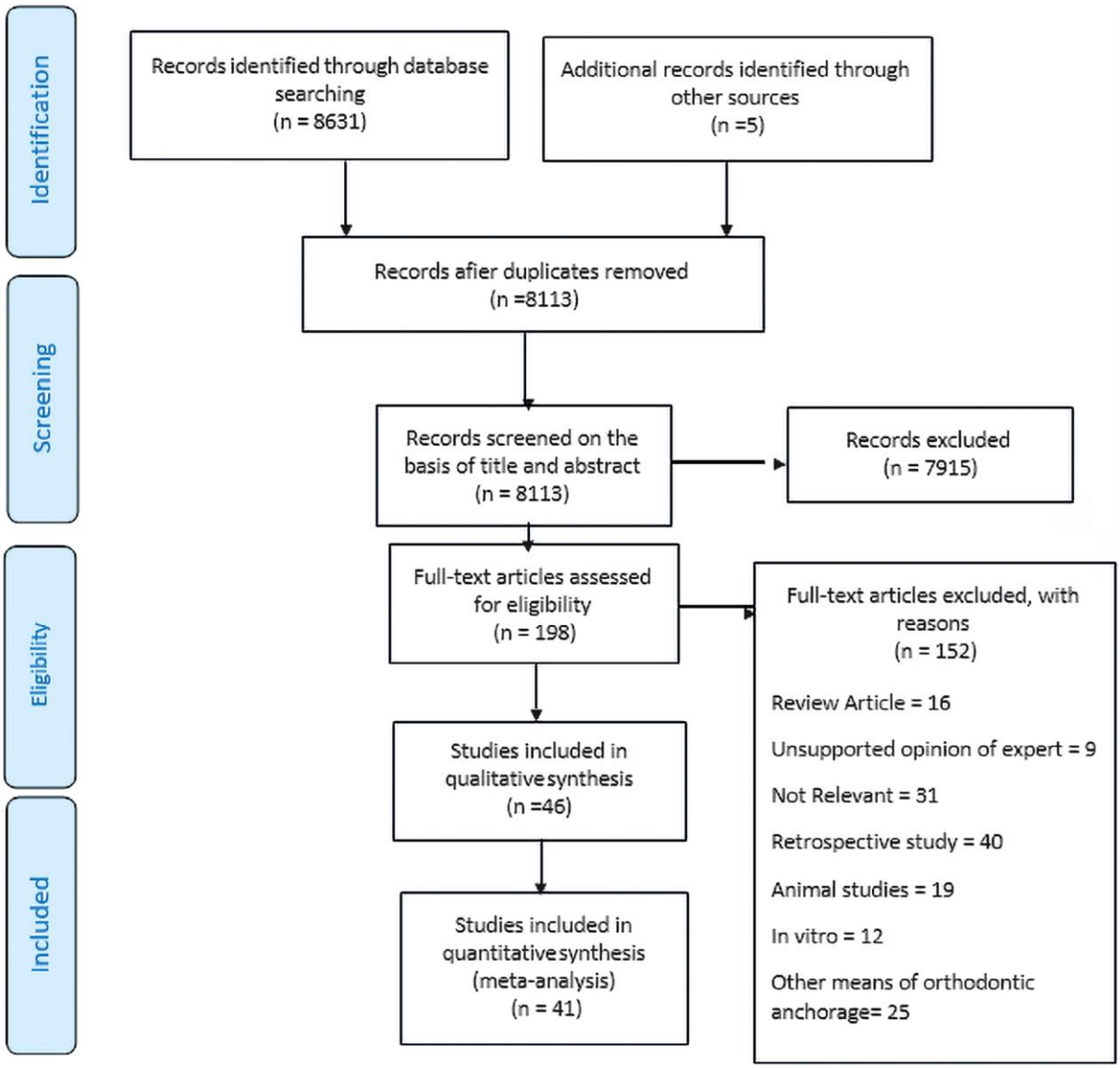

Figure 1. Flow diagram of data collection

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46 studies that satisfied the primary inclusion criteria were included in the final sample. There were 30 PCSs [24, 32–45] and 16 RCTs [36–39] among the included studies. There was one split mouth trial conducted with PCSs.

The lack of statistical data required to calculate the effect sizes five studies were almost excluded from the meta-analysis: three PCSs and two RCTs [27, 36, 37, 38, 41]. They were, nevertheless, taken into account when evaluating the studies' quality. When further information was required, the authors were approached twice via email; if no response was obtained, the work was withdrawn. Table 2 lists key features of the 46 featured research projects, which together comprised 3466 miniscrews. Regarding the study environment, 36 (78%) of the research were solely based in academic environments, whilst the remaining 10 studies were conducted in private, hospital, mixed, or unidentified environments. The average number of miniscrews used per research was about 77, and the number of miniscrews used per subject typically ranged from 1 to 4. The locations of miniscrews that were inserted varied significantly, as did the miniscrew manufacturers employed in the included investigations. The miniscrews that were inserted had a diameter of 1.2 to 2 mm and a length of 5 to 15 mm. As shown, the recorded miniscrew failure rate varied from 0 to 40,8%.

