International Journal of Endocrinology

Оригінальні дослідження
Original Researches

UDC 616.61-02:616.379-008.64:[616.7-008:612.015.31]-07 DOI: https://doi.org/10.22141/2224-0721.21.2.2025.1509

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Early markers of renal damage in type 2 diabetes: role of vitamin D-binding protein

For citation: Mìžnarodnij endokrinologìčnij žurnal. 2025;21(2):128-133. doi: 10.22141/2224-0721.21.2.2025.1509

Abstract. ***Background.*** *Diabetic kidney damage leading to end-stage renal failure is the most frequent and prognostically unfavorable complication of diabetes mellitus. Recently, increasing attention has been focused on the extraskeletal functions of vitamin D, the role of vitamin D-binding protein (VDBP), and their pathogenetic link to kidney damage in people with type 2 diabetes. The purpose of the work is to investigate the role of VDBP as an early marker of kidney damage in individuals with type 2 diabetes and to assess the strongest correlations between early markers of kidney dysfunction in diabetic kidney disease. The search for early markers of kidney damage is a pressing task today with the increase in diabetes.* ***Materials and methods.*** *A total of 123 patients with type 2 diabetes participated in the study. The groups were formed based on the estimated glomerular filtration rate (eGFR): group I (eGFR ≥ 90 ml/min/1.73 m², n = 28) — preserved renal filtration capacity or hyperfiltration; group II (eGFR 60–90 ml/min/1.73 m², n = 46) — stage 2 chronic kidney disease (CKD); group III (eGFR < 60 ml/min/1.73 m², n = 49) — stage 3 CKD.* ***Results.*** *Cystatin C as the most sensitive marker for the early diagnosis of CKD significantly increased with decreasing eGFR: its level in group I was 0.76 (0.56–1.12), in group II — 0.49 (0.42–0.55), and in group III — 0.43 (0.40–0.47) mg/L (p < 0.001). VDBP directly proportionally correlated with daily urinary albumin-to-creatinine ratio (r = 0.253, p = 0.0235), cystatin C (r = 0.343, p = 0.0019), age (r = 0.248, p = 0.0264) and was inversely associated with eGFR (r = –0.268, p = 0.0163). No correlation was found between VDBP and vitamin D (25OH) levels in study participants.* ***Conclusions.*** *VDBP may be considered an early marker of kidney damage in people with type 2 diabetes. A strong association with renal damage was demonstrated for cystatin C, which also had a statistically significant direct correlation with serum VDBP.*

Keywords: *vitamin D; type 2 diabetes mellitus; diabetic kidney disease; vitamin D-binding protein; chronic kidney disease; chronic systemic inflammation*

Introduction

Diabetic kidney damage leading to end-stage renal failure is the most frequent and prognostically unfavorable complication of diabetes mellitus (DM). The steady increase in the number of these patients necessitates the development of new approaches for timely diagnosis, prognosis, and prevention of complications. The identification of early markers of kidney damage is a pressing task today, given the increasing prevalence of DM.

Vitamin D regulates calcium and phosphate homeostasis and performs many other extraskeletal functions through genomic and non-genomic effects. It is a hormone belonging to the group of fat-soluble secosterols, known as calciferols. Most vitamin D is synthesized in the skin as pre-vitamin D_3, while a smaller portion comes from dietary sources. Vitamin D_3, which has a half-life of approximately 12 hours, binds to vitamin D-binding protein (VDBP), facilitating its transport in the blood. It undergoes hydroxylation in the liver to form 25-hydroxyvitamin D_3 ($25(OH)D_3$), which is subsequently hydroxylated by 1α-hydroxylase in the kidney or peripheral tissues to produce the active form ($1,25(OH)_2D_3$) [1, 2].

Considering the pathogenetic mechanisms of kidney damage, vitamin D deficiency may serve as an early marker of bone-mineral disorder syndrome in cases of impaired renal function. Under physiological conditions, vitamin D must be metabolically activated in the kidneys. However, in patients with chronic kidney disease (CKD), including dia-

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betic nephropathy, the kidneys are unable to produce a sufficient amount of the active form of vitamin D ($1,25(OH)_2D_3$). On the other hand, the kidneys are considered a classic target for $1,25(OH)_2D$ due to the strong expression of the vitamin D receptor in renal tissue [3, 4].

