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ASSESSMENT OF CARDIOVASCULAR RISK IN PATIENTS WITH TYPE 2 DIABETES AND ALBUMINURIC DIABETIC KIDNEY DISEASE PHENOTYPE

ANALIZA KARDIOVASKULARNOG RIZIKA KOD OSOBA SA TIPOM 2 DIJABETESA I ALBUMINURIČNIM FENOTIPOM DIJABETESNE BOLESTI BUBREGA

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Summary

Introduction. The aim of this study is analysis of cardiovascular risk in non-albuminuric and albuminuric patients with type 2 diabetes and diabetic kidney disease. **Material and Methods**. The study included 136 patients with type 2 diabetes and chronic kidney disease (estimated glomerular filtration rate <90 ml/min/1.73 m^2). Patients were divided into two groups: Group A (patients without albuminuria) and Group B (patients with albuminuria). The cardiovascular risk was assessed through a retrospective analysis of data from electronic medical records. **Results**. We found statistically significantly more patients with stage 3a (Group A: 10% vs. Group B: 54%) and stage 3b (Group A: 7% vs. Group B: 13%; p<0.05) chronic kidney disease in the albuminuric group. These patients also had a longer duration of diabetes (Group A: 13.43±9.56 vs. Group B: 17.14±9.17 years; p<0.05), a higher frequency of male subjects (Group A: 44% vs. Group B: 63.9%; p<0.05) and a higher prevalence of smokers. The presence of hypertension was significantly more frequent in Group B (Group A: 89% vs. Group B: 97.2%; p<0.05). There was no significant difference between the groups in terms of age and metabolic control. However, coronary heart disease (Group A: 36% vs. Group B: 55.6%; p<0.05), peripheral artery disease (Group A: 16% vs. Group B: 22.2%; p<0.05), and stroke (Group A: 5% vs. Group B: 22.2%; p<0.05) were significantly more common in patients with type 2 diabetes and albuminuria. **Conclusion.** The albuminuric phenotype of diabetic kidney disease is associated with greater kidney function impairment, a longer duration of diabetes, and a higher prevalence in men. The presence of albuminuria significantly increases cardiovascular risk in people with type 2 diabetes and chronic kidney disease. Using renoprotective antihyperglycemic agents is essential in this group of patients, as they have an increased mortality risk.

Key words: Cardiovascular Diseases; Risk Factors; Diabetes Mellitus, Type 2; Diabetic Nephropathies; Renal Insufficiency, Chronic ; Albuminuria; Phenotype

Sažetak

Uvod. Cilj ove studije je analiza kardiovaskularnog rizika kod osoba bez albuminurije i osoba sa albuminurijom i sa tipom 2 dijabetesa i dijabetesnom bolešću bubrega. **Materijal i metode.** Studija je obuhvatila 136 bolesnika sa tipom 2 dijabetesa i hroničnom bubrežnom insuficijencijom (procenjena brzina glomerulske filtracije < 90 ml/min/1,73 m^2). Na osnovu prisustva albuminurije, analiza je sprovedena u dve grupe: grupa A bolesnici bez albuminurije i grupa B bolesnici sa albuminurijom. Analiza kardiovaskularnog rizika je sprovedena retrospektivnom analizom podataka iz istorija bolesti. **Rezultati.** Registrovano je statistički značajno više pacijenata sa stadijumom 3a (A: 10% vs B: 54%) i 3b (A: 7% vs B: 13%; p < 0,05) hronične bubrežne insuficijencije u grupi pacijenata sa albuminurijom. U ovoj grupi registrovano je značajno duže trajanje dijabetesa (A: 13,43 ± 9,56 vs B: 17,14 ± 9,17 godina; p < 0,05), značajno veća učestalost muškog pola (A: 44,0% vs B: 63,9%; p < 0,05) i navike pušenja. Takođe registrovano je značajno češće prisustvo arterijske hipertenzije (A: 89% vs B: 97,2%; p < 0,05). U analiziranoj kohorti pacijenti se nisu razlikovali u pogledu godina starosti i metaboličke kontrole. Koronarna bolest je bila značajno češće prisutna kod bolesnika sa tipom 2 dijabetesa i albuminurijom (A: 36,0% vs B: 55,6%; p < 0,05) kao i periferna vaskularna bolest (A: 16% vs B: 22,2%; p < 0,05) i cerebrovaskularni insult (A: 5% vs B: 22,2%; p < 0,05). **Zaključak.** Albuminurični fenotip dijabetesne bolesti bubrega je praćen većim stepenom oštećenja bubrežne funkcije, dužim trajanjem dijabetesa i češći je kod muškaraca. Prisustvo albuminurije značajno povećava kardiovaskularni rizik kod osoba sa tipom 2 dijabetesa i hronične bubrežne bolesti u vidu češće pojave koronarne, periferne vaskularne bolesti i cerebrovaskularnog insulta. S obzirom da ove osobe imaju povećanu stopu mortaliteta neophodna je pravovremena terapija primenom renoprotektivnih antihiperglikemijskih lekova.