Risk of bias of included studies

Nine of the included RCTs' trials were deemed to have an adequate random sequence generation domain, whereas the other trials were deemed to have a high possibillity of bias or an uncertain risk (Table 3). Only five trials were rated as having a low possibility of bias in the allocation concealment domain; the remaining studies were rated as having a high risk of bias or an unknown risk of bias. Because orthodontic treatment is a medical procedure, it was not possible to blind participants or staff in the trials that were included. Though blinding of assessors was feasible and done so in six trials, blinding was either not done or the reporting was insufficient in the ten other investigations. In the trials that were included, there were no dropouts. As a result, the low risk of bias assessment was applied to all included trials. In three experiments, the selective bias domain was found to have a minimal risk of bias. The residual research was deemed to possess an ambiguous risk of bias due to the absence of information provided to facilitate assessment. Only four trials (out of 39) had a summary rating of minimal risk of bias. After evaluating each of the six domains, it was determined that the remaining trials had an overall high risk of bias [40–51].

According to the NOS [14, 22–36], the great majority of prospective cohort studies were medium quality in terms of quality evaluation (Table 4). One study [80] was deemed to have low quality, whereas three studies [17–29] were deemed to have high quality.

Overall miniscrews failure rate (primary outcomes)

The main finding of this review, the miniscrew failure rate, was recorded in 41 out of 46 trials. A random-effect model was constructed by pooling the retrieved data from 3250 miniscrews. According to Figure 2, the combined failure rate was 13.5% (95% CI 11.5–15.9, P = 0.001, I^2 = 57.1%).Thirty investigations yielded data on 1391 miniscrews, of which less than 100 miniscrews were included in each study and combined in a random-effect model. The miniscrew failure rate of 12.5% (95% CI 9.7–16.1, P < 0.001, I^2 = 60.23%) was comparable to the effect size summary point estimates from all the investigations. Data from the 11 experiments where each research comprised more than 100 miniscrews were then evaluated in a random-effect model, the total number of miniscrews inserted was 1893. Miniscrew failure rates were 14.3% (95% CI 11.5–17.7, P = 0.027, I^2 = 71.5%). In studies including over 100 miniscrew placements, the rate also did not substantially differ from the main analysis's estimations of the effect size.

Assessment of the miniscrew failure risk factors (secondary outcomes)

Studies have documented the diameter and length of miniscrews more than any other characteristic, with the exception of placement (maxilla or mandible). We looked into the soft tissue type, diameter, length, age, place of insertion, and smoking status. Planned subgroup analysis was utilized to evaluate factors associated

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Table 2. Features of the included articles

