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Early diagnosis of mineral and bone disorders in patients with diabetic kidney disease on the background of type 2 diabetes

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Abstract. ***Background.*** *Today, diabetes mellitus is an actual problem, characterized by a progressive increase in the number of patients with a high frequency of complications that require early diagnosis and timely treatment. Diabetic nephropathy is among the most common microvascular lesions. Patients may have clinical manifestations of diabetic kidney disease that go beyond the classic symptoms and have extrarenal consequences in the form of bone mineral disorders. The purpose of the work is to carry out a comprehensive assessment of early markers of kidney damage and changes in bone disorder indicators in patients with type 2 diabetes and to identify correlations between the studied parameters.* ***Materials and methods.*** *Eighty patients with type 2 diabetes participated in the study. They were divided according to the glomerular filtration rate: GFR < 60 ml/min/m² (1st group, n = 26), GFR ≥ 60 ml/min/m² (2nd group, n = 54).* ***Results.*** *Analysis of early markers of kidney damage revealed some significant differences between the groups. Indicators of daily urine albumin-creatinine ratio, serum cystatin C, parathyroid hormone, uric acid, and vitamin D-binding protein were significantly higher in patients with GFR < 60 ml/min/m². The average level of vitamin D (25OH) in both groups corresponded to a deficient state, and the 1st group was marked by a statistically significantly lower level compared to the 2nd group: 12.32 ± 4.84 and 16.72 ± 5.82 ng/ml, respectively (p = 0.001). In the 1st group, vitamin D deficiency was observed in 92.3 % of cases, and in the 2nd group, in 74.1 % (p = 0.56). According to the correlation analysis, some reliable relationships were found: in the 1st group, there was a negative correlation between GFR and parathyroid hormone (r = –0.816, p < 0.001). An inverse correlation was revealed between GFR and cystatin C in the 1st (r = –0.862, p < 0.001) and 2nd groups (r = –0.322, p = 0.18). Among all examined participants, there was a linear negative correlation between GFR and uric acid (r = –0.452, p < 0.001). Vitamin D (25OH) didn't have a significant relationship with GFR, however, we found a negative correlation with the daily urine albumin-creatinine ratio (r = –0.253, p = 0.024) and cystatin C (r = –0.303, p = 0.006), which confirms the role of cholecalciferol in mineral bone disorders in patients with chronic kidney disease. In our study, an inverse correlation was found between GFR and vitamin D-binding protein in the 1st (r = –0.436, p = 0.26) and 2nd group (r = –0.283, p = 0.038), which probably indicates a possible compensatory response of transport protein to initial mineral bone disorders in patients with diabetic kidney disease.* ***Conclusions.*** *Early detection of bone mineral disorders in diabetic kidney disease is important to increase the efficiency of managing patients with type 2 diabetes and timely treatment, prevention of cardiovascular complications and bone metabolism disorders.*

Keywords: *diabetes mellitus; diabetic kidney disease; chronic kidney disease; vitamin D deficiency; mineral bone disorders; hyperparathyroidism; albuminuria; vitamin D-binding protein*

Introduction

Diabetes mellitus (DM) is an actual problem today, characterized by a progressive increase in the number of patients with a high frequency of complications. According to the International Diabetes Federation forecasts, the number of people with diabetes will increase to 783 million by 2045. The highest rate of increase in the prevalence of diabetes is expected from 2021 to 2045 in middle-income countries (21.1 %) compared to high- (12.2 %) and low-income ones (11.9 %) [1]. DM is a progressive chronic disease that can cause severe micro- and macrovascular lesions requiring early diagnosis and timely treatment. Such a microvascular

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complication as diabetic nephropathy appears to be the most common complication of type 2 diabetes (T2DM) and is associated with the duration of diabetes [2]. Diabetic kidney disease (DKD) is the most common cause of end-stage renal disease worldwide [3]. Among the nosological forms of chronic kidney disease (CKD), diabetic lesions take the first place, and cardiovascular complications are among the prominent causes of death [4]. Mineral bone and osteoporotic changes in patients of different ages also play a significant role in CKD [5], so the problem of treatment and prevention of complications is multidisciplinary.