Ključne reči: kardiovaskularne bolesti; faktori rizika; dijabetes melitus tip 2; dijabetesna nefropatija; hronična bubrežna insuficijencija; albuminurija; fenotip

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Abbreviations

T2D – type 2 diabetes
CVD – cardiovascular disease
CKD – chronic kidney disease
DKD – diabetic kidney disease
eGFR – estimated glomerular filtration rate
BMI – body mass index
HbA1c – glycated hemoglobin
AST – aspartate aminotransferase
ALT – alanine aminotransferase
g-GT – gamma-glutamyl transpeptidase
LDL-C – low-density lipoprotein-cholesterol
HDL-C – high-density lipoprotein-cholesterol
TC – total cholesterol
TG – triglycerides
CRP – C-reactive protein
SD – standard deviation
SGLT2 – sodium-glucose cotransporter 2

Introduction

The number of people with diabetes, a multifactorial disorder affecting the metabolism of carbohydrates, lipids, and proteins, is increasing worldwide. According to the International Diabetes Federation (IDF) data from 2021, an estimated 10.5% of the global population lives with diabetes, and this number is expected to rise to 12.2% by 2045. Diabetes is considered a direct cause of more than 1.5 million deaths per year [1–3].

Type 2 diabetes (T2D) accounts for 90% of the global burden and is considered the "equivalent of cardiovascular risk" [4]. Patients with T2D have a 2 to 4 times higher risk of cardiovascular diseases such as coronary heart disease, cerebrovascular and peripheral vascular disease. Consequently, people with T2D face a significantly increased risk of mortality, especially after the age of 45 [5, 6]. This increased risk is associated with insulin resistance and hyperinsulinemia, endothelial dysfunction, dyslipidemia, hypertension, obesity, hypercoagulability, and low grade inflammation.

Diabetic kidney disease (DKD) is clinically defined as diabetes with persistent albuminuria (albumin-to-creatinine ratio ≥30 mg/g) and/or a persistently low estimated glomerular filtration rate (eGFR <60 mL/min/1.73 m^2) [7]. T2D is the leading cause of chronic kidney disease (CKD) worldwide, and one-third of diabetes patients suffering from (CKD). CKD is a major risk factor for cardiovascular events in people with T2D [3, 7]. The risk of cardiovascular diseases is 6-7 times higher in people with DKD, and the presence of albuminuria significantly increases this risk [7–9]. The first clinical manifestation of DKD is often the presence of albuminuria. However, it is now recognized that, in addition to the classic clinical course, there can also be a reduction in renal function in normoalbuminuric patients. Recent observations indicate that 20-40% of T2D patients have reduced kidney function even in the absence of pathological albuminuria. This group of patients is identified as having the "non-albuminuric" phenotype of DKD. The pathogenesis of this phenotype is unclear, but certain clinical and pathological characteristics are hypothesized. Risk factors for non-albuminuric DKD include female gender, hypertension, active smoking, and the use of renin-angiotensin-aldosterone system inhibitors [10–16].

The aim of this study was to analyze cardiovascular risk in non-albuminuric and albuminuric patients with T2D and CKD during a retrospective study at the Clinic for Endocrinology, Diabetes and Metabolic Diseases of the University Clinical Center of Serbia.