Author	Design	Setting	No. of patients	No. of miniscrews		Type of miniscrews	Dimensions		Success criteria	Failure rate (%)	Handling of failure
				Total	Patient (per jaw)		Diameter (mm)	Length (mm)			
Aboul-Ela *et al.* (40)	RCT	University	13	26	2 (2)	AbsoAnchor (Dentos, Daegu, Korea)	1.3	8	Stability	7.7	Repositioned
Al-Sibaie and Hajeer (38)	RCT	University	30	56	2 (2)	Dewimed®, Tuttlingen, Germany	1.6	7	Stability	5%	Replaced
Alves *et al.* (52)	PCS	University	15	41	2–3 (2–3)	(INP, São Paulo, Brazil)	1.4/2	6/8	Not recorded	14.6	Replaced
Apel *et al.* (53)	PCS	University	25	76	2–4 (2)	Tomas-pin (Dentaurum, Ispringen, Germany)	1.6	8	Stability/Infection	10.5	Excluded
Basha *et al.* (41)	RCT	University	14	14	2 (2)	Stainless steel	1.3	8	Stability	28.6	Replaced
Bayat and Bauss (54)	PCS	Private	88	110	1–4 (1–2)	LOMAS (Mondeal Medical Systems, Tuttlingen,Germany)	2	7/9/11	Stability/Infection	18.2	Not recorded
Bechtold *et al.* (42)	RCT	University	30	76	1–2 (1–2)	Orlus 18107, Ortholution	1.8	7	Not recorded	13.4%	Replaced
Berens *et al.* (61)	PCS	Private	85	239	1–3 (1–2)	AbsoAnchor (Dentos, Daegu, Korea)/ Dual-Top (Jeil Medical, Seoul, Korea)	1.4/1.8/2	Not recorded	Stability	15.1	Rescrewed/ excluded
Blaya *et al.* (66)	PCS	University/ private	30	30	1 (1)	Sin Implant System (São Paulo, Brazil)	1.2	10	Stability	0	Not recorded
Chaddad *et al.* (43)	RCT	Not recorded	10	32	2–4 (2)	C-Implant (Implantium,Seou, Korea)/Dual-Top (Jeil Medical, Seoul, Korea)	1.4-2	6-10	Stability/infection/treatment completion	12.5	Not recorded
Cheng *et al.* (65)	PCS	University	44	92	Not recorded	Leibinger (Freiburg, Germany)/Mondeal (Tuttlingen, Germany)	2	5-15	Stability/infection/treatment completion	8.7	Not recorded
Davoody *et al.* (77)	PCS	University	25	26	2 (2)	NR	1.8-2	8-9	Not recorded	16%	Replaced
El-Beialy *et al.* (64)	PCS	University	12	40	Not recorded	AbsoAnchor (Dentos, Daegu, Korea)	1.2	8	Stability	17.5	Excluded
Falkensammer *et al.* (37)	RCT	University	26	Not recorded	Not recorded	Dual Top G2 8x6mm, JeilMedical Corporation, Seoul, Korea)	1.6	8	Not recorded	NR	Not recorded
Garfinkle *et al.* (44)	PCS	University	13	82	4–8 (4)	Osteomed (Addison, Tex)	1.6	6	Stability/treatment completion	19.5	Not recorded
Gelgör *et al.* (63)	PCS	University	25	25	1 (1)	IMF Stryker (Leibinger, Germany)	1.8	14	Stability	0	Not recorded
Gupta *et al.* (55)	PCS	University	20	40	2(2)	Custome made (Denticon, Mumbai)	1.4	8	Stability	22.5	Not recorded
Hedayati *et al.* (62)	PCS	University	10	27	3 (1–2)	Orthognathic screws	2	9/11	Stability	18.5	Repositioned
Herman *et al.* (71)	PCS	Not recorded	16	49	1-2 (1–2)	Ortho Implant (IMTEC, Ardmore, Okla), Sendax MDI	1.8	6/8/10	Stability	40.8	New/ Excluded
Iwai *et al.* (70)	PCS	University	80	142	2 (2)	Orthodontic anchor screws (ISA, BIODENT, Tokyo, Japan)	1.6	8	Stability/mobility/ contacted root	8.5%-5.6%	Not recorded
Khanna *et al.* (56)	PCS	University	25	100	Not recorded	S.K. Surgical Pvt. Ltd.	1.3	9	Not recorded	Not recorded	Not recorded
Kim *et al.* (57)	PCS	University	25	50	2 (2)	C-Implant (Implantium, Seoul, Korea)	1.8	8.5	Stability	4	Replaced
Lehnen *et al.* (45)	RCT	Not recorded	25	60	2 (2)	Tomas-pin (Dentaurum, Ispringen, Germany)	1.6	8	Not recorded	11.7	Excluded
Liu *et al.* (46)	RCT	Not recorded	34	68	2 (2)	(Cibei, Ningbo, China)	1.2	8	Stability	11.8	Replaced
Luzi *et al.* (69)	PCS	University	98	140	Not recorded	Aarhus Mini-Implants (Medicon, Germany)	1.5/2	9.6/11.6	Stability/treatment completion	15.7	Excluded
Ma *et al.* (47)	RCT	University		60	4 (2)	AbsoAnchor (Dentos, Daegu, Korea)/Dual-Top (Jeil Medical, Seoul, Korea)	1.8	5/6	Not recorded	Not recorded	Not recorded
Miyazawa *et al.* (68)	PCS	University	18	44	Not recorded	(Jeil Medical, Seoul, Korea)	1.6	8	Treatment completion	9.1	Not recorded
Motoyoshi *et al.* (24)	PCS	University	41	124	1–4 (1–2)	ISA orthodontic implants (BIODENT, Tokyo, Japan)	1.6	8	Stability	14.5	Not recorded
Motoyoshi *et al.* (76)	PCS	University	57	169	1–4 (1–2)	(BIODENT, Tokyo, Japan)	1.6	8	Stability/treatment completion	14.8	Not recorded
Motoyoshi *et al.* (74)	PCS	University	32	87	Not recorded	ISA orthodontic implants (BIODENT, Tokyo, Japan)	1.6	8	Stability/treatment completion	12.6	Not recorded
Motoyoshi *et al.* (67)	PCS	University	52	148	Not recorded	ISA orthodontic implants (BIODENT, Tokyo, Japan)	1.6	8	Stability	9.5	Excluded
Motoyoshi *et al.* (75)	PCS	University	65	209	1–4 (1–2)	ISA orthodontic implants (BIODENT, Tokyo, Japan)	1.6	8	Stability/treatment completion	11.5	Not recorded
Polat-Ozsoy *et al.* (80)	PCS	University	11	22	2 (2)	AbsoAnchor (Dentos, Daegu, Korea)	1.2	6	Stability/Infection	13.6	Replaced
Sandler *et al.* (36)	RCT	Hospital	71	44	2(2)	American Orthodontics	1.6	8	Not recorded	2.8%	Not recorded
Sar *et al.* (58)	PCS	University	28	28	2(2)	Stryker, Leibinger, Germany	2	8	Not recorded	Not recorded	Not recorded
Sarul *et al.* (73)	Split mouth PCS	University	27	54	2 (2)	OrthoEasy Pin (Forestadent, Phorzheim, Germany)	Not recorded	6/8	Mobility/stability	26%	Not recorded
Sharma *et al.* (39)	RCT	University	46	30	2(2)	Denticon	1.2	8	Stability	3%	Replaced
Son *et al.* (78)	PCS	University	70	140	2 (2)	(ISA self-drill type anchor screw; Biodent, Tokyo, Japan)	1.6	8	Mobility/stability	4%	Not recorded
Thiruvenkatachari *et al.* (72)	PCS	University	10	18	1–2 (1–2)	Titanium microimplant	1.3	8	Stability	0	Not recorded
Türköz *et al.* (48)	RCT	University	62	112	1–2 (1–2)	AbsoAnchor (Dentos, Daegu, Korea)	1.4	7	Stability	22.3	Not recorded
Yoo *et al.* (60)	PCS	University	132	227	Not recorded	Biomaterial Korea	1.5	7	Stability/problems in loading	19.5	Not recorded
Upadhyay *et al.* (49)	RCT	University	33	72	4 (2)	Modified Ti fixation screws	1.3	8	Stability	6.9	Replaced
Upadhyay *et al.* (51)	PCS	University	30	30	2 (2)	Modified Ti fixation screws	1.3	8	Stability	10	Replaced
Upadhyay *et al.* (59)	PCS	University	40	46	2 (2)	Ti mini-implants	1.3	8	Not recorded	4.3	Replaced
Upadhyay *et al.* (79)	PCS	University	34	28	2 (2)	Ti mini-implants	1.3	8	Not recorded	Not recorded	Not recorded
Wiechmann *et al.* (50)	RCT	Not recorded	49	133		AbsoAnchor (Dentos, Daegu, Korea)/dual-Top (Jeil Medical, Seoul, Korea)	1.2/1.6	5/10	Stability/treatment completion/ infection	23.3	Not recorded