A possible limitation of current screening methods for DKD is the non-albuminuric phenotype of diabetic nephropathy, which is becoming increasingly common and has no specific therapy [6]. Early diagnosis of renal pathological changes in DM, taking into account various markers of kidney damage, including some indicators of bone mineral disorders, and timely implementation of renoprotection measures are extremely relevant.

Impaired secretory function of the kidneys in CKD is often associated with hyperactivation of the renin-angiotensin-aldosterone system, hypertension, hyperkalemia, anemia, and CKD. Bone mineral disorders predict a very high risk of death, cardiovascular events, and progression of CKD to end-stage renal disease [7].

Mineral disorders of bone tissue in patients with CKD (CKD-MBD — chronic kidney disease-mineral and bone disorder) are caused by numerous biochemical and hormonal disorders and are associated with a high risk of bone fractures, progression of pathological renal changes, cardiovascular events, and mortality [8]. The term "CKD-MBD" summarizes all changes, including the development of osteoporosis without primary damage to the parathyroid glands [9]. Secondary hyperparathyroidism can be a sign of mineral and bone disorders, bone diseases and vascular calcification.

The role of MBD in patients with CKD is important in the pathogenesis of cardiovascular diseases. In patients with CKD-MBD, urinary phosphate excretion decreases and the concentration of fibroblast growth factor 23 (FGF23) and parathyroid hormone (PTH) in the blood increases. At the same time, the serum calcitriol level decreases due to an increase in FGF23. It has already been proven that increased levels of PTH and FGF23 cause left ventricular hypertrophy, arrhythmia, and calcification of the cardiovascular system [10]. Thus, it is important to carry out therapeutic correction of CKD-MBD, which will simultaneously contribute to the prevention of cardiovascular diseases.

The aim of the work: to carry out a comprehensive assessment of early markers of kidney damage and changes in MBD indicators in patients with type 2 diabetes, as well as to identify correlations of the studied parameters.

Materials and methods

The research was carried out in the Department of General Endocrine Pathology (Kyiv City Endocrinological Center, Kyiv). The principles of the Declaration of Helsinki were followed. All participants signed the appropriate form of informed consent to participate in this study. Inclusion criteria were patients with a diagnosis of T2DM in a state of subcompensation, whose disease duration was more than 5 years.

Exclusion criteria were age under 18 years, patient refusal, participation in another study, type 1 diabetes, previous intake of vitamin D preparations, pregnancy, lactation, diseases such as pyelonephritis in the acute phase, primary hyperparathyroidism, a history of nephrectomy, cancer, acute heart failure or acute kidney injury.

Eighty patients with T2DM were included in the study. The groups were formed according to the level of glomerular filtration rate (GFR): GFR < 60 ml/min/m^2 (1st group, n = 26), GFR ≥ 60 ml/min/m^2 (2nd group, n = 54). GFR was estimated according to the Chronic Kidney Disease Epidemiology Collaboration equation based on serum creatinine. Creatinine, uric acid (UA), magnesium were determined by the colorimetric method. The enzyme-linked immunosorbent assay was used to study serum vitamin D (25OH), vitamin D-binding protein (VDBP), PTH, and cystatin C. HbA1c was measured by the method of high-performance liquid chromatography. The albumin-creatinine ratio (ACR) in daily urine was calculated with the determination of the level of albuminuria by the immunoturbidimetric method and creatinine by the colorimetric method.

Statistical data were processed using SPSS software (version 23, IBM Corp., Armonk, NY, USA). The normality of the law of distribution of data of continuous variables was assessed using the Shapiro-Wilk test. Data were presented as mean with standard deviation (mean ± SD) or median with first and third quartiles (median (Q1-Q3)) and unpaired t-test or Wilcoxon test were used to study the difference between group means according to the normality law distribution. Differences between indicators were considered significant at $p < 0.05$.

