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GENDER-ASSOCIATED FEATURES IN DIABETIC KIDNEY DISEASE

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Abstract. Gender-associated features in diabetic kidney disease. Safarova S.S. *Diabetic kidney disease (DKD) is the leading cause of end-stage renal failure. Evidence indicates gender differences in the progression of this disease. This study aimed to determine gender differences in prevalence and identify gender-associated risk factors contributing to the development of diabetic kidney disease in individuals with type 2 diabetes mellitus (T2DM). The cross-sectional study included 132 patients with T2DM ranging in age from 50 to 65 years. Subjects were stratified by sex (80 women and 52 men). Gender differences have been studied in relation to the incidence and prevalence of DKD, their phenotypes and clinical manifestations, and several risk factors that have different effects on both sexes. The outcome of clinical kidney function assessment showed that 70% subjects were diagnosed with DKD (71% of women and 67% of men). The study indicated an association between the duration of T2DM and urinary albumin levels, as well as between arterial hypertension and triglyceride levels, which are independent risk factors for DKD development. Notably, older women with T2DM have a higher prevalence of DKD than older men. The albuminuric component of DKD was more frequently observed in men. Additionally, men were more likely to have adverse risk factors, including dyslipidemia, lower high-density lipoprotein cholesterol, and glomerular filtration rate, which are factors involved in the mechanisms of DKD. In summary, the results indicate that: 1) women with type 2 diabetes mellitus are at a higher risk of developing a normoalbuminuric phenotype of diabetic kidney disease, while men are at a higher risk of developing an albuminuric phenotype of diabetic kidney disease leading to renal failure and end-stage renal disease; 2) gender differences are most noticeable among older adults and may have significant implications for the development of more effective diagnostic and treatment methods for diabetic kidney disease, tailored to individual needs.*

Реферат. Гендерно-асоційовані особливості при діабетичній хворобі нирок. Сафарова С.С. *Діабетична хвороба нирок (ДЗН) є основною причиною термінальної ниркової недостатності. Докази вказують на гендерні відмінності в прогресуванні цього захворювання. Це дослідження мало на меті визначити гендерні відмінності в поширеності та виявити гендерно-асоційовані фактори ризику, що сприяють розвитку діабетичної хвороби нирок в осіб із цукровим діабетом 2 типу (ЦД 2 типу). Перехресне дослідження включало 132 пацієнтів з ЦД2 віком від 50 до 65 років. Суб'єкти були стратифіковані за статтю (80 жінок і 52 чоловіки). Гендерні відмінності були вивчені щодо захворюваності та поширеності ДЗН, їх фенотипів і клінічних проявів, а також кількох факторів ризику, які мають різний вплив на обидві статі. Результати клінічної оцінки функції нирок показали, що в 70% суб'єктів діагностовано ДЗН (71% жінок і 67% чоловіків). Дослідження показало зв'язок між тривалістю ЦД 2 типу та рівнем альбуміну в сечі, а також між артеріальною гіпертензією та рівнем тригліцеридів, які є незалежними факторами ризику розвитку ДЗН. Примітно, що літні жінки з ЦД 2 типу мають більшу поширеність ДЗН, ніж літні чоловіки. Альбуміновий компонент ДЗН частіше спостерігався в чоловіків. Крім того, чоловіки частіше мали несприятливі фактори ризику, включаючи дисліпідемію, низький рівень холестерину ліпопротеїнів високої щільності та швидкість клубочкової фільтрації, які є факторами, залученими в механізми ДЗН. У підсумку результати показують, що: 1) жінки з цукровим діабетом 2 типу мають вищий ризик розвитку нормоальбумінуричного фенотипу діабетичної хвороби нирок, тоді як чоловіки мають вищий ризик розвитку альбумінуричного фенотипу діабетичної хвороби нирок, що призводить до ниркової недостатності та термінальної стадії ниркової недостатності; 2) гендерні відмінності найбільш помітні серед людей похилого віку та можуть мати велике значення для розробки більш ефективних методів діагностики та лікування діабетичного захворювання нирок, адаптованих до індивідуальних потреб.*