with miniscrew failure whenever feasible. The impact of the study design on the estimation of the mini-screw failure rate was evaluated. For the sensitivity analysis, 14 RCTs totaling 876 miniscrews were combined into a single random-effect model and 13.1 percent (95%

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Table 3. Risk of bias assessment of the included RCTs.

Author	Study type	Random sequence generation	Allocation concealment	Blinding of outcome assessors	Incomplete outcome data	Selective reporting	Other bias	Overall risk of bias
Aboul-Ela et al. (40)	RCT	Yes	Unclear	No	Yes	Unclear	No	High risk
Al-Sibaie and Hajeer (38)	RCT	Yes	Yes	Yes	Yes	Yes	Yes	Low risk
Basha et al. (41)	CCT	No	No	No	Yes	Unclear	Yes	High risk
Bechtold et al. (42)	RCT	Yes	Unclear	No	Yes	Unclear	No	High risk
Chaddad et al. (43)	CCT	No	No	No	Yes	Unclear	No	High risk
Falkensammer et al. (37)	RCT	Yes	Yes	Yes	Yes	Unclear	Yes	Low risk
Garfinkle et al. (44)	RCT	Unclear	Unclear	No	Yes	Unclear	No	High risk
Lehnen et al. (45)	RCT	Unclear	Unclear	Yes	Yes	Unclear	Yes	High risk
Liu et al. (46)	RCT	Yes	Unclear	No	Yes	Unclear	No	High risk
Ma et al. (47)	RCT	Yes	Unclear	Yes	Yes	Unclear	No	High risk
Sandler et al. (36)	RCT	Yes	Yes	Yes	Yes	Yes	No	Low risk
Sharma et al. (39)	RCT	Yes	Yes	Yes	Yes	Yes	Yes	Low risk
Türköz et al. (48)	RCT	Unclear	Unclear	No	Yes	Unclear	No	High risk
Upadhyay et al. (51)	CCT	No	No	No	Yes	Unclear	Yes	High risk
Upadhyay et al. (49)	RCT	Yes	Yes	Unclear	Yes	Unclear	Yes	Unclear
Wiechmann et al. (50)	RCT	Unclear	Unclear	No	Yes	Unclear	Yes	High risk