Results

The characteristics of the examined patients of both groups are presented in Table 1. The average age of the patients in the 1st group was 66.81 ± 8.34 years and in the 2nd — 60.74 ± 10.05 years (p = 0.290). A statistically significant difference was found in the duration of DM in the 1st and 2nd groups, respectively: 12 (10; 20) and 10 (5; 13) years (p = 0.016). The ACR in daily urine was significantly higher in the 1st group compared to the 2nd: 5.25 (2.3; 160.7) and 1 (0.6; 2.9) mg/mmol, p < 0.001, which corresponded to microalbuminuria.

Another sensitive marker for early diagnosis of kidney lesions, cystatin C, was also significantly different: 0.75 (0.52; 0.99) in the 1st group and 0.45 (0.39; 0.52) mg/l in the 2nd (p < 0.001).

The median of the main indicator for assessing the filtration capacity of the kidneys (GFR) in patients from the 1st group was 48.1 (32.4; 57.2), which statistically significantly differed from the 2nd group — 83.45 (72.4; 92.7) ml/min/m^2 (p < 0.001). The median of vitamin D in both groups corresponded to a deficient state (using the classification according to the recommendations of the of Ukrainian experts on the diagnosis, prevention and treatment of vitamin D deficiency in adults) [11], and the 1st group was characterized by a statistically significantly lower level of vitamin D (25OH) compared to the 2nd group (12.32 ± 4.84 and 16.72 ± 5.82 ng/ml, respectively; p = 0.001). In the 1st group, vitamin D (25OH) defi-

Table 1. Characteristics of the examined patients with type 2 diabetes

Indicators	GFR < 60 (n = 26)	GFR ≥ 60 (n = 54)	p
Age (years), average	66.81 ± 8.34	60.74 ± 10.05	0.290
Duration of diabetes (years), median	12 (10; 20)	10 (5; 13)	0.016
BMI (kg/m^2), average	30.960 ± 4.546	31.62 ± 6.00	0.618
GFR (ml/min/m^2), median	48.1 (32.4; 57.2)	83.45 (72.4; 92.7)	< 0.001
Vitamin D (25OH) (ng/ml), average	12.32 ± 4.84	16.72 ± 5.82	0.001
PTH (pg/ml), median	78.68 (53.12; 133.67)	52.54 (42.44; 72.31)	0.008
Cystatin C (mg/l), median	0.75 (0.52; 0.99)	0.45 (0.39; 0.52)	< 0.001
Serum VDBP (ng/ml), median	125.82 (99.27; 168.8)	101.07 (75.34; 131.18)	0.028
UA (μmol/l), median	424.3 (369.7; 473.5)	316.85 (271.4; 357)	< 0.001
ACR daily urine (mg/mmol), median	5.25 (2.3; 160.7)	1 (0.6; 2.9)	< 0.001
HbA1c (%), average	8.76 ± 2.11	9.17 ± 2.17	0.426
Magnesium (mmol/l), median	0.76 (0.73; 0.81)	0.78 (0.75; 0.83)	0.191

ciency was observed in 92.3 % of cases (n = 24), and in the 2nd group — in 74.1 % (n = 40), p = 0.56.

When assessing the level of PTH, the median values were significantly higher in patients with GFR < 60 ml/min/m^2: 78.68 (53.12; 133.67) than in persons with preserved renal filtration capacity: 52.54 (42.44; 72.31) pg/ml, p = 0.008, which confirms hyperactivity of parathyroid tissue in renal failure.

The median of UA in the blood corresponded to hyperuricemia in the group of patients with GFR < 60 ml/min/m^2: 424.3 (369.7; 473.5) in contrast to the group with GFR ≥ 60 ml/min/m^2: 316.85 (271.4; 357) μmol/l, p < 0.001. No statistical difference was found in HbA1c, however, lower glycemia was observed in patients from the 1st group, probably due to lower insulinase activity in severe kidney damage, which affects the improvement of carbohydrate metabolism and may even provoke the risk of hypoglycemia. The median magnesium levels in both groups corresponded to the reference values, but in patients from the 2nd group they were higher (0.76 (0.73; 0.81) and 0.78 (0.75, 0.83) mmol/l, p = 0.191). As it is already known, hypomagnesemia increases insulin resistance by suppressing the translocation of glucose transporter type 4, which contributes to the initiation and progression of diabetes, and the development of macro- and microvascular complications, in particular diabetic nephropathy [12].