The prevalence of diabetic kidney disease (DKD) in patients with type 2 diabetes mellitus (T2DM) is approximately twice as high as in patients without diabetes, despite universal or targeted screening and

new medications [1]. DKD presents with albuminuria and also reduces renal filtration function, and is ultimately characterized by a progressive decline in estimated glomerular filtration rate (eGFR) toward end-stage renal disease (ESRD) [2]. In addition to the classic albuminuria phenotype, two new albuminuria-independent phenotypes have emerged: a) "normoalbuminuric chronic kidney disease"; b) "progressive renal decline", which suggests that progression from DKD to ESRD may occur through two different pathways –albuminuric and non-albuminuric [3]. The absence of gender-specific data in previous studies has resulted in the assumption that the connection between risk factors and DKD outcomes is identical for both men and women. Nevertheless, in recent years, an increasing amount of data has surfaced, confirming the presence of clinically significant gender disparities in the associations between specific risk factors for the onset of DKD in T2DM [4].

Gender differences in the association between risk factors and diabetes may not only be important for the early diagnosis of DKD, but may also influence the selection of appropriate treatment that will significantly improve kidney function and reduce the risk of death [5].

Aim – to determine gender differences in prevalence and identify gender-associated risk factors contributing to the development of diabetic kidney disease in individuals with type 2 diabetes mellitus.

MATERIALS AND METHODS OF RESEARCH

Research Subjects

This cross-sectional study included 132 patients with T2DM, comprising 80 (61%) women and 52 (39%) men, aged between 45 and 65 years. The study was conducted at the Clinical Centre of the Medical University between 2020 and 2021.

Inclusion and exclusion criteria

According to the following inclusion and exclusion criteria outlined below, were determined participants of the research study were determined: patients aged 50-65 years with T2DM who were using oral hypoglycemic drugs (Metformin) or insulin therapy. Exclusion criteria: dialysis treatment for more than 1 month, polycystic kidney disease, organ or bone marrow transplantation, use of immunosuppressive drugs for kidney disease within the last 6 months, chemotherapy for 2 years, significant cardiovascular conditions, and liver cirrhosis.

Measuring Methods

All patients enrolled were assessed for general characteristics including gender, age, height, weight, body mass index (BMI), renal ultrasound and blood pressure measurement. Hypertension was diagnosed as average systolic/diastolic blood pressure ≥ 140/90 mmHg, or use of antihypertensive medication (angiotensin-converting enzyme inhibitors and beta-blockers). Among women, menopause status was accorded to the World Health Organization's definition of menopause [6]. Laboratory tests were performed to measure their serum lipid profile, total cholesterol (TC), high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), triglycerides (TG), creatinine, blood sugar awareness, glycated hemoglobin (HbA1c), insulin measured using electrochemiluminescence assay (Roche Diagnostics). The estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI formula [1, 5] and calculated Homeostasis model assessment index of insulin resistance index (HOMA-IR).

Ethical approval

The study protocol was approved by the Biomedical Ethics Committee of Azerbaijan Medical University (extract from the minutes of the meeting No. 02/14 dated 10/14/2018), and informed consent was obtained from all subjects. The study was conducted in accordance with the Declaration of Helsinki of the World Medical Association (World Medical Association Declaration of Helsinki).

Data analysis

The data were analyzed using IBM SPSS Statistics software for Windows (version 23, Chicago, IL, USA). Data were summarized using mean (M)± standard deviation (SD); analysis was performed using the Mann-Whitney U test; the relationship between various characteristics in the study sample was determined using the Spearman correlation coefficient (r); statistical significance was accepted at $p<0.05$ [6].

RESULTS AND DISCUSSION

The outcome of the clinical assessment of kidney function revealed that 92 (70%) patients had DKD, with 57 (71%) out of 80 women and 35 (67%) out of 52 men being affected. The characteristics of all 132 patients are detailed in Table.