confidence interval 9.7–18, Q = 31.5, P < 0.001, I^2 = 55.6%) of them failed. Remarkably, this closely resembled the pooled failure rate of 27 PCSs, including 2374 miniscrews, which was 13.5% (95% CI 11.1-16.4, Q = 76.54, P < 0.001, I^2 = 67.34%). The impact of miniscrew length and design on miniscrew failure rate estimation was also evaluated. To evaluate the impact of miniscrew length on failure rate, a cut-off 8 mm in length was employed. For miniscrews measuring 8 mm or more, the failure rate was 12.2% (95% CI 6.7–21.4, Q = 15.2, DF = 5, P < 0.001, I^2 = 67.2%) for long miniscrews and 12.7% (95% CI 10.5–15.4, Q = 47.26, P < 0.001, DF = 26, I^2 = 44.9%) for short miniscrews. In the non-self-drill miniscrews group, the miniscrew failure rate was 14.9% (95% CI 10.4–20.8, Q = 20.7, DF = 8, P < 0.001, I2 = 88.9%). This was not significantly different from the estimated effect in the self-drill miniscrews group (14.2%, 95% CI 5.6–31.8, Q = 51.57, P < 0.001, I^2 = 71.41%). There was one article [44], which comprised 110 miniscrews, that examined the relationship between smoking and miniscrew failure rates. A total of 73 miniscrews were assigned to nonsmokers, 18 to light smokers (≤10 cigarettes per day), while the remaining screws were assigned to heavy smokers (≥10 cigarettes per day). The corresponding failure rates were 9.5, 11%, and 57.8%. Additionally, a study [43] examined the impact of gingiva type at the place of implantation. There were thirty-two miniscrews in the trial; 11 of them were were put in tissue that was keratinized. and did not fail;

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Table 4. Risk of bias assessment of articles according to Newcastle–Ottawa Scale (NOS).

	Selection				Comparability	Outcome				
Study	Representativeness of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at the start of the study	Comparability of the cohorts	Assessment of outcome	Was follow-up long enough?	Adequacy of follow-up	NOS score	Overall assessment
Alves *et al.* (52)	1	0	1	1	0	1	1	1	6	Medium
Apel *et al.* (53)	1	0	1	1	0	1	1	1	6	Medium
Bayat and Bauss (54)	0	1	1	1	1	0	0	1	5	Medium
Berens *et al.* (61)	1	0	1	1	0	1	1	1	6	Medium
Blaya *et al.* (66)	1	0	1	1	0	1	1	1	6	Medium
Cheng *et al.* (65)	1	0	1	1	0	0	1	1	5	Medium
Davoody *et al.* (77)	1	1	1	1	1	0	1	1	7	High
El-Beialy *et al.* (64)	0	0	1	1	0	1	1	1	5	Medium
Gelgör *et al.* (63)	1	0	1	1	0	1	1	1	6	Medium
Gupta *et al.* (55)	1	1	1	1	0	0	1	1	6	Medium
Hedayati *et al.* (62)	1	0	1	1	0	1	1	1	6	Medium
Herman *et al.* (71)	1	0	1	1	0	1	1	1	6	Medium
Iwai *et al.* (70)	1	1	1	1	0	0	1	1	6	Medium
Khanna *et al.* (56)	1	0	1	1	0	0	1	0	4	Medium
Kim *et al.* (57)	1	0	1	1	0	1	1	1	6	Medium
Luzi *et al.* (69)	1	0	1	1	0	1	1	1	6	Medium
Miyazawa *et al.* (68)	1	0	1	1	0	1	1	1	6	Medium
Motoyoshi *et al.* (67)	1	0	1	1	0	0	1	1	5	Medium
Motoyoshi *et al.* (76)	1	0	1	1	0	0	1	1	5	Medium
Motoyoshi *et al.* (74)	1	0	1	1	0	0	1	1	5	Medium
Motoyoshi *et al.* (75)	1	0	1	1	0	1	1	1	6	Medium
Motoyoshi *et al.* (24)	1	0	1	1	0	0	1	1	5	Medium
Polat-Ozsoy *et al.* (80)	1	0	1	0	0	0	0	1	3	Low
Sar *et al.* (58)	1	0	1	1	0	0	1	1	6	Medium
Sarul *et al.* (73)	1	1	1	1	0	0	1	1	6	Medium
Son *et al.* (78)	1	0	1	1	1	1	1	1	7	High
Thiruvenkatachari *et al.* (72)	1	0	1	1	0	1	1	1	6	Medium
Yoo *et al.* (60)	0	0	1	1	1	1	1	1	6	Medium
Upadhyay *et al.* (59)	1	0	1	1	0	1	1	1	6	Medium
Upadhyay *et al.* (79)	1	0	1	1	1	1	1	1	7	High

the remaining 11 miniscrews, 4 out of 21 miniscrews (19%), were placed in that was not keratinized and failed.

