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RISK FACTORS FOR CARDIOVASCULAR AND RENAL DISEASE IN TYPE 2 DIABETES MELLITUS IN PATIENTS WITH NORMAL AND MILDLY REDUCED GLOMERULAR FILTRATION RATE

Marcel Stoiță[1], Amorin Remus Popa[1,2]
[1]Faculty of Medicine and Pharmacy, University of Oradea, Romania
[2]Clinical County Emergency Hospital of Oradea, Romania
Corresponding author: Marcel Stoiță[1]
Email: stoitamarcel2020@gmail.com

Rezumat

În acest studiu sunt investigați factorii de risc cardiovascular care, așa cum se arată în literatură, reprezintă și factori de risc pentru modificarea precoce a funcției glomerulare la pacienții cu diabet zaharat de tip 2. Pacienții au fost împărțiți în funcție de rata lor de filtrare glomerulară în 2 grupuri, un grup de pacienți cu RFG ≥90 mL/min/1,73 m^2 (118 pacienți) și celălalt cu GFR între 60-89 mL/min 1,73 m^2 (126 pacienți). Vârsta înaintată, hipertensiunea arterială, controlul glicemic slab, IMC-ul crescut, LDL-colesterolul ridicat, nivelul ridicat de trigliceridelor, rezistența crescută la insulină și nivelul ridicat de apolipoproteină-B au avut o prevalență semnificativ mai mare la pacienții cu diabet zaharat de tip 2 cu funcție renală ușor redusă. Chiar și pacienții cu RFG ușor redusă (fără boală renală diabetică confirmată) au o agregare importantă de factori de risc cardiovascular și identificarea lor timpurie este importantă pentru controlul acestora, pentru a preveni în continuare declinul glomerular.

***Cuvinte cheie**: diabet zaharat tip 2, factori de risc pentru boala renală, factori de risc cardiovascular.*

Abstract

In this study are investigated the cardiovascular risk factors that as shown in literature also represent risk factors for early glomerular function alteration in type 2 diabetes mellitus patients. The patients were divided according to their glomerular filtration rate in 2 groups, one group of patients with GFR ≥90 mL/min/1.73 m^2 (118 patients) and the other with GFR between 60-89 mL/min/1.73 m^2 (126 patients). Older age, hypertension, poor glycemic control, increased BMI, high LDL-cholesterol, high triglyceride level, insulin resistance and high level of apolipoprotein-B appeared to be more prevalent in patients with type 2 diabetes mellitus with mildly reduced kidney function. Even patients with mildly reduced GFR (without confirmed diabetic kidney disease) have an important aggregation of cardiovascular risk factors and their early identification is important for controlling them in order to further prevent glomerular decline.

***Keywords:** diabetes mellites type 2, kidney disease risk factors, cardiovascular risk factors, dyslipidemia.*

Introduction

Diabetic kidney disease represents the impaired renal function as a direct consequence of diabetes mellitus presence[1]. Although there are multiple definitions of this disease according to numerous associations, diabetic kidney disease is generally defined as progressive impairment of renal function in a patient with diabetes mellitus type 1 or 2 reflected by increased glomerular albumin excretion, decreased glomerular filtration rate, increased prevalence of hypertension and the occurrence over time of many cardiovascular complications[2]. Diabetic kidney disease is a major cause of morbidity and mortality in patients with diabetes mellitus despite numerous advances in its treatment. In developed countries, diabetic kidney disease is the leading cause of end-stage chronic kidney disease[1]. In patients with type 1 diabetes mellitus, diabetic kidney disease generally appears after about 10 years of diabetes, while in patients with type 2 diabetes mellitus, diabetic kidney disease can already be identified in 3% of patients at the time of diagnosis[1,3].

The importance of the permanent study of diabetic kidney disease lies in its very high prevalence of over 40% in patients with diabetes mellitus in the United States and the enormous costs it generates on health systems, it is estimated that in the United States the costs for patients with diabetic kidney disease were $ 25 billion in 2011[1].

Diabetic kidney disease is an ongoing challenge for researchers in diabetes and kidney disease. If only recently it was considered that albuminuria is absolutely necessary for the diagnosis of diabetic kidney disease, today there are more and more data that there are 2 phenotypes, one albuminuric, characterized by increased urinary excretion of albumin, and one non-albuminuric, characterized by decreased filtration glomerular filtration rate[4]. Also, in a patient with diabetes there may be certain pathologies that produce chronic kidney disease independently of diabetes[2].

The purpose of our study was to investigate the factors that influence glomerular filtration rate in type 2 diabetes mellitus patients with mildly reduced glomerular filtration rate.

Material and methods

In this study our purpose was to investigate the clinical-biochemical characteristics of patients with type 2 diabetes with a slightly low glomerular filtration rate and, respectively, a normal glomerular filtration rate. Thus, the patients were investigated based on the presence of cardiovascular risk factors, factors that are known to play a particularly important role in the decline of glomerular function in

patients with type 2 diabetes. In addition to the traditional risk factors for declining glomerular function, were explored the correlations between apolipoprotein B and insulin resistance and glomerular filtrate rate.

