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The Role of Aldosterone in the Development of Chronic Kidney Disease in Individuals with Type 2 Diabetes

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Abstract: *modern statistics confirm that diabetes has become an epidemic of the 21st century. According to the forecasts of the International Diabetes Federation, by 2045, the number of people with diabetes is expected to reach 784 million. Approximately 90% of cases involve type 2 diabetes, which is a major contributor to the development of chronic kidney and cardiovascular diseases. The role of aldosterone in the progression of persistent kidney filtration rate disorders is particularly important due to the high prevalence of microvascular complications in individuals with type 2 diabetes, especially diabetic nephropathy. The activation of the renin-angiotensin-aldosterone system, alongside inflammatory processes, fibrotic changes in the kidneys, endothelial dysfunction, and disturbances in carbohydrate metabolism, are key pathogenetic factors in the development and progression of cardio-renal-metabolic syndrome. This syndrome, officially recognized by the American Heart Association, encompasses chronic kidney disease, which significantly worsens the clinical condition and prognosis of individuals with type 2 diabetes. Understanding the relationship between aldosterone levels and irreversible changes in kidney filtration rate in patients with type 2 diabetes is essential for exploring the mechanisms of the renin-angiotensin-aldosterone system's impact on kidney function in diabetic nephropathy. This study analyzed a range of parameters, including age, anthropometric indicators, carbohydrate metabolism, physical data, aldosterone levels, vitamin D (25OH) levels, and the albumin-to-creatinine ratio in daily urine. Participants were grouped according to their glomerular filtration rate, with a rate of <60 ml/min/1.73 m² indicating persistent pathological changes in the kidneys among individuals with type 2 diabetes. The results revealed a negative correlation between aldosterone levels and glomerular filtration rate in individuals with persistent kidney changes caused by diabetic nephropathy. These changes serve as risk factors for cardiovascular diseases. Elevated aldosterone levels, albuminuria, decreased glomerular filtration rate, and reduced vitamin D (25OH) levels were identified as early indicators of chronic kidney disease in individuals with type 2 diabetes.*

Keywords: Type 2 Diabetes; Chronic Kidney Disease; Aldosterone; Cardiovascular Risks; Renin-Angiotensin-Aldosterone System.

Introduction

According to modern statistics, diabetes mellitus (DM) has reached pandemic proportions. Data from the International Diabetes Federation indicate that by 2045, the number of individuals with type 2 diabetes (T2D) worldwide may reach 784 million [1]. It is known that this condition currently affects 1 in 10 adults globally [2]. Approximately 90% of cases involve T2D, which primarily affects older individuals. However, the number of affected individuals is rapidly increasing, with alarming trends among children

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and young adults (under 40 years old) [3]. Among people with T2D, most have at least one complication, with cardiovascular complications being the leading cause of morbidity and mortality in this population [4].

Despite optimal control of blood pressure, dyslipidemia, and glucose levels, a high risk of developing cardiovascular diseases (CVD) and chronic kidney disease (CKD) remains. These conditions are strongly interconnected in people with diabetes [5]. The combination of hypertension and diabetes may synergistically contribute to the progression of kidney damage through mechanisms that remain incompletely understood [6]. The progression of CKD in individuals with T2D typically follows a sequence of stages, beginning with normal or increased estimated glomerular filtration rate (eGFR) and eventually leading to progressive renal function decline, CKD, and even end-stage renal disease [7].

The complex pathogenesis of diabetic kidney disease (DKD) involves multiple pathways, including inflammatory, fibrotic, metabolic, and hemodynamic factors [8]. One cause of renal hyperfiltration and increased intraglomerular pressure is the overactivation or hyperproduction of the mineralocorticoid hormone aldosterone, a component of the renin-angiotensin-aldosterone system (RAAS). Angiotensin II, acting on type 1 receptors, contributes to the progression of DKD through mechanisms such as vasoconstriction, increased tubular Na+ reabsorption, enhanced oxidative stress, and induction of renal production of fibrogenic and inflammatory cytokines [9].