Discussion

Thirty prospective cohort studies and sixteen randomised clinical trials using miniscrews to enhance orthodontic anchoring were included in this systematic review. Most of the included trials were deemed to have a high potential for bias. Randomization and allocation concealment procedures were either documented insufficiently or not at all in the majority of these trials. Most prospective cohort studies had a medium level of quality. This is explained by the fact that the majority of the cohort studies that were included lacked a comparison group, which resulted in a lower NOS score. The meta-analysis determined that the miniscrew failure rate was 13.5% (95% CI 11.5–15.9). Sensitivity analysis revealed a nearly identical 14.3% combined failure rate of mini-screws to the total estimated effect after removing small studies, suggesting sufficient robustness of the findings. This result was rather different from the failure rate that Papageorgiou et al. [7] had previously reported, which was 13.5% (95% CI 11.5–15.8). One possible explanation for the slight variation between the two estimates is that we included a few more studies in our meta-analysis [18, 22, 24, 25, 29, 37, 38, 44]. Second, we eliminated studies that had been included in the earlier meta-analysis [10], studies having an ambiguous design, and studies written in a language other than English. Subgroup analyses were used to evaluate factors associated with miniscrew failure. The results of this meta-analysis suggested that, in comparison to miniscrews with diameters of 1.4–1.6 mm (13.6%, 95% CI 10.3–17.1) and 1.7–2 mm (14.4%, 95% CI 8.8–23.5), those with a diameter of less than 1.3 mm had a lower failure rate (10.7%, 95% CI 7.6–15). Nonetheless, there were 450 small-diameter included miniscrews, 1586 medium-diameter included miniscrews, and 391 large-diameter included miniscrews. The findings' degree of conclusiveness might have been impacted by the variability and differences in sample sizes among the miniscrews that were included. Papageorgiou et al. [7] discovered that miniscrews with small and large diameters had similar failure rates: 10.9 percent (95% CI 7.7–15.3) and 14.3 percent (95% CI 7.4–25.8), respectively. Nonetheless, they discovered that the failure rate of medium-diameter mini-screws was 12.7% (95% CI

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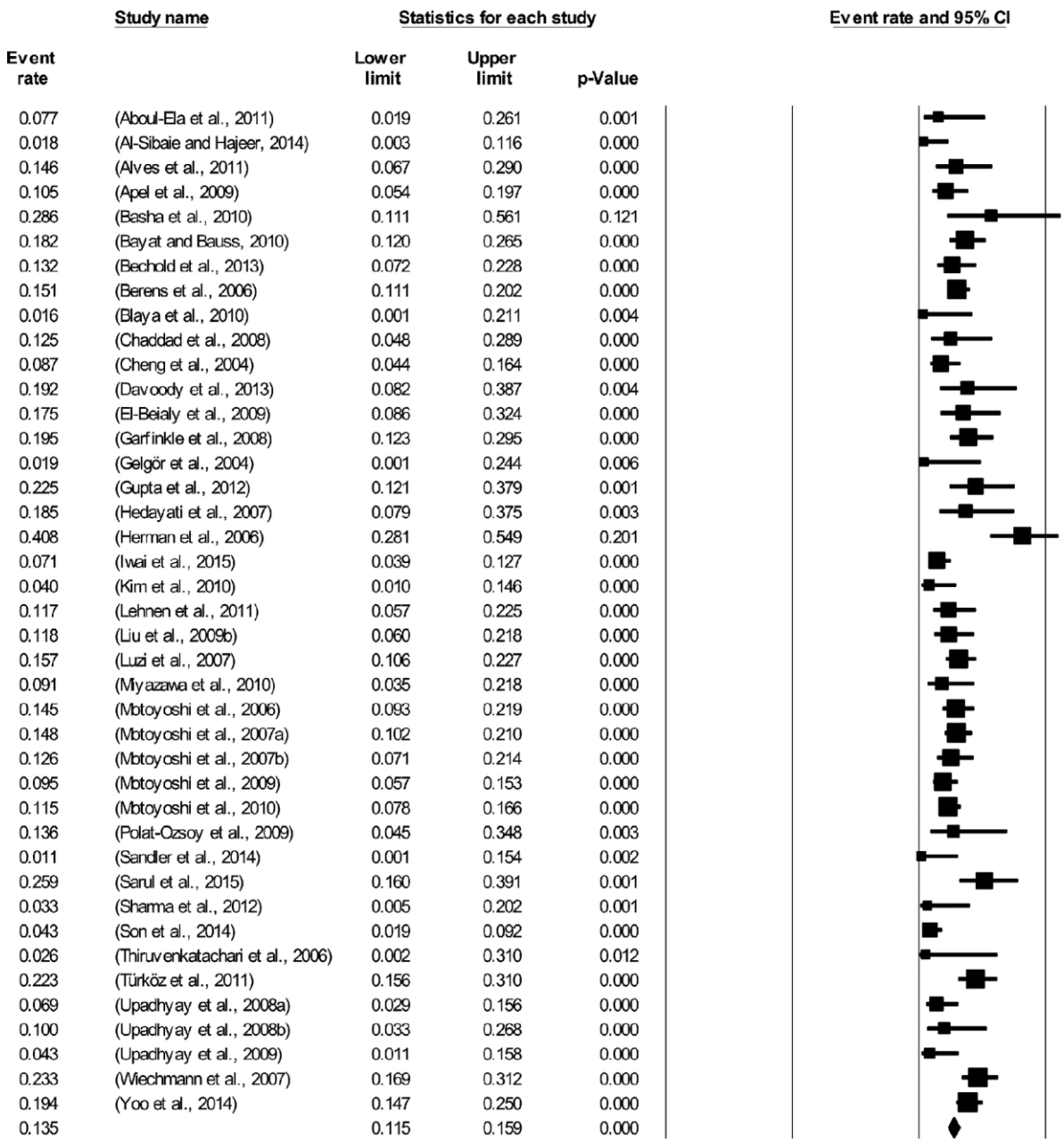