The impairment of the kidneys' ability to produce and absorb a sufficient amount of calcitriol, and thus to maintain the homeostasis of vitamin D, phosphate, and calcium, is one of the key pathophysiological components of bone metabolic disorders in CKD. Additionally, an important factor in the pathophysiology of vitamin D deficiency is the urinary loss of vitamin D and VDBP, which has been documented in these individuals [5]. Vitamin D metabolism impairment plays a key role in the pathogenesis of bone-mineral disorders but may also be a contributing factor in the development of diabetic kidney disease in patients with diabetes mellitus. It is known that the transport of vitamin D and glucose by the epithelial cells of the proximal tubules of the nephron shares common mechanisms.

Vitamin D binds to VDBP in the tubular lumen, and the complex is transported into the proximal tubular epithelial cell via the megalin/cubilin system. Inside the cell, vitamin D is released and metabolized in the mitochondria, while the megalin/cubilin complex is degraded in lysosomes. Vitamin D then diffuses into the interstitial space, where it binds to VDBP. Glucose is transported into the proximal tubular epithelial cell through sodium-glucose cotransporter 2 (SGLT2). Inhibition of SGLT2 by SGLT2 inhibitors (SGLT2i) increases the amount of Na^+ in the tubular lumen, which may enhance phosphate reabsorption and further alter the parathyroid hormone-vitamin D-FGF23 axis [6–8].

Recently, researchers have increasingly focused on the extraskeletal functions of vitamin D and its metabolism, particularly the role of VDBP [9–11]. The extraskeletal effects of vitamin D are mediated through its ability to interact with vitamin D receptors (VDR) in various organs and tissues [12].

The aim of the work: to investigate the role of VDBP as an early marker of kidney damage in individuals with type 2 DM; to assess the strongest correlations between early markers of kidney dysfunction in diabetic kidney disease (DKD).

Materials and methods

The study was conducted at the Department of General Endocrine Pathology of the Kyiv City Endocrinology Center (Kyiv, Ukraine). All ethical aspects were considered in accordance with the principles of the Helsinki Declaration. Before participating in the study, all patients signed an informed consent form. The study included patients diagnosed with type 2 DM in a state of subcompensation. Exclusion criteria included: age under 18 years, patient refusal to participate, participation in another study, presence of type 1 diabetes, prior use of vitamin D supplements, pregnancy, or lactation. Additionally, patients with acute pyelonephritis, primary hyperparathyroidism, a history of nephrectomy, oncological diseases, acute renal or cardiac pathology were excluded.

A total of 123 patients with type 2 DM participated in the study. The groups were divided based on the estimated glomerular filtration rate (eGFR) into three categories: group I (eGFR ≥ 90 ml/min/1.73 m^2, n = 28) — corresponding to preserved renal filtration capacity or hyperfiltration; group II (eGFR 60–90 ml/min/1.73 m^2, n = 46) — stage 2 CKD; group III (eGFR < 60 ml/min/1.73 m^2, n = 49) — stage 3 CKD.

Creatinine in blood and daily urine, uric acid, and blood cholesterol were measured using the colorimetric method. The eGFR was calculated using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula, taking into account serum creatinine level. The albumin-to-creatinine ratio (ACR) in 24-hour urine was determined. Albuminuria levels were measured using the immunoturbidimetric method. Enzyme-linked immunosorbent assay (ELISA) was used to assess VDBP, vitamin D (25(OH)D), parathyroid hormone, and cystatin C.

Statistical analysis was performed using SPSS software (version 23, IBM Corp., Armonk, NY, USA). The normality of continuous variable distributions was assessed using the Shapiro-Wilk test. Data were presented as the mean with standard deviation (Mean ± SD) or as the median with the first and third quartiles (Median (Q1-Q3)). Comparisons were made using ANOVA with the post hoc Scheffé test for normally distributed data or the Kruskal-Wallis test with the post hoc Dunn test for non-normally distributed data. Correlation analysis was conducted using Spearman's coefficient. Differences were considered statistically significant at $p < 0.05$.