End-stage renal failure, as per the MDRD equation (http://www.mdrd.com/), with an eGFR below 30 ml/min/1.73 m^2 was detected in 13 patients (10%). An increase in serum creatinine concentration was observed in 16 patients (12%) (6 women and 11 men). Among the patients, 59 (73.8%) women and 20 (38.5%) men did not exhibit albuminuria. Compared with patients with albuminuria but without renal failure, patients with nonalbuminuric renal failure were notably older, with the majority being women. The prevalence of microalbuminuria was higher in men with T2DM compared to women ($p<0.001$). Therefore, male gender is an independent risk factor for developing the albuminuric phenotype of DKD. A decrease in eGFR <60 ml/min and/or micro/macroalbuminuria was present in 67.3% of men with T2DM (38.4% isolated micro/macroalbuminuria,

5.8% isolated low eGFR, 23.1% both) and 43.5% of women with T2DM (16.4% micro/macroalbuminuria, 15.3% isolated low eGFR, 11.8% both). In women, low estradiol was directly associated with change in GFR (r=0.481, p=0.02). It was found that the longer duration of diabetes (r=0.243, p=0.01 in men vs. r=0.409, p=0.03 in women, respectively) and the younger age (r=0.297, p=0.04 in men vs. r=0.344, p=0.05 in women, respectively) are strongly associated with microalbuminuria. High triglyceride levels (r=0.277, p=0.01 in men vs. r=0.351, p=0.04 in women, respectively) and systolic blood pressure (r=0.378, p=0.04 in men vs. r=0.446, p=0.02 in women, respectively) were correlated with high BMI levels. Correlation analysis revealed statistically significant relationships between the amount of albuminuria and the levels of triglycerides and glucose in the venous blood in a subgroup of men. In women, a relationship was found between eGFR and systolic blood pressure and BMI (r=0.563, p=0,042). When evaluating correlations, it was discovered that age, blood pressure, duration of diabetes, fasting plasma glucose concentration, and HbA1c values were associated with the incidence of DKD in patients with T2DM.

Characteristics of the sample of patients with type 2 diabetes mellitus, (M ± SD)

Characteristic	Women n=80	Men n=52	p
Age (years)	55.3±2.6	54.1±3.8	ns
BMI (kg/m2)	31.2±2.4	29.7±3.3	<0.05
Duration of DM (years)	8.3±4.6	9.6±2.4	<0.01
HbA1c, (%)	7.3±1.5	7.6±2.8	<0.05
Glucose, mg/dL	154.9±45.1	187.5±58.3	<0.005
Insulin, ME/l	9.4±8.6	3.7±1.5	<0.005
HOMA-IR	4.2±2.2	2.7±1.8	<0.01
Hypertension, (%)	23 (27.1)	20 (38.6)	ns
Heart Disease, (%)	13 (15.3)	10 (19.2)	ns
Oral Treatment only, (%)	39 (48.8)	18 (34.6)	<0.001
Insulin Treatment only, (%)	16 (20)	12 (23.1)	<0.05
Oral and Insulin treatment, (%)	25 (31.2)	22 (42.3)	<0.05
Total cholesterol, mmol/L	5.8±0.9	6.2±1.1	ns
Triglycerides, mmol/L	1.76±0.3	2.18±0.7	<0.01
HDL, mg/dL	53.32±23.7	51.70±90.6	ns
LDL, mg/dL	138.32±23.7	141.70±90.6	<0.05
Microalbuminuria, mg/L	185±12.4	268±19.5	<0.001
eGFR (ml/min/1.73 m^2)	73.1±9.3	61.5±7.6	<0.005

