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.

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

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
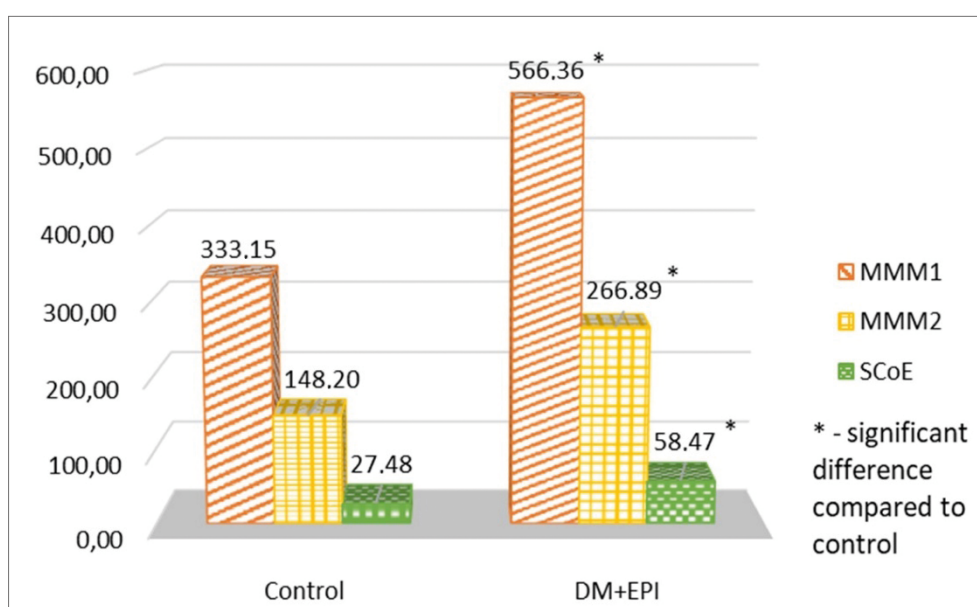

Figure 1 – EI indicators

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

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.

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.