Results

The characteristics of the examined patients in the three groups are presented in Table 1. The mean age of patients in group I was 54.720 ± 8.894 years, in group 2 — 63.190 ± 9.172 years, and in group 3 — 66.110 ± 8.058 years ($p < 0.01$). A statistically significant difference was found in diabetes duration between group I and group III: 5 (3; 20) and 11.5 (9; 21) years, respectively ($p < 0.05$). All examined patients had obesity. Participants in group 1 had the highest BMI (31.11 ± 6.52 kg/m^2), although the difference was not statistically significant compared to the other groups ($p = 0.942$). Additionally, vitamin D (25(OH)D) deficiency was observed in all individuals with type 2 DM, with the lowest level found in group III (15.0 (10.2–20.7)) compared to group I (16.3 (13.1–21.6)) and group II (15.8 (13.6–18.7) ng/mL) ($p = 0.530$).

Serum VDBP levels increased in patients with impaired kidney function: in group I, VDBP was 99.9 (72.1–112.8) ng/mL, in group II — 114.424 (77.056–152.482) ng/mL, and in group III — 125.8 (86.4–166.3) ng/mL ($p = 0.143$). The increase in VDBP levels in patients with CKD is likely a consequence of vitamin D imbalance, chronic inflammation, and alterations in kidney function affecting protein metabolism. This may represent a compensatory response of the body aimed at preserving the available pool of vitamin D [13].

The level of parathyroid hormone statistically differed between group I and group III (50.116 (38.14; 68.2) and 78.68 (53.12; 133.67) pg/mL, $p = 0.008$). It is already known that in patients with renal insufficiency, parathyroid hormone levels increase due to impaired calcium, phosphorus, and vitamin D_3 metabolism. However, its excessive production may lead to pathological changes in the bones and cardiovascular system [14].

In our groups, total cholesterol levels did not differ statistically significantly, but hyperlipidemia was observed on average in all patients. The highest levels were recorded in individuals from the group I (6.20 ± 2.07) compared to the group II (5.50 ± 1.38) and group III (5.56 ± 1.62 mmol/L), p = 0.185. Uric acid levels differed significantly between the groups (p < 0.01), with the highest value observed in patients with impaired renal function (eGFR < 60 mL/min/1.73 m^2) at 439.15 (394.3; 471.45) μmol/L. This confirms the association between hyperuricemia and decreased renal function in the context of type 2 DM, which plays a causal role in the progression of CKD by exacerbating inflammation, oxidative stress, and vascular dysfunction [15]. Cystatin C, as the most sensitive marker for the early diagnosis of CKD, significantly increased with decreasing eGFR: levels in group I were 0.76 (0.56–1.12), in group II — 0.49 (0.42–0.55), and in group III — 0.43 (0.40–0.47) mg/L (p < 0.001). ACR in daily urine differed between groups (p< 0.01) and was highest in the group with eGFR < 60 mL/min/1.73 m^2 — 8.2 (2.3; 69.45) mg/mmol. The elevated ACR in the eGFR < 60 mL/min/1.73 m^2 group indicates impaired glomerular and tubular function, endothelial barrier deterioration, and nephropathy progression. This may serve as an early marker of CKD and a predictor of further decline in renal function. HbA1c levels did not differ statistically between the groups.

To study the correlations between early markers of renal impairment in individuals with type 2 DM, we constructed a correlation matrix using Spearman's rank correlation coefficient (Table 2). The strongest correlation was found between eGFR and cystatin C (r = –0.654, p < 0.0001).

Table 1. Characteristics of the examined individuals with type 2 DM

Indicator	Group I (n = 28)	Group II (n = 46)	Group III (n = 49)	p
Age (years)	54.720 ± 8.894[2, 3]	63.190 ± 9.172[1]	66.110 ± 8.058[1]	< 0.01
Duration of diabetes (years)	5 (3; 20)[3]	10 (5; 13)	11.5 (9; 21)[1]	< 0.05
BMI (kg/m^2)	31.11 ± 6.52	30.79 ± 5.21	30.610 ± 4.706	0.942
eGFR (ml/min/1.73 m^2)	94.15 (93; 104.3)[2, 3]	73.4 (66.8; 82.4)[1, 3]	45.45 (32.7; 56.85)[1, 2]	< 0.01
Vitamin D(25OH) (ng/ml)	16.3 (13.1–21.6)	15.8 (13.6–18.7)	15.0 (10.2–20.7)	0.530
Parathyroid hormone (pg/mL)	50.116 (38.14; 68.2)[3]	52.546 (42.44; 72.31)	78.68 (53.12; 133.67)[1]	0.008
Cystatin C (mg/l)	0.43 (0.40–0.47)[3]	0.49 (0.42–0.55)[1]	0.76 (0.56–1.12)[1, 2]	< 0.001
Serum VDBP (ng/ml)	99.9 (72.1–112.8)	114.424 (77.056–152.482)	125.8 (86.4–166.3)	0.143
Uric acid (μmol/L)	313.1 (254; 401.4)[3]	320.65 (272.4; 368.75)[3]	439.15 (394.3; 471.45)[1, 2]	< 0.01
Total cholesterol (mmol/l)	6.20 ± 2.07	5.50 ± 1.38	5.56 ± 1.62	0.185
Daily urine ACR (mg/mmol)	0.9 (0.6; 2.5)[3]	1.26 (0.6; 4.2)[3]	8.2 (2.3; 69.45)[1, 2]	< 0.01
HbA1c (%)	9.22 ± 2.22	8.81 ± 2.14	8.7 ± 2.3	0.651