Long-term observations have demonstrated that inhibition of angiotensin II synthesis or blockade of angiotensin II type 1 receptors provides cardio-renal protection in patients with DKD [10]. Additionally, excessive aldosterone levels and associated activation of mineralocorticoid receptors (MRs) disrupt insulin secretion and insulin-mediated metabolic effects, thereby promoting diabetes and its associated cardiometabolic syndrome [11]. The activation of RAAS, involvement of inflammatory processes, fibrotic kidney changes, endothelial dysfunction, and carbohydrate metabolism disturbances are recognized as key pathogenetic factors in the development and progression of the cardio-renal-metabolic (CRM) syndrome, which has been officially recognized by the American Heart Association [12]. CKD, as a core component of CRM, is considered a critical factor influencing the severity of a patient's condition. Therefore, further investigation into the relationship between aldosterone and CKD progression in individuals with T2D is warranted.

Aim

The study aimed to investigate the role of aldosterone in the development of CKD in individuals with T2D and to analyze the correlations between aldosterone levels and key indicators of renal filtration capacity depending on eGFR.

Materials and Methods

A prospective cohort study included 69 individuals with T2D, divided into two groups based on eGFR levels calculated using the CKD-EPI formula: Group I (eGFR < 60 ml/min/m², $n = 32$) and Group II (eGFR ≥ 60 ml/min/m², $n = 37$). The following parameters were analyzed: age, gender, BMI (body mass index), eGFR, glycated hemoglobin (HbA1c), systolic blood pressure (SBP), diastolic blood pressure (DBP), aldosterone, albumin-to-creatinine ratio (ACR) in daily urine, and vitamin D (25OH).

The study was conducted at the Kyiv City Endocrinology Center in the General Endocrinology Department. All procedures adhered to the principles of the Declaration of Helsinki and were approved by the Bioethics Commission (protocol No. 163, dated 07.11.2022). The study methodology was fully explained to participants, and all patients provided written informed consent to participate. Inclusion criteria: age 18–80 years, T2D duration ≥ 5 years, and informed patient consent. Exclusion criteria: acute cardiovascular diseases, acute renal or hepatic failure, participation in another study, pregnancy, lactation, history of nephrectomy, malignancies, or eGFR below 25 ml/min/m².

Serum creatinine was measured using the colorimetric method, and eGFR was calculated using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula. Aldosterone levels were assessed using the immunoassay method (Aldosterone Diametra, Italy), with a normal serum range of 14.6–

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174 pg/mL. ACR in daily urine was calculated by determining albumin levels (immunoturbidimetric method) and creatinine content (colorimetric method). HbA1c levels were measured using high-performance liquid chromatography.

Statistical analysis: data were processed using the Medstat software. The Shapiro-Wilk test was used to assess the normality of the distribution of continuous variables. Data were presented as mean ± standard deviation (mean ± SD) or median with interquartile ranges (median (Q1–Q3)), while categorical variables were expressed as percentages. The Wilcoxon test was used to compare group means according to normality distribution. Fisher's exact test was used to compare categorical variables. Correlation analysis was performed using Pearson's univariate correlation. Differences were considered statistically significant at $p < 0.05$.

Results

The patients in the study were divided into 2 groups based on eGFR levels: Group I – eGFR < 60 ml/min/m² (n = 32) and Group II – eGFR ≥ 60 ml/min/m² (n = 37). The mean age of participants in Group I was 64.45 ± 8.77 years, compared to 60.79 ± 10.81 years in Group II (p = 0.065). The duration of diabetes was significantly longer in individuals with renal insufficiency (Group I): 13 years versus 10 years (p = 0.021). Women predominated in Group I, while men were more prevalent in Group II. The BMI of all participants corresponded to obesity, with no statistically significant differences between the groups. Glycemic control, assessed by HbA1c, was worse in Group II, but the difference was not statistically significant. A summary of the baseline characteristics of patients in both groups is presented in Table 1.