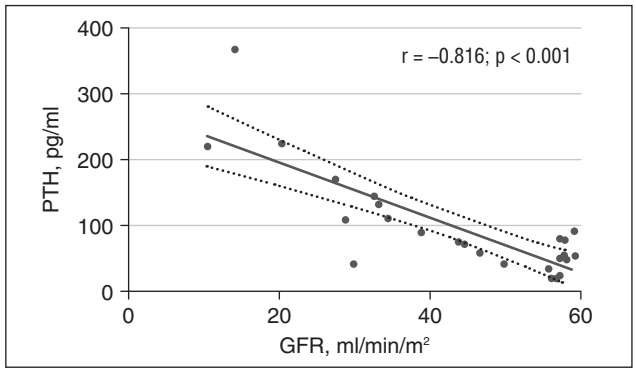

Figure 1. Correlation between GFR and PTH in patients with GFR < 60 ml/min/m²

We conducted a correlation analysis that demonstrated some statistically significant relationships. Thus, in patients from the 1st group, the correlation analysis showed a negative relationship between GFR and PTH (r = –0.816, p < 0.001) (Fig. 1); in the 2nd group, no connection between these indicators was found.

A negative correlation was found between GFR and cystatin C in the 1st (r = –0.862, p < 0.001) and 2nd groups (r = –0.322, p = 0.18) (Fig. 2A, 2B), which indicates a higher sensitivity of the serum marker cystatin C with a significant decrease in GFR. GFR and the level of UA had no correlation in separate groups — a linear negative correlation was found among all the examined (r = –0.452, p < 0.001) (Fig. 3C). In our study, vitamin D was not significantly associated with GFR, but since it is considered an indicator of MBD in patients with CKD, we further investigated its association with other early markers of renal damage in DM. A negative correlation was found in both groups between the levels of vitamin D and cystatin C (r = –0.303, p = 0.006) and daily urinary ACR (r = –0.253, p = 0.024) (Fig. 3A, 3B).

Researchers report that the level of fibroblast growth factor increases with DKD and the biosynthesis of $1,25(OH)_2D_3$ is actively inhibited [13]. In the pathogenesis of diabetic nephropathy, the filtration of albumins and the loss of VDBP with urine increase [14]. When analyzing the results, an inverse correlation was found between GFR and VDBP in the 1st (r = –0.436, p = 0.26) and in the 2nd groups (r = –0.283, p = 0.038) (Fig. 2C, 2D), which may indicate a possible compensatory reaction of the transport protein in response to the initial violations of MBD in patients with diabetic kidney damage.

Discussion

The problem of high mortality due to complications of DM is a challenge for the healthcare systems of all countries, regardless of socioeconomic level. Timely diagnosis and effective treatment of kidney damage in a patient with diabetes require a multidisciplinary approach in order to prevent complications. Therefore, identifying early markers of kidney damage is an important task the doctor faces. The index of albuminuria and ACR are the KDIGO 2023 recommended