A comprehensive assessment of the condition of patients with T2DM revealed that the prevalence of DKD in elderly women is higher than in elderly men. This is likely due to women living longer than men, with age and postmenopausal status modifying the association between sex and DKD [8]. Men were more likely to have an albuminuric component of DKD compared to women. Additionally, men were more likely to have adverse risk factors, such as dyslipidemia, lower HDL cholesterol, and lower eGFR, which are identified as factors involved in the mechanisms of DKD. This suggests that male gender is an independent risk factor for end-stage renal disease [9]. According to the findings, women with

T2DM are at a higher risk of developing a normoalbuminuric phenotype of DKD, while men are at greater risk of developing an albuminuric phenotype of DKD leading to renal failure and end-stage renal failure, especially in old age. These data indicate that male sex significantly influences the progression of renal dysfunction, while younger premenopausal women are at a lower risk of developing DKD, likely due to the protective role of estrogens against renal failure [10]. In postmenopausal women, DKD was associated with a decrease in eGFR, which is evidently linked to oxidative stress and damage to the glomeruli and tubules. It has been suggested that postmenopausal estrogen deficiency may contribute to the progression of glomerulosclerosis, thereby exacerbating the harmful effects on the kidneys [11].

Of all the risk factors analyzed in our study, the strongest association was found between the duration of diabetes and DKD in both sexes. In addition to the significant influence of T2DM, the risk of developing ESRD is associated with obesity, which is an independent predictor of DKD in individuals with type 2 diabetes [12]. Women have been found to have higher BMI and obesity compared to men of the same age, which may also contribute to gender differences in the development of DKD. Obesity causes a state of hyperfiltration, which, if maintained over time, can lead to a decrease in eGFR, as seen in diabetic nephropathy. Notably, overweight and obese women are at a higher risk of developing hypertension compared to overweight and obese men. Research indicates that the prevalence of hypertension increases over the age of 60 and in women after menopause [13]. Decrease in estradiol levels after menopause is associated with changes in the lipid profile and the accumulation of abdominal fat. Therefore, changes in estradiol levels may lead to disturbances in metabolism and adipocyte physiology, contributing to obesity. Higher body weight is associated with an increased risk of developing hypertension, which is linked to increased sympathetic activity, increased angiotensin-converting enzyme 2 production and renin release, resulting in adrenal aldosterone production and subsequent sodium retention [6]. Men, in particular have been reported to have higher renin activity than women, regardless of age and ethnicity. Increased visceral fat is associated with increased inflammatory mediators, increased oxidative stress, and decreased endothelial vasodilation. These pathophysiological changes lead to disruptions of the mechanisms of pressure natriuresis, glomerular hypertension, endothelial dysfunction, vasoconstriction, and matrix proliferation [14].

The prevalence of DKD in T2DM is high worldwide, and to reduce it, it is necessary to identify potential risk factors for the development of DM and its complications [15]. Age, BMI, arterial hypertension, triglyceride concentration, urinary protein concentration, plasma albumin concentration, and duration of diabetes mellitus in patients with DKD were identified as potential risk factors in the present study. The prevalence of DKD in T2DM was found to be higher in older patients. The study showed an association between the duration of diabetes mellitus and urinary albumin levels, as well as arterial hypertension and triglyceride levels, which are independent risk factors for the development of DKD in T2DM [16].

Thus, screening of renal function and related clinical and laboratory parameters in patients with T2DM should be carried out in the early stages to prevent further deterioration of renal function and progression to end-stage renal disease [17]. Although the role of biological gender is not yet fully understood, the data from this clinical study demonstrate the importance of understanding the gender effect and the mechanisms underlying DKD in T2DM that require further study [18].

CONCLUSION

1. Women with type 2 diabetes mellitus are at a higher risk of developing a normoalbuminuric phenotype of diabetic kidney disease, while men are at a higher risk of developing an albuminuric phenotype of diabetic kidney disease leading to renal failure and end-stage renal disease.
2. Gender differences are most noticeable among older adults and may have significant implications for the development of more effective diagnostic and treatment methods for diabetic kidney disease, tailored to individual needs.

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