Material and Methods

This retrospective study was conducted at the Clinic for Endocrinology, Diabetes and Metabolic Diseases of the University Clinical Center of Serbia in Belgrade. Initially, the study included 267 patients with type 2 diabetes (T2D) who were hospitalized at the Department for Metabolic Disorders, Intensive Treatment and Cell Therapy in Diabetes from 2018 to 2022. After excluding patients with normal kidney function (eGFR ≥90 ml/min/1.73 m^2), we analyzes 135 patients with CKD. These patients were divided into two groups: patients without albuminuria (group A, N=100) and patients with albuminuria (group B, N=35). Albuminuria was verified as albumin excretion rate of 30-300 mg/24 h in two separate samples, in the absence of urinary tract infection.

We recorded anthropometric data, including body mass index (BMI), calculated as BMI = weight (kg)/height (m^2), and socio-epidemiological data, including age, gender, duration of diabetes, smoking habits, and presence of arterial hypertension. We also noted current therapies for diabetes, hypertension and dyslipidemia.

Biochemical parameters recorded included glycated hemoglobin (HbA1c), hemoglobin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (g-GT), low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C), total cholesterol (TC), triglycerides (TG), creatinine, uric acid, and C-reactive protein (CRP).

We documented the presence of chronic complications of diabetes, including macrovascular complications (coronary artery disease, stroke, and peripheral vascular disease) and microvascular complications (nephropathy, neuropathy and retinopathy).

The glomerular filtration rate (GFR) was calculated using the MDRD (Modification of Diet in Renal Disease Study) equation, based on gender, age, race and serum creatinine values. CKD stages were defined as follows: stage 1 without kidney failure (eGFR≥90 ml/min/1.73 m^2), stage 2 (eGFR 60-89 ml/min/1.73 m^2), stage 3a (eGFR 40-59 ml/min/1.73 m^2), stage 3b (eGFR 30-44 ml/min/1.73 m^2), stage 4 (eGFR 15-29 ml/min/1.73 m^2) and stage 5 (eGFR<15 ml/min/1.73 m^2).

Data were analyzed using Statistical Package for the Social Sciences (SPSS) software (Advanced Statistics, version 22.0, Chicago, IL, USA). Data are presented as mean±standard deviation (SD), median, and frequencies (%).Normal distribution was tested using the Kolmogorov-Smirnov test. Differences

Table 1. Socio-demographic and anthropometric characteristics of patients with T2D and CKD (mean ± standard deviation or frequency).
Tabela 1. *Socio-demografske i antropometrijske karakteristike osoba sa tipom 2 dijabetesa i hroničnom bubrežnom insuficijencijom (aritmetička sredina ± standardna devijacija ili učestalost)*

Parameter/*Parametar*	Group A/*Grupa A*	Group B/*Grupa B*	Significance/*Značajnost*
Age (years)/*Starosna dob (godine)*	67.03±9.74	68.58±9.46	p=NS
Sex (M/F)/*Pol (M/Ž)*	44/56%	63.9/36.1%	p<0.05
Diabetes duration (years) *Dužina trajanja dijabetesa (godine)*	13.43±9.56	17.14±9.17	p<0.05
BMI (kg/m^2)/*ITM (kg/m^2)*	30.7±2.1	31.4±1.7	p<0.05
Smoking/*Pušenje*	26%	33.3%	p<0.05
Arterial hypertension/*Hipertenzija*	89%	97.2%	p<0.05

Legend: BMI - body mass index; *Legenda: ITM – indeks telesne mase*

were tested for significance using Student's *t*-test, for numeric characteristics and Mann-Whitney U test for nonparametric data. The chi-square test was used for categorical characteristics. A two-sided *p*- value <0.05 was considered statistically significant.

Results

The socio-demographic and anthropometric characteristics of the patients are shown in **Table 1**.

There was a significant difference in the duration of diabetes, with a statistically longer duration recorded in the group with albuminuria (Group A: 13.43±9.56 years vs. Group B: 17.14±9.17 years; p<0.05). Additionally, a statistically significantly higher frequency of male subjects was registered in a group of patients with T2D and albuminuria (Group A: 44% vs. Group B: 63.9%; p<0.05). There was no significant difference in age among the patients (Group A: 67.03±9.74 years vs. Group B: 68.58±9.46 years; p>0.05). Both groups were overweight or obese, with no statistically significant difference in BMI (Group A: 30.7±2.1 vs. Group B: 31.4±1.7, p>0.05).