Figure 2. Forest plot of overall miniscrews failure rate (random-effect model)

8.1–19.3). After doing two retrospective tests, Lim and his colleagues discovered that the miniscrew diameter had no discernible impact on the miniscrew's success [41, 45]. Moreover, there was very little roughly 0.8% difference between the large and medium size diameters. This was demonstrated in previous studies that diameter greater than 1.6 mm seems to give no substantial benefit as wide mini-screws are associated with increased risk of root contact than narrow miniscrews [22]. The miniscrews in this meta-analysis were subdivided into short (≤8 mm) and long (>8 mm) group. Most of the studies used short miniscrews. Previous research has shown that a diameter of more than 1.6 mm appears to offer no discernible advantage since wide miniscrews are linked to a higher risk of root contact than narrow miniscrews [22]. In this meta-analysis, the miniscrews were separated into two groups: short (≤8 mm) and long (>8 mm). Short miniscrews were used in the majority of the investigations. The short miniscrew failure rate was 12.7 percent (95% CI 10.5–15.4), which is marginally higher than the

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long miniscrew failure rate of 8.3 percent (95% CI 3.1–20.2). Theoretically, longer miniscrews should have a lower failure rate since they provide better mechanical retention in the bone than shorter miniscrews, albeit the physician will decide whether or not this difference is clinically relevant. According to Lim et al. [32], miniscrews that were 6 mm or shorter had a greater failure rate (25%) than miniscrews that were longer than 6 mm (<12%). This results is not definitive and should be regarded cautiously because it may be the result of the significant heterogeneities in the subgroup analysis. Furthermore, in this review an arbitrary cut-off point of 8 mm was adopted to assess the effect of length of miniscrew on the failure rate; hence, the possibilities of the overlap of the findings on either side of the cut-off point is high, i.e. those miniscrews with 7.9 mm or less will be included in the short group.

Our analysis of a limited number of included trials revealed that the design of the miniscrews had no bearing on the failure rate. Self-drilling miniscrews had a failure rate of 14.2% (95% CI 5.6-31.8) while non-self-drilling miniscrews had a failure rate of 14.9% (95% CI 10.4–20.8). Papageorgiou et al. [7] found a similar result for the self-drilling group (7.7%, 95% CI 4.8–12.0) but a much lower percentage (17.7%, 95% CI 5.1–44.9) for the non-self-drilling miniscrews. The reason for this disagreement could be that we extracted miniscrew design data from nine trials as opposed to the three studies in Papageorgiou and team review [7]. This could have affected the failure rate estimation. Furthermore, this might be the result of the substantial heterogeneities in the subgroup analysis; as such, this results is inconclusive and needs to be read cautiously. In an interesting finding, Chen et al. [17] in their retrospective investigation discovered that, although not statistically significant, the failure rate of self-drilling miniscrews was greater (33%) than that of non-self-drilling (10%) [13]. Due to the probable difference in buccal plate thickness, adolescents have a higher failure rate than adults when it comes to age, which is a patient-related factor [17]. The majority of the studies included in this evaluation included both adult patients (over 18) and younger patients (≤18). Compared to the failure rate published by Papageorgiou et al. [7], who observed that the failure rate in patients younger than 20 years was 12.6 (95% CI 6.4–23.3), the miniscrew failure rate for young patients was 8.6% (95% CI 4.7–15.1). The discrepancy between both estimations was not significant and could be the result of the change in the included studies between those two meta-analyses. In a similar vein, our analysis showed that the failure rate of miniscrews inserted into adults was 11.2% (95% CI 6.6-28.7), but Papageorgiou and colleagues review reported a failure rate of 15.5% (95% CI 11.2-21.0) [7]. On the other hand, retrospective research [12, 34] revealed that older patients had a greater failure rate, most likely as a result of poor periodontal health and smoking. Moreover, since more miniscrews were implanted in younger participants than in adults, these results might just be the result of a smaller sample size.