The study revealed that aldosterone levels were significantly higher in Group I compared to Group II (84.06 vs. 48.543 pg/mL, p = 0.049). In Group I, aldosterone was negatively correlated with eGFR (r = -0.369, p = 0.04) (Figure 1). No correlation was found between aldosterone levels and ACR in daily urine. This suggests that aldosterone primarily affects renal functional activity rather than contributing to albuminuria development. Since eGFR < 60 ml/min/m² is associated with damage to more than half of the nephrons, irreversible changes in renal filtration capacity begin to develop.

The median ACR in Group I was significantly higher than in Group II: 412.3 (333.4; 473.3) vs. 0.9 (0.6; 2.69), p < 0.001. Systolic and diastolic blood pressure showed no statistically significant differences between the groups.

Table 1. Baseline characteristics of patients in Groups I and II

Parameters	Group I (eGFR < 60 ml/min/1.73 m²)	Group II (eGFR ≥ 60 ml/min/1.73 m²)	P-value
Age (years), mean ± SD	64,45 ± 8,77	60,79 ± 10,81	0,065
Duration of diabetes (years), median (Q1; Q3)	13 (11; 20)	10 (6; 14)	**0,021**
Gender (F/M), %	F -51,61%, M – 48,39	F– 44,44 %, M – 55,56 %	
BMI (kg/m²), mean ± SD	30,96 ± 4,61	31,96 ± 6,36	0,462
eGFR (ml/min/1.73 m²), mean ± SD	47 ± 14,85	83,03 ± 11,51	**<0,001**
HbA1c (%), mean ± SD	8,81 ± 2,06	9,29 ± 2,27	0,366
SBP (mmHg), mean ± SD	144,5 ± 25,99	139,4 ± 12,41	0,322
DBP (mmHg), mean ± SD	89,2 ± 9,63	84,44 ± 9,76	0,462
Aldosterone (pg/mL), median (Q1; Q3)	84,06 (37,89;133,49)	48,54 (21,24; 107,83)	**0,049**
Vitamin D (25OH) (ng/mL), median (Q1; Q3)	13,53 (9,11; 17,22)	16,51 (13,07; 20,05)	**0,027**
ACR (mg/g), median (Q1; Q3)	412,3 (333,4; 473,3)	0,9 (0,6; 2,69)	**<0,001**

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Abbreviations:

eGFR: Estimated Glomerular Filtration Rate (ml/min/1.73 m²)

BMI: Body Mass Index (kg/m²)

HbA1c: Glycated Hemoglobin (%)

SBP: Systolic Blood Pressure (mmHg)

DBP: Diastolic Blood Pressure (mmHg)

ACR: Albumin-to-Creatinine Ratio (mg/g) (in urine)

25OH: 25-Hydroxyvitamin D (ng/mL)

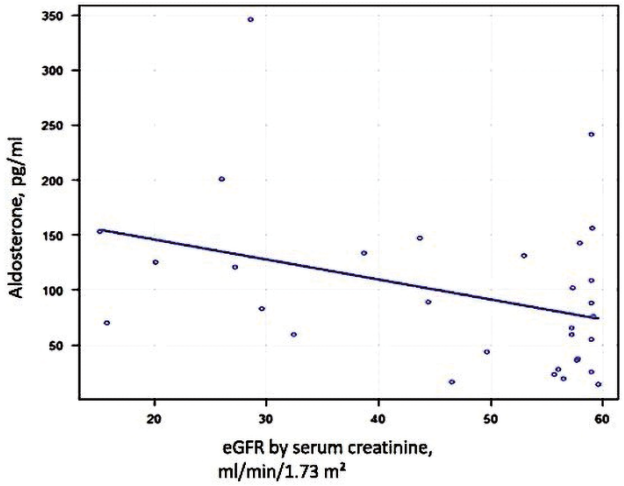

Figure 1. Correlation between aldosterone levels and eGFR based on serum creatinine in people with TD2 from Group I

All examined patients (Figure 2) demonstrated a deficiency in vitamin D(25OH), with significantly lower levels of vitamin D (25OH) in Group I compared to Group II (13.53 ng/mL vs. 16.51 ng/mL; p = 0.027). This finding underscores the critical role of vitamin D(25OH), in contributing to endothelial dysfunction in CKD and TD2, as well as its association with an elevated risk of developing comorbid cardiovascular pathologies.