A statistically significant higher frequency of smokers was found in albuminuric patients with T2D (Group A: 26% vs. Group B: 33.3%; p<0.05).

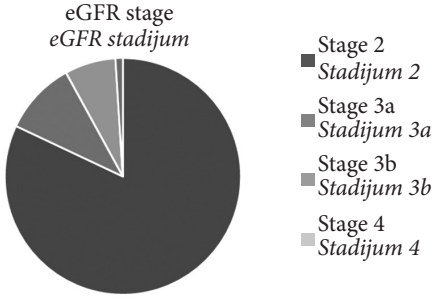
In the group of patients without albuminuria (Group A), the highest percentage of patients had stage 2 CKD (82%), followed by stage 3a (10%), stage 3b (7%), and stage 4 (1%) (p<0.05). In contrast, in the group of patients with albuminuria (Group B), 27.8% had stage 2, 47.2% had stage 3a, 11.1% had stage 3b, and 13.9% of patients had stage 4 CKD (p<0.05). Terminal stage CKD was not recorded in either group.

Analyses revealed a significant difference in average eGFR value between the groups, with a significantly lower eGFR observed in the group of patients with albuminuria (Group A: 53.78±9.24 vs. Group B 69.136±9.37, p<0.05),as shown in **Graphs 1 and 2**.

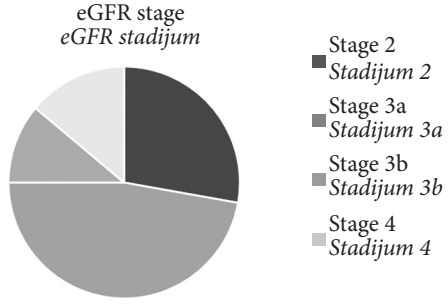
The albuminuric group also had significantly higher creatinine (Group A: 89.66±26.51 vs. Group B: 124.53±49.44 μmol/L; p<0.01) and uric acid levels (Group A: 337.67±81.65 vs. Group B: 372.82±87.66 mmol/l; p<0.05), as shown in **Table 2**.

There were no differences in the parameters of long-term metabolic control, such as HbA1c (Group A: 9.73±2.11 vs. Group B: 9.24±1.85; p>0.05).

Similarly, the lipid profile parameters showed no statistically significant differences between the group (TC: 4.63±1.17 vs. 4.28±1.03; LDL-C: 4.18±1.51 vs. 2.33±0.81; HDL-C: 1.07±0.31 vs. 0.96±0.27; TG:



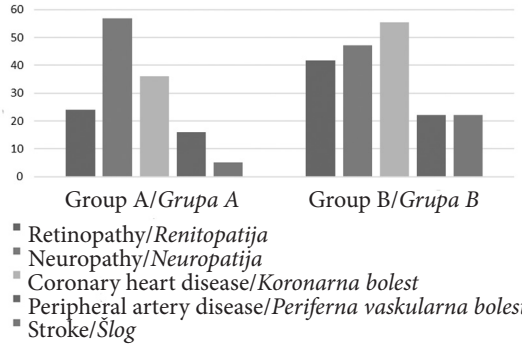
Graph 1. eGFR stages in patients with T2D and CKD without albuminuria
The values are presented as frequencies.
Grafikon 1. *eGFR stadijumi kod osoba sa tipom 2 dijabetesa i hroničnom bubrežnom insuficijencijom bez albuminurije*
Vrednosi su prikazane kao učestalosti.



Graph 2. eGFR stages in patients with T2D and CKD with albuminuria
The values are presented as frequencies.
Grafikon 2. *eGFR stadijumi kod osoba sa tipom 2 dijabetesa i hroničnom bubrežnom insuficijencijom sa albuminurijom*
Vrednosti su prikazane kao učestalosti.