Notes: Mean ($\bar{x}$) and standard deviation (± SD) are presented in the case of a normal distribution or median (Me) and interquartile range (QI-QIII) in the case of a non-normal distribution. ANOVA and Scheffe's posterior test in the case of a normal distribution or Kruskal-Wallis test and Dunn's posterior test in the case of a non-normal distribution were used for comparison: [1, 2, 3] — the difference from groups I, II, III is statistically significant, p < 0.05; eGFR — estimated glomerular filtration rate; BMI — body mass index; ACR — daily urinary albumin ratio; VDBP — vitamin D-binding protein; HbA1c — glycated hemoglobin.

Table 2. Correlations between the main laboratory markers in individuals with type 2 DM

Indicators	VDBP	ACR	Cystatin C	Age	Uric acid	Vitamin D (25OH)	HbA1c	eGFR
VDBP								
ACR	0.253 p = 0.0235							
Cystatin C	0.343 p = 0.0019	0.392 p = 0.0003						
Age	0.248 p = 0.0264	0.084 p > 0.05	0.325 p = 0.0032					
Uric acid	–0.123 p > 0.05	0.208 p = 0.0359	0.354 p = 0.0014	0.037 p > 0.05				
Vitamin D (25OH)	–0.146 p > 0.05	–0.199 p = 0.0441	–0.193 p > 0.05	0.009 p > 0.05	0.013 p > 0.05			
HbA1c	–0.05 p > 0.05	0.077 p > 0.05	–0.224 p = 0.0457	–0.140 p > 0.05	–0.310 p = 0.0015	–0.173 p > 0.05		
eGFR	–0.268 p = 0.0163	–0.386 p = 0.0001	**–0.654 p < 0.0001**	–0.419 p < 0.0001	–0.409 p < 0.0001	0.008 p > 0.05	0.117 p > 0.05	

Notes: Spearman's correlation coefficient and the level of significance of its difference from 0 are indicated. Correlation matrix.

Table 3. Comparative characteristics of early markers of kidney damage in type 2 DM depending on the level of vitamin D (25OH)

Indicator	Vitamin D(25OH) ≥ 30 ng/ml (n = 72)	Vitamin D(25OH) 20–30 ng/ml (n = 34)	Vitamin D(25OH) < 20 ng/ml (n = 17)	p
Total cholesterol (mmol/l)	5.78 (4.62–6.81)	5.49 (4.69–6.24)	5.96 (4.25–6.59)	0.579
HbA1c (%)	8.5 (7.35–8.93)	8.1 (7.15–9.05)	8.85 (7.20–10.50)	0.390
Cystatin C (mg/l)	0.47 (0.40–0.59)	0.44 (0.43–0.54)	0.53 (0.44–0.66)	0.302
VDBP (ng/ml)	69.9 (58.9–141.3)	93.8 (68.0–141.8)	111.7 (89.4–143.9)	0.286
eGFR (ml/min/1.73 m^2)	75.9 (59.1–92.5)	73.2 (57.5–87.5)	63.8 (57.1–71.3)	0.254

Notes: Median (Me) and interquartile range (QI-QIII) are presented. Kruskal-Wallis test and Dunn's posterior test were used for comparison.

VDBP showed a direct positive correlation with the ACR in daily urine (r = 0.253, p = 0.0235), cystatin C (r = 0.343, p = 0.0019), and age (r = 0.248, p = 0.0264), while it was inversely correlated with eGFR (r = –0.268, p = 0.0163). No correlation was found between VDBP levels and vitamin D (25(OH)D) in the participants of our study.