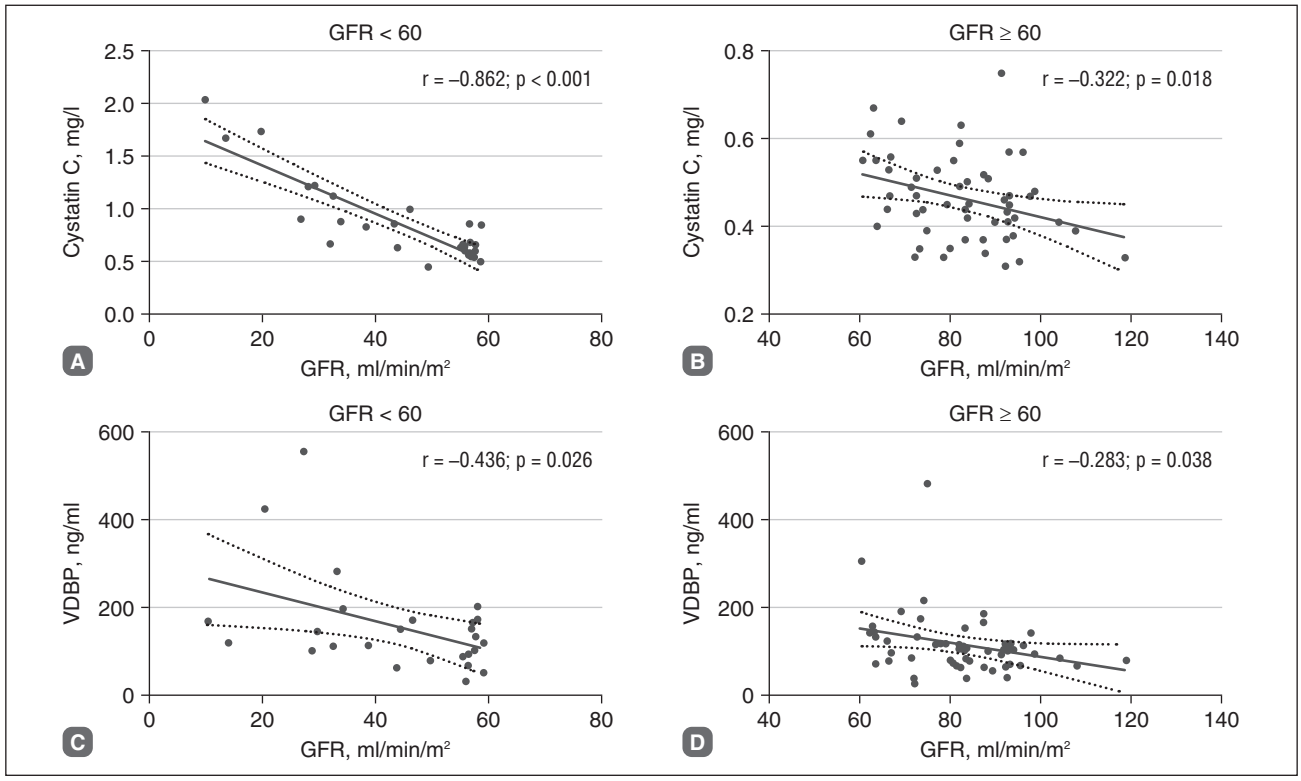

Figure 2. Correlations of GFR with cystatin C and VDBP in both groups

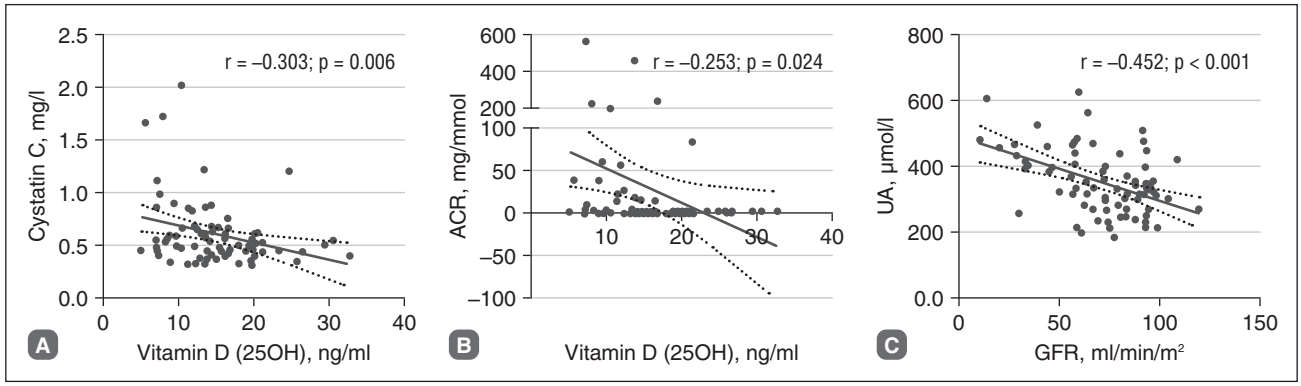

Figure 3. Correlations of vitamin D (25OH), ACR, UA, and cystatin C in both groups regardless of GFR