According to our research, miniscrews inserted into the maxilla had a failure rate of 11.0 percent (95% CI 8.8–13.7), but miniscrews inserted into the mandible had a failure rate of 16.5 percent (95% CI 11.6–22.7). The mandible has a higher failure rate than the maxilla, which could be attributed to factors such as its narrower vestibule, less cortical bone surrounding the mini-screws, and higher bone density [34]. When interpreting the data, it is crucial to take into account the considerable level of heterogeneities in the subgroup analysis. In our analysis, we only found data from one study [24] about the impact of smoking on the failure rate of mini-screws. It seems that smoking negatively affects the stabillity of miniscrews even though the evidence for this claim is extremely scant. Only one study [43] looked into the kind of mucosa insertion and how it related to the miniscrews failure rate. Eleven miniscrews inserted into the keratinized tissue did not fail, according to Chadad et al.

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Conflict of Interest

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Consent to publication

The Author gives her permission for publication

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Стабільність використання тимчасових анкоражних пристроїв у сучасній ортодонтії: систематичний огляд

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Анотація: *ортодонтичному лікуванні TADs в основному використовуються для фіксації, коли пацієнт не дотримується рекомендацій лікаря. У сучасній ортодонтичній літературі наводяться різні показники невдач. Метою нашого дослідження була точна оцінка стабільності TADs та потенційних факторів ризику для механічно фіксованих TADs. До грудня 2017 року для пошуку в електронних базах даних використовувалися MEDLINE, Scopus та Cochrane Library. Було перевірено списки літератури та проведено додатковий пошук поточних і неопублікованих даних. Також було проведено ручний пошук у відповідних журналах та сірій літературі. Ми зібрали опубліковані англійською мовою проспективні когортні дослідження (ПКД) та рандомізовані контрольовані дослідження (РКД), в яких детально описано частоту невдач мінігвинтів діаметром менше 2 мм при використанні їх як ортодонтичних анкерів. У цьому дослідженні було проведено вилучення даних, оцінку ризику упередженості та сліпий і дублюючий відбір досліджень. За допомогою моделі випадкових ефектів було визначено частоту відмов і відповідні змінні ризику для міні-гвинтів, а також супутні 95-відсоткові довірчі інтервали (ДІ). Для оцінки гетерогенності досліджень було використано тести I^2 і Chi^2. Для визначення ризику упередженості було використано шкалу Ньюкасла-Оттави та шкалу Кокрана. Надійність результатів метааналізу була перевірена за допомогою аналізу підгруп та аналізу чутливості. Це дослідження охоплювало 30 проспективних клінічних випробувань, а також 16 рандомізованих клінічних випробувань. Оскільки статистичних даних для розрахунку розміру впливу було недостатньо, п'ять досліджень було виключено з метааналізу. У моделі випадкових ефектів було об'єднано приблизно 3250 міні-гвинтів з 41 випробування. Міні-гвинти показали загальний рівень відмови 13,5% (95% ДІ 11,5%–15,9%). Аналіз груп поділу показав, що куріння та тип ясен мали статистично значущий вплив на рівень відмови міні-гвинтів, тоді як діаметр, довжина та конструкція міні-гвинтів, вік пацієнтів та місце введення не мали значущого впливу. Висновок: ТАД мають прийнятно низький рівень відмови. Через високий ступінь гетерогенності та незбалансованість груп у включених дослідженнях, слід бути обережними при інтерпретації результатів. Для підтвердження результатів цього огляду необхідні значні розміри вибірки з високоякісних рандомізованих клінічних досліджень.*

Ключові слова: Ортодонтичні Анкоражні Процедури; Ортодонтичне переміщення зубів; Патологічний прикус; Ортодонтія, корекційна; Ортодонтичні апарати, Ортодонтія, профілактична; Ортодонтія, попереджуюча.

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