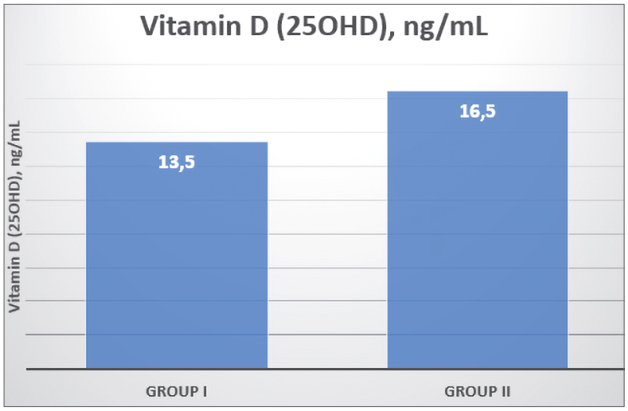

Figure 1. Level of vitamin D(25OH) in patients depending on the group by eGFR

Discussion

The results of the study demonstrate the significant role of aldosterone in the progression of CKD in individuals with T2D. It has been established that elevated aldosterone levels are negatively correlated with eGFR, confirming its influence on the functional capacity of the kidneys. Patients with eGFR < 60 mL/min/1.73 m² exhibited significantly higher aldosterone levels compared to those with eGFR ≥ 60 mL/min/1.73 m². This indicates that RAAS hyperactivity is one of the key mechanisms in the progression of nephropathy in T2D. Interestingly, aldosterone in T2D patients did not correlate with albuminuria levels, suggesting its predominant effect on the functional rather than structural activity of the kidneys. This aligns with the well-known fact that damage to more than half of the nephrons leads to irreversible changes in the filtration capacity of the kidneys.

Aldosterone, as a key hormone of RAAS, plays a central role in regulating electrolyte balance and blood pressure.

Its action is mediated through the activation of MRs in the distal nephron tubules, resulting in increased sodium reabsorption and potassium excretion. This maintains extracellular fluid volume and hemodynamic stability [13]. In people with T2D, MR hyperactivation is associated with the development of cardiorenal complications, particularly diabetic nephropathy and heart failure. Elevated aldosterone levels contribute to fibrosis and inflammation in the kidneys and heart, driven by the activation of pro-inflammatory pathways and increased oxidative stress [14]. Endothelial dysfunction, typical for T2D, is a consequence of aldosterone's effects on vascular endothelium. Aldosterone reduces the bioavailability of nitric oxide (NO), a key vasodilator, leading to increased vascular tone and blood pressure. Additionally, aldosterone stimulates the expression of adhesion molecules such as ICAM-1 and VCAM-1, promoting the development of atherosclerosis [15]. Aldosterone plays a direct role in kidney changes in T2D people and the CRM syndrome.

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This syndrome affects major organs, such as the heart, kidneys, brain, and liver, and includes interrelated pathologies: cardiovascular diseases, kidney diseases, and T2D [12].

Another important finding was the presence of vitamin D (25OH) deficiency in all examined patients. In the group with eGFR < 60 mL/min/1.73 m², vitamin D (25OH) levels were significantly lower. D-deficiency is associated with endothelial dysfunction, a risk factor for CRM syndrome progression. This may explain why patients with low vitamin D (25OH) levels are more prone to cardiovascular complications. Vitamin D (25OH) deficiency may influence glucose homeostasis in CKD, which is frequently observed in individuals with impaired renal function. Due to diabetic nephropathy (DN), not only is the metabolism and production of the active metabolite (1,25(OH)2D3) disrupted, but glomerular hyperfiltration and altered tubular reabsorption may lead to proteinuria and the loss of 25(OH) D along with vitamin D-binding protein [16]. Vitamin D status can directly affect glucose metabolism. Vitamin D (25OH) regulates insulin release by modulating intracellular calcium in β-cells, increases insulin receptor expression, and its deficiency is associated with secondary hyperparathyroidism, which can reduce insulin secretion [17]. The data suggest a link between vitamin D deficiency and glucose metabolism disorders in CKD populations [16].