Table 2. Metabolic and biochemical parameters of patients with T2D and CKD (mean ± standard deviation or frequency).
Tabela 2. *Metabolički i biohemijski parametri kod osoba sa tipom 2 dijabetesa i hroničnom bubrežnom insuficijencijom (aritmetička sredina ±standardna devijacija ili učestalost)*

Parameter/*Parametar*	Group A/*Grupa A*	Group B/*Grupa B*	Significant/*Značajnost*
Creatinine values/*Vrednosti kreatinina (μmol/L)*	89.66±26.51	124.53±49.44	p<0.01
Uric acid/*Mokraćna kiselina (mmol/l)*	337.67±81.65	372.82±87.66	p<0.05
Glycated haemoglobin *Glikozilirani hemoglobin (HbA1c)*	9.73±2.11%	9.24±1.85%	p>0.05
Total cholesterol/*Ukupni holesterol (mmol/l)*	4.63±1.17	4.28±1.03	p>0.05
LDL cholesterol/*LDL holesterol (mmol/l)*	4.18±1.51	2.33±0.81	p>0.05
HDL cholesterol/*HDL holesterol (mmol/l)*	1.07±0.31	0.96±0.27	p>0.05
Triglycerides/*Trigliceridi (mmol/l)*	2.23±1.15	2.35±1.34	p>0.05



Graph 3. Micro- and macrovascular complications in patients with T2D and CKD
The values are presented in percentages. p<0.05; Group A – individuals with T2D without albuminuria; Group B – individuals with T2D and albuminuria
Grafikon 3. *Učestalost mikrovaskularnih i makrovaskularnih komplikacija kod osoba sa tipom 2 dijabetesa i hroničnom bubrežnom insuficijencijom*
Vrednosti su prikazane u procentima. p < 0,05; Grupa A – osobe sa tipom 2 dijabetesa bez albuminurije; Grupa B – osobe sa tipom 2 dijabetesa i albuminurijom

2.23±1.15 vs. 2.35±1.34 mmol/l; p>0.05), as shown in **Table 2**.

Hypertension was significantly more frequent in patients with T2D and albuminuria (Group A: 89% vs. Group B: 97.2%; p<0.05), and these patients were more often on antihypertensive therapy (Group A: 89.0% vs. Group B: 97.2%; p<0.05). However, there were no statistically significant differences in systolic (Group A: 131.95±16.69 vs. Group B: 131.39±18.96 mmHg; p>0.05) or diastolic blood pressure (Group A: 78.15±9.58 vs. Group B: 77.36±10.92 mmHg; p>0.05) between the groups.

A significantly higher number of patients with T2D and albuminuria used aspirin (Group A: 53.0% vs. Group B: 60%; p<0.05) and statins (Group A: 48% vs. Group B: 63.9%; p<0.05). However, there was no statistically significant difference in the current diabetes therapies (metformin, sulphonylureas and insulin) between the groups.

Coronary heart disease was significantly more prevalent in patients with T2D and albuminuria (Group A: 36% vs. Group B: 55.6%; p<0.05) as were peripheral artery disease (Group A: 16% vs. Group B: 22.2%; p <0.05) and stroke (Group A: 5% vs. Group B: 22.2%; p<0.05), as shown in **Graph 3**. The presence of atrial fibrillation was similar between the groups (Group A: 9.0% vs. Group B: 8.3%; p>0.05).

Additionally, retinopathy was more frequent in patients with T2D and albuminuria (Group A: 24% vs. Group B: 41.7%; p<0.05), while neuropathy was more common in patients with T2D without albuminuria (Group A: 57% vs. Group B: 47.2%), as illustrated in **Graph 3**.

Discussion

Our study compared patients with T2D and reduced kidney function (eGFR <90 ml/min/1.73 m^2) between those with albuminuric and non-albuminuric phenotypes. We analyzed various parameters including age, gender, diabetes duration, glomerular filtration rate, creatinine and uric acid levels, lipid profile, presence of hypertension, smoking habits, HbA1c levels, use of aspirin and statintherapy, current diabetes therapy, and macrovascular and microvascular complications.

Previous studies have established that T2D is leading major independent risk factor for chronic kidney disease. Persistent hyperglycemia leads to renal inflammation and tubulointerstitial fibrosis, progressively reducing kidney function [17]. This underscores the importance of regular kidney function monitoring and risk factor management in T2D patients.

Our findings indicate that T2D patients with the albuminuric phenotype have a significantly longer duration of diabetes and on lower average eGFR values, with a higher prevalence of advanced CKD stages. Despite the extended diabetes duration (over 15 years in both groups), none had progressed to end-stage of renal disease. This aligns with previous research suggesting that T2D with CKD and albuminuric phenotype is more prevalent in males [17].