When assessing the vitamin D (25(OH)D) status in the examined patients, the levels of basic laboratory parameters were evaluated depending on the group (Table 3). A vitamin D (25(OH)D) level of ≥ 30 ng/mL was considered optimal, 20–30 ng/mL indicated insufficiency, and < 20 ng/mL was classified as deficiency, according to the recommendations of the Institute of Medicine (IOM) and the Endocrine Society.

Discussion

An increasing number of studies have demonstrated that vitamin D deficiency is associated with a wide range of diseases, including not only osteoporosis and osteomalacia but also DM, cardiovascular diseases, multiple sclerosis, rheumatoid arthritis, other autoimmune disorders, and several types of cancer [16]. Early detection of CKD in patients remains a significant challenge in efforts to reduce the burden of this complication in individuals with type 2 DM. VDBP is a highly polymorphic, single-chain serum glycoprotein that facilitates the delivery of circulating vitamin D to tissues [17]. Its two primary roles in vitamin D physiology include prolonging the half-life of vitamin D and maintaining its plasma levels through renal reabsorption [18]. In addition to binding and transporting vitamin D and its metabolites, VDBP can act as a macrophage-activating factor and participate in immune responses, contributing to the development of tubulointerstitial fibrosis [19, 20].

Some studies indicate that VDBP significantly correlates positively with urinary albumin, which may be associated with low serum vitamin D levels [21]. In normally functioning kidneys, VDBP, as part of the 25-(OH) vitamin D_3/VDBP complex, is reabsorbed through megalin-mediated endocytosis and catabolized by proximal tubular epithelial cells, thereby reducing its urinary excretion. Evidence suggests that excessive urinary excretion of VDBP may indicate tubular dysfunction, and its presence in urine is a potential biomarker for the early prediction and detection of DKD [20, 22]. In their studies, P.V. Rao et al. [23] and F.L. Nauta et al. [24] reported elevated levels of VDBP among other markers of diabetic nephropathy in individuals with type 2 DM compared to non-diabetic individuals, particularly in the presence of albuminuria. Other studies have shown that key factors involved in the development of glomerulosclerosis and interstitial fibrosis in CKD, such as TGF-β and angiotensin II [25, 26], may enhance urinary VDBP excretion by negatively regulating receptor-mediated endocytosis [27].

In our study, we investigated the role of VDBP in the development of early diabetic kidney damage, specifically examining its levels in serum. It was confirmed that serum VDBP levels increase in patients with impaired renal function, which may be attributed to several key mechanisms. First, in type 2 DM, renal function decline and vitamin D metabolism disturbances are frequently observed. The kidneys play a crucial role in vitamin D metabolism, particularly in converting 25(OH)D into its active form, $1,25(OH)_2D_3$. In CKD, there is a dysregulation of vitamin D synthesis, transport, and degradation. The body compensatorily increases VDBP levels to maintain the circulating vitamin D pool [28]. Second, CKD is accompanied by chronic inflammation, which affects hepatic protein synthesis, including VDBP. Inflammatory processes may stimulate VDBP production similarly to an acute-phase response [29]. Third, protein excretion alterations in CKD associated with type 2 DM may occur. Normally, VDBP is filtered through the glomerulus and reabsorbed in the proximal tubules. However, in DCD, protein reabsorption decreases, potentially leading to compensatory increased synthesis of VDBP [30].

In our study, VDBP directly correlated with the ACR in daily urine (r = 0.253, p = 0.0235), cystatin C (r = 0.343, p = 0.0019), and age (r = 0.248, p = 0.0264), while it inversely correlated with eGFR (r = –0.268, p = 0.0163). This suggests that VDBP is associated with renal function status, and its elevation may serve as a marker of progressive renal dysfunction in type 2 DM, particularly with aging. However, we did not find a correlation between VDBP levels and vitamin D (25(OH)D). This may be due to the influence of renal function (in cases of impaired renal clearance, VDBP may accumulate even if 25(OH)D levels remain low), inflammation (VDBP levels may increase in response to inflammation, infections, or stress, which are common in CKD [29]), genetic factors (different genetic isoforms of VDBP affect its affinity for 25(OH)D and its circulating levels [31, 32]), and the limited sample size in our study. This confirms that 25(OH)D levels do not always directly depend on VDBP, especially in patients with impaired renal function associated with type 2 DM.