parameters for the verification of kidney damage, assessing the severity of proteinuria, effectiveness of treatment, and stratification of the risk of mortality [15]. We conducted a comprehensive assessment of possible early markers of kidney damage in patients with T2DM, namely indicators of ACR, cystatin C, VDBP, and UA. It should be noted that the loss of albumin with urine was significantly higher in the 1st group compared to the 2nd, according to ACR (Table 1).

KDIGO 2022 [15] guidelines on the management of a patient with CKD recommended to determine the level of cystatin C for calculating GFR as a sensitive and accurate marker. According to the results of the study, it is noted that cystatin C was significantly higher in the 1st group than in the 2nd one. Cystatin C is also reported to be a better estimate of true kidney function, as it excludes muscle loss due to long-term critical illness [16]. The assessment of mineral and bone metabolism was based on the analysis of vitamin D (25OH), PTH, and VDBP levels. Today, vitamin D (25OH) is considered not only a marker for the regulation of calcium-phosphorus metabolism but also as a prohormone that participates in many biological processes. It is also known as a separate component of the multifactorial development of insulin resistance [17].

The results of the examination show that the level of 25(OH)D in both groups corresponded to the indicators of a deficient state regardless of the level of GFR. However, with the loss of renal functions, the deficiency state was more pronounced — the 1st group was marked by a statistically significantly lower level of 25(OH)D compared to the 2nd group. The development of secondary hyperparathyroidism is inherent in a decrease in GFR, a tendency which was noted in patients of the 1st group (GFR < 60 ml/min/m²) with median PTH of 78.68 (53.12; 133.67) pg/ml. It is already known that hyperphosphatemia, hypocalcemia, D-hypovitaminosis stimulate the synthesis and secretion of PTH, as well as the proliferation of cells of the parathyroid glands. At

first, the parathyroid tissue grows diffusely, then its nodular growth spreads during the progression of kidney disease, which causes a lower sensitivity of the parathyroid glands to inhibition of PTH synthesis [18]. Vitamin D binds to its transport carrier VDBP, which is filtered through the glomeruli of the kidneys and absorbed by the receptor in the proximal tubules. We investigated the level of VDBP in blood serum, which had a significant inverse correlation with GFR in all patients, with a stronger correlation in the 1st group. It has already been proven that patients with type 2 diabetes and CKD had a higher aldosterone level, which was accompanied by a higher frequency of hypertension and albuminuria/proteinuria [19]. Despite the sufficient delivery of substrates to the proximal tubules of the kidneys, since higher levels of serum VDBP were observed in the 1st group, albuminuria progressed along with a decrease in vitamin D. Considering modern views on VDBP and MBD parameters as markers of early kidney damage, further studies are needed to estimate the effect of renin-angiotensin-aldosterone system blockers on urinary albumin filtration, including VDBP.

Conclusions

Early diagnosis of kidney damage and bone metabolism disorders in patients with type 2 diabetes has extremely important prognostic value, and parameters of MBD such as levels of PTH, vitamin D (25OH), VDBP, along with ACR and cystatin C, can be considered early markers of damage in CKD.

The study showed that the level of vitamin D (25OH) in both groups corresponded to the indicators of a deficient state, and it was statistically significantly lower in the group with GFR < 60 ml/min/m^2 than in patients with GFR ≥ 60 ml/min/m^2 (12.32 ± 4.84 and 16.72 ± 5.82 ng/ml, p = 0.001).