Cardiovascular risk increases with the diabetes duration, and CKD exacerbates the risk in T2D patients [18]. Reduced eGFR independently heightens the risk of cardiovascular complications, including

recurrent myocardial infarctions, left ventricular dysfunction and conduction disorders [19–21].

Our study found that participants with the albuminuric phenotype had a longer diabetes duration and higher incidence of coronary artery disease, peripheral artery disease, and stroke.

Low-density lipoprotein cholesterol is a known independent cardiovascular risk factor, with current guidelines targeting levels below 1.8 mmol/L or 50% reduction from baseline [22, 23].

Despite comparable levels of total cholesterol, LDL cholesterol and triglycerides between the two groups, and higher statin usage in the albuminuric group, neither group achieved the target LDL levels.

The lack of difference in HbA1c levels, which were unsatisfactory, may be attributed to poor glycemic control, the primary reason for hospitalization of these patients.

Hypertension is another independent cardiovascular risk factor, particularly in T2D patients with albuminuria. A meta-analysis of 40 clinical studies highlighted that every 10 mmHg reduction in systolic blood pressure significantly reduces the cardiovascular event frequency [24]. Current guidelines of the American Diabetes Association emphasize controlling all cardiovascular risk factors in T2D patients to prevent complications [23]. Effective management includes high-potency stains, lipid profile, antihypertensive treatment and strict blood pressure control aiming for targets below 130/80 mmHg [22, 23].

Microvascular complications, specifically retinopathy, were significantly more prevalent in T2D and CKD patients with the albuminuric phenotype.

These findings highlight the need for stringent cardiovascular risk management in this group to prevent CKD progression and cardiovascular complications. Achieving adequate glycemic control through antihyperglycemic agents with cardio-renal benefits, such as sodium-glucose cotransporter 2 (SGLT2) inhibitors, is crucial for these patients, particularly those with the albuminuric phenotype of DKD [22–26].

Conclusion

The prevalence of albuminuric phenotype of diabetic kidney disease increases with the duration of diabetes and is more common among males. The presence of albuminuria significantly elevates the cardiovascular risk in individuals with type 2 diabetes and chronic kidney disease, manifesting as higher incidence coronary artery disease, peripheral artery disease, and stroke. Therefore, it is essential to use renoprotective antihyperglycemic agents in this group of patients to mitigate the increased mortality risk.

References

1. Magliano DJ, Boyko EJ; International Diabetes Federation. IDF diabetes atlas [Internet]. 10th ed. Brussels: International Diabetes Federation; 2021 [cited 2024 Jan 15]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK581934/

2. Chatterjee S, Khunti K, Davies MJ. Type 2 diabetes. Lancet. 2017;389(10085):2239-51.

3. Koye DN, Magliano DJ, Nelson RG, Pavkov ME. The global epidemiology of diabetes and kidney disease. Adv Chronic Kidney Dis. 2018;25(2):121-32.

4. Hajar R. Diabetes as "coronary artery disease risk equivalent": a historical perspective. Heart Views. 2017;18(1):34-7.

5. Bertoluci MC, Rocha VZ. Cardiovascular risk assessment in patients with diabetes. Diabetol Metab Syndr. 2017;9(1):25.

6. Damaskos C, Garmpis N, Kollia P, Mitsiopoulos G, Barlampa D, Drosos A, et al. Assessing cardiovascular risk in patients with diabetes: an update. Curr Cardiol Rev. 2020;16(4):266-74.

7. Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. KDIGO 2020 clinical practice guideline for diabetes management in chronic kidney disease. Kidney Int. 2020;98(4S):S1-115.

8. Romero-González G, Rodríguez-Chitiva N, Cañameras C, Paúl-Martínez J, Urrutia-Jou M, Troya M, et al. Albuminuria, forgotten no more: underlining the emerging role in cardiorenal crosstalk. J Clin Med. 2024;13(3):777.

9. Žeravica R, Ilinčić B, Čabarkapa V, Sakač V, Crnobrnja V, Stošić Z. Plasma endothelin-1 levels and albuminuria in patients with type 2 diabetes mellitus. Med Pregl. 2016;69(5-6):140-5.