Conclusions

VDBP may be considered an early marker of kidney damage in people with type 2 DM. VDBP associated with renal function, albuminuria, inflammation, and vitamin D metabolism. In addition to classical indicators of renal dysfunction (eGFR, ACR) cystatin C demonstrated the strongest association with kidney damage and also showed a statistically significant direct correlation with serum VDBP. A strong association with renal damage was demonstrated for cystatin C, which also had a statistically significant direct correlation with serum VDBP.

These findings contribute to the improvement of early diagnosis of diabetic kidney damage in individuals with type 2 DM, allowing for the identification of at-risk groups even before the development of overt nephropathy.

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Received 09.01.2025
Revised 04.03.2025
Accepted 07.03.2025

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Conflicts of interests. Authors declare the absence of any conflicts of interests and own financial interest that might be construed to influence the results or interpretation of the manuscript.

Information about funding. The source of funding for the publication of the article is the funds of the authors.

Authors' contribution. V.M. Yerokhovych — collection and analysis of information, examination of patients, search, and processing of specialized literature on the topic, writing the text of the article; O.V. Karpenko — collection and analysis of information, examination of patients, writing the text of the article; Ye.I. Ilkiv — search and processing of specialized literature on the topic, participation in laboratory research, collection of information, writing the text of the article; N.M. Kobyliak — statistical processing, manuscript preparation for printing; I.A. Paliienko — data analysis, processing of specialized literature on the topic; I.V. Dumka — search and processing of specialized literature on the topic; Yu.I. Komisarenko — conceptualization, research design, information analysis, manuscript preparation for publication.

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Ранні маркери ураження нирок при цукровому діабеті 2-го типу: роль вітамін-D-зв'язуючого білка

Резюме. ***Актуальність.*** Найчастішим і прогностично несприятливим ускладненням цукрового діабету (ЦД) є діабетичне ураження нирок, що призводить до термінальної ниркової недостатності. Останнім часом все більша увага приділяється екстраскелетним функціям вітаміну D, ролі вітамін-D-зв'язуючого білка (VDBP) та їхнього патогенетичному зв'язку з ураженням нирок в осіб із ЦД 2-го типу. ***Мета роботи:*** дослідити роль VDBP у розвитку раннього ураження нирок у пацієнтів із ЦД 2-го типу та оцінити найсильніші кореляційні зв'язки між ранніми маркерами ниркової дисфункції при ЦД. ***Матеріали та методи.*** У дослідженні взяли участь 123 хворі на ЦД 2-го типу. Групи були сформовані на основі розрахункової швидкості клубочкової фільтрації (рШКФ): I група (рШКФ ≥ 90 мл/хв/1,73 м^2, n = 28) — збережена фільтраційна здатність нирок або гіперфільтрація; II група (рШКФ 60–90 мл/хв/1,73 м^2, n = 46) — хронічна хвороба нирок (ХХН) другої стадії; III група (рШКФ < 60 мл/хв/1,73 м^2, n = 49) — третя стадія ХХН. ***Результати.*** Цистатин C як найбільш чутливий маркер ранньої діагностики ХХН вірогідно зростав зі зниженням рШКФ: його рівень в групі I становив 0,76 (0,56–1,12), у групі II — 0,49 (0,42–0,55), у групі III — 0,43 (0,40–0,47) мг/л (p < 0,001). VDBP прямо пропорційно корелював зі співвідношенням альбумін/креатинін добової сечі (r = 0,253; p = 0,0235), цистатином C (r = 0,343; p = 0,0019), віком (r = 0,248; p = 0,0264) та обернено — із рШКФ (r = –0,268; p = 0,0163). Не було виявлено кореляції між VDBP і рівнями 25(OH)D в учасників нашого дослідження. ***Висновки.*** VDBP можна вважати раннім маркером ураження нирок в осіб із ЦД 2-го типу. Сильний зв'язок з ураженням нирок був продемонстрований для цистатину C, який також мав статистично значущу пряму кореляцію з VDBP у сироватці крові.

Ключові слова: вітамін D; цукровий діабет 2-го типу; діабетична хвороба нирок; вітамін-D-зв'язуючий білок; хронічна хвороба нирок; хронічне системне запалення