Patients with GFR < 60 ml/min/m^2 and type 2 diabetes have a high risk of developing secondary hyperparathyroidism, in contrast to individuals with preserved renal filtration capacity.

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Рання діагностика мінеральних і кісткових розладів у пацієнтів із діабетичною хворобою нирок на тлі цукрового діабету 2-го типу

Резюме. ***Актуальність.*** Цукровий діабет є актуальною проблемою сьогодення, яка характеризується прогресуючим зростанням кількості пацієнтів із високою частотою ускладнень, що потребують ранньої діагностики та своєчасних лікувальних заходів. Одним із найпоширеніших мікросудинних уражень є діабетична нефропатія. Пацієнти можуть мати клінічні прояви діабетичної хвороби нирок, які виходять за межі класичних симптомів і мають екстраренальні наслідки у вигляді мінерало-кісткових розладів. ***Мета роботи:*** провести комплексну оцінку ранніх маркерів ураження нирок і змін показників мінеральної щільності кісткової тканини в пацієнтів із цукровим діабетом 2-го типу, а також виявити взаємозв'язки досліджуваних параметрів. ***Матеріали та методи.*** У дослідженні взяли участь 80 пацієнтів із цукровим діабетом 2-го типу, які були розподілені за рівнем швидкості клубочкової фільтрації: рШКФ < 60 мл/хв/м^2 (перша група, n = 26), рШКФ ≥ 60 мл/хв/м^2 (друга група, n = 54). ***Результати.*** Аналіз ранніх маркерів ураження нирок в обстежених групах виявив деякі суттєві відмінності. Показники співвідношення альбуміну та креатиніну в добовій сечі, сироваткового цистатину С, паратгормону, сечової кислоти, вітамін-D-зв'язуючого білка були вірогідно вищими в пацієнтів із рШКФ < 60 мл/хв/м^2. Середній уміст вітаміну D в обох групах відповідав дефіцитному стану, причому перша група відзначалася статистично вірогідно нижчим рівнем порівняно з другою — 12,32 ± 4,84 та 16,72 ± 5,82 нг/мл відповідно (p = 0,001). У першій групі дефіцит вітаміну D спостерігався в 92,3 % випадків, у другій — у 74,1 % (p = 0,56). При кореляційному аналізі знайдені деякі вірогідні зв'язки: у першій групі — негативна кореляція між рШКФ та ПТГ (r = –0,816, p < 0,001). Спостерігався обернений зв'язок між рШКФ та цистатином С у 1-й (r = –0,862, p < 0,001) та 2-й групах (r = –0,322, p = 0,18). Серед усіх обстежених учасників виявлено лінійну негативну кореляцію між рШКФ та рівнем сечової кислоти (r = –0,452; p < 0,001). Вітамін D не мав вірогідного зв'язку з рШКФ, проте ми знайшли негативну кореляцію зі співвідношенням альбуміну й креатиніну в добовій сечі (r = –0,253, p = 0,024) та цистатином С (r = –0,303, p = 0,006), що підтверджує роль холекальциферолу в порушенні мінеральної щільності кісткової тканини в пацієнтів із діабетичною хворобою нирок. У нашому дослідженні виявлено зворотну кореляцію між рШКФ та вітамін-D-зв'язуючим білком у першій (r = –0,436, p = 0,26) та другій групі (r = –0,283, p = 0,038), що, ймовірно, вказує на можливу компенсаторну реакцію транспортного білка на початкові мінерало-кісткові порушення в пацієнтів із діабетичним ураженням нирок. ***Висновки.*** Раннє виявлення мінеральних і кісткових розладів при діабетичній хворобі нирок є важливим щодо підвищення ефективності ведення пацієнтів із цукровим діабетом 2-го типу та своєчасного лікування, профілактики ускладнень з боку серцево-судинної системи й порушень кісткового метаболізму.

Ключові слова: цукровий діабет; діабетична хвороба нирок; хронічна хвороба нирок; дефіцит вітаміну D; мінеральні та кісткові розлади; гіперпаратиреоз; альбумінурія; вітамін-D-зв'язуючий білок