The findings emphasize the need for early diagnosis and monitoring of aldosterone levels, eGFR, albuminuria, and vitamin D levels in T2D people. Using RAAS inhibitors or MRs antagonists may be a promising strategy to slow CKD progression in such patients. These findings could form the basis for further research and improved approaches to CKD treatment in T2D people.

Conclusions

A negative correlation between aldosterone and GFR has been found in individuals with persistent renal changes due to DN, which are risk factors for the development of CKD and the occurrence of cardiovascular pathology. The absence of a correlation between aldosterone levels and ACR in daily urine may indicate diverse mechanisms in DN development: aldosterone influences sodium retention, fibrosis, and inflammatory processes in the kidneys, whereas ACR serves as a marker of glomerular permeability and endothelial damage. Increased aldosterone and albuminuria, as well as decreased eGFR and vitamin D (25OH) levels, are early indicators of DN development, which can be used for early diagnosis and improved patient outcomes. This opens up opportunities for enhancing screening programs and developing new strategies to prevent disease progression and complications. The use of these markers in clinical practice will enable a more personalized approach to patient management, helping to improve prognosis and the effectiveness of therapeutic interventions.

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.

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Роль альдостерону в розвитку хронічної хвороби нирок у осіб з цукровим діабетом 2 типу

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Анотація: *Сучасна статистика підтверджує, що діабет став епідемією 21 століття. За прогнозами Міжнародної діабетичної федерації, до 2045 року очікується, що кількість хворих на діабет досягне 784 мільйонів. Приблизно 90% випадків пов'язані з діабетом 2 типу, який є основною причиною розвитку хронічних захворювань нирок і серцево-судинної системи. Роль альдостерону в прогресуванні стійких порушень швидкості фільтрації нирок є особливо важливою через високу поширеність мікросудинних ускладнень у осіб з ЦД 2 типу, особливо діабетичної нефропатії. Активація ренін-ангіотензин-альдостеронової системи поряд із запальними процесами, фіброзними змінами в нирках, ендотеліальною дисфункцією, порушенням вуглеводного обміну є ключовими патогенетичними факторами розвитку та прогресування кардіо-ренально-метаболічного синдрому. Цей синдром, офіційно визнаний Американською кардіологічною асоціацією, охоплює хронічну хворобу нирок, яка значно погіршує клінічний стан і прогноз хворих на діабет 2 типу. Розуміння взаємозв'язку між рівнями альдостерону та незворотними змінами швидкості фільтрації в нирках у пацієнтів із діабетом 2 типу має важливе значення для вивчення механізмів впливу ренін-ангіотензин-альдостеронової системи на функцію нирок при діабетичній нефропатії. У цьому дослідженні аналізувався ряд параметрів, включаючи вік, антропометричні показники, вуглеводний обмін, фізичні дані, рівень альдостерону, рівень вітаміну D (25OH), а також співвідношення альбуміну та креатиніну в добовій сечі. Учасників об'єднали в групи відповідно до їх швидкості клубочкової фільтрації зі швидкістю <60 мл/хв/1,73 м², що вказує на стійкі патологічні зміни в нирках у осіб з діабетом 2 типу. Результати виявили негативну кореляцію між рівнем альдостерону та швидкістю клубочкової фільтрації в осіб із стійкими змінами нирок, спричиненими діабетичною нефропатією. Ці зміни є факторами ризику серцево-судинних захворювань. Підвищений рівень альдостерону, альбумінурія, зниження швидкості клубочкової фільтрації та зниження рівня вітаміну D (25OH) були ідентифіковані як ранні показники хронічної хвороби нирок у осіб з діабетом 2 типу.*

Ключові слова: цукровий діабет 2 типу, хронічна хвороба нирок, альдостерон, серцево-судинні ризики, ренін-ангіотензин-альдостеронова система.