10. Dal Canto E, Ceriello A, Rydén L, Ferrini M, Hansen TB, Schnell O, et al. Diabetes as a cardiovascular risk factor: an overview of global trends of macro and micro vascular complications. Eur J Prev Cardiol. 2019;26(2 Suppl):25-32.

11. Harjutsalo V, Groop PH. Epidemiology and risk factors for diabetic kidney disease. Adv Chronic Kidney Dis. 2014;21(3):260-6.

12. Thomas MC, Cooper ME, Zimmet P. Changing epidemiology of type 2 diabetes mellitus and associated chronic kidney disease. Nat Rev Nephrol. 2016;12(2):73-81.

13. Laranjinha I, Matias P, Mateus S, Aguiar F, Pereira P, Perneta Santos M, et al. Diabetic kidney disease: is there a non-albuminuric phenotype in type 2 diabetic patients? Nefrologia. 2016;36(5):503-9.

14. Korbut AI, Klimontov VV, Vinogradov IV, Romanov VV. Risk factors and urinary biomarkers of non-albuminuric and albuminuric chronic kidney disease in patients with type 2 diabetes. World J Diabetes. 2019;10(11):517-33.

15. Yamamoto Y, Hanai K, Mori T, Yokoyama Y, Yoshida N, Murata H, et al. Kidney outcomes and all-cause mortality in people with type 2 diabetes exhibiting non-albuminuric kidney insufficiency. Diabetologia. 2022;65(1):234-45.

16. Penno G, Solini A, Orsi E, Bonora E, Fondelli C, Trevisan R, et al. Non-albuminuric renal impairment is a strong predictor of mortality in individuals with type 2 diabetes: the Renal Insufficiency and Cardiovascular Events (RIACE) Italian multicentre study. Diabetologia. 2018;61(11):2277-89.

17. Klimontov VV, Korbut AI. Albuminuric and non-albuminuric patterns of chronic kidney disease in type 2 diabetes. Diabetes Metab Syndr. 2019;13(1):474-9.

18. Qian Y, Feldman E, Pennathur S, Kretzler M, Brosius FC 3rd. From fibrosis to sclerosis: mechanisms of glomerulosclerosis in diabetic nephropathy. Diabetes. 2008;57(6):1439-45.

19. Rana JS, Liu JY, Moffet HH, Jaffe M, Karter AJ. Diabetes and prior coronary heart disease are not necessarily risk equivalent for future coronary heart disease events. J Gen Intern Med. 2016;31(4):387-93.

20. Amod A, Emerson SS, Marso SP, Mcguire DK, Pieber TR, Pop-Busui R, et al. Chronic kidney disease (CKD) and risk of mortality, cardiovascular (CV) events, and severe hypoglycemia in type 2 diabetes (T2D)-DEVOTE results. Diabetes. 2018;67(Suppl 1):530-P.

21. Wanner C, Lachin JM, Inzucchi SE, Fitchett D, Mattheus M, George J, et al. Empagliflozin and clinical outcomes in patients with type 2 diabetes mellitus, established cardiovascular disease, and chronic kidney disease. Circulation. 2018;137(2):119-29.

22. Vichova T, Knot J, Ulman J, Maly M, Motovska Z. The impact of stage of chronic kidney disease on the outcomes of diabetics with acute myocardial infarction treated with percutaneous coronary intervention. Int Urol Nephrol. 2016;48(7):1137-43.

23. Marx N, Federici M, Schütt K, Müller-Wieland D, Ajjan RA, Antunes MJ, et al. 2023 ESC guidelines for the management of cardiovascular disease in patients with diabetes: developed by the task force on the management of cardiovascular disease in patients with diabetes of the European Society of Cardiology (ESC). Eur Heart J. 2023;44(39):4043-140.

24. American Diabetes Association Professional Practice Committee. 10. Cardiovascular disease and risk management: standards of care in diabetes-2024. Diabetes Care. 2024;47(Suppl 1):S179-218.

25. Emdin CA, Rahimi K, Neal B, Callender T, Perkovic V, Patel A. Blood pressure lowering in type 2 diabetes: a systematic review and meta-analysis. JAMA. 2015;313(6):603-15.

26. Zelniker TA, Wiviott SD, Raz I, Im K, Goodrich EL, Bonaca MP, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet. 2019;393(10166):31-9.

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