The study was performed between March 15, 2019 - July 1, 2019, including patients with type 2 diabetes from the Internal Medicine Clinic II - Diabetes of the Oradea County Emergency Hospital. Patients were evaluated during the day hospitalization. Since the aim of the study was to assess the risk factors associated with a slight decrease in glomerular filtration rate, in the study the patients were divided into 2 groups, a group of patients with type 2 diabetes and GFR <90 mL/min/1.73 m^2 but GFR ≥60 mL/min/1.73 m^2 which represented the group of patients with slightly low glomerular filtration rate and a control group consisting of patients with type 2 diabetes mellitus and GFR ≥90 mL/min/1.73m^2 representing patients with normal glomerular filtration rate. Because the prevalence of normal renal function is less commonly found in patients with type 2 diabetes mellitus, in the first group was included every second patient with type 2 diabetes evaluated in the time above specified who had a slightly lower glomerular filtration rate and the in second group was included each patient with type 2 diabetes and normal glomerular filtration rate. Other inclusion criteria were: patients aged 18 to 75 years, patients who signed informed consent for inclusion in the study.

Exclusion criteria were as follows: patients with moderate to severely low or severely low filtration rate, patients with GFR <60 mL/min/1.73 m^2, known patients with chronic renal disease such as: chronic glomerulonephritis or chronic pyelonephritis, patients with fasting blood glucose ≥300 mg/dL that could have led to dehydration and false low GFR, patients with modified urine examination including leukocyturia, microscopic or macroscopic hematuria, patients with neoplastic disease, patients with liver cirrhosis, patients with endocrine disease severe such as myxedema, Cushing's disease, patients with senile dementia.

The glomerular filtration rate was expressed in mL/min/1.73 m^2 and calculated using the CKD-EPI formula. GFR was considered slightly low between 60-89 mL/min/1.73 m^2 and the normal GFR ≥90 mL/min/1.73 m^2. We did not use the term chronic kidney disease as it could not be demonstrated that in the reference group the GFR values are chronically low, at least 2 determinations within 6 months. In each of the 2 categories, with a slightly low and normal glomerular filtration rate, it was desired to include a number of 150 patients, but after applying the inclusion and exclusion criteria in the group of patients with low glomerular filtration rate, 118 patients remained and in the group with normal filtration rate 126 patients.

Statistical analysis has been done with the help of Medcalc software, t-test has been used for comparison of mean values, while Chi-squared test has been used for comparing frequency. A value of $p<0.05$

Results and discussion

The results of the study are presented in table 1 and table 2. The study demonstrates that the lipid profile has a major influence on the glomerular filtration rate. Dyslipidemia is considered a risk factor for chronic kidney disease. Literature data shows that patients with type 2 diabetes mellitus with normal glomerular function at the beginning of the follow-up period and elevated total cholesterol had a statistically significantly higher

progression to chronic kidney disease compared to patients with normal total cholesterol[5].

Elevated LDL-cholesterol levels and elevated triglyceride levels have been confirmed as risk factors for albuminuria in patients with type 2 diabetes in large trials such as DCCT or EDIC[6]. Hypertriglyceridemia and elevated triglyceride/HDL-cholesterol were associated with higher creatinine and albuminuria levels in a study that included over 10,000 patients[7]. The presence of diabetes-specific dyslipidemia with high total cholesterol, high levels of small and dense LDL-cholesterol particles, hypertriglyceridemia and low HDL-cholesterol is a cause of atherosclerosis in the renal microcirculation, but also increased lipids at the glomerular level leads to the appearance of increased inflammation and fibrosis at the glomerular level[8].

The renal structures affected by lipid accumulation are mesangial cells and glomerular podocytes due to inflammation and excess production of the extracellular matrix which will lead to glomerulosclerosis[9]. Target values defined by the American Diabetes Association for lipid parameters are LDL-cholesterol <100 mg/dL, triglycerides <150 mg/dL, HDL-cholesterol <40 mg/dL for men and <50 mg/dL for women[10]. Therefore, screening for dyslipidemia is mandatory for every patient with type 2 diabetes and should be included in the periodic evaluation of each patient[11]. Apolipoprotein-B is an indicator of the total number of circulating atherogenic particles so apolipoprotein-B correlates with the intensity of cardiovascular risk[12]. In this study I determined the total value of apolipoprotein B; it is known that apolipoprotein B circulates in 2 isoforms apolipoprotein B-48 and apolipoprotein B-100.

Previous research has shown that high levels of apolipoprotein B-48 are associated with lower glomerular filtration rate and elevated proteinuria[13]. High levels of apolipoprotein B-100 correspond to elevated triglyceride-rich lipoproteins[14], indeed this was confirmed in the study we conducted and it is known that hypertriglyceridemia negatively affects the local glomerular environment with the secretion of a significant amounts of cytokines in response to lipid loading[15]. Apolipoprotein-B proved to be in the study we performed a strong determinant of the glomerular filtration rate, the high values of apolipoprotein-B corresponding to the low values of the glomerular filtration rate even after adjusting according to multiple cofactors.

In this study hypertension, poor glycemic control and body mass index were confirmed as risk factors for a slight decrease in glomerular filtration rate. These factors are traditional factors and their control is extremely important but there are new risk

Parameter	GFR 60-90 mL/min/1.73m^2 (n =118)	Standard deviation	GFR>90mL/ min/1.73m^2 (n =126)	Standard deviation	p-value
Age (years)	62.48	8.07	56.26	7.92	<0.01
Sex (% men)	66.94%	-	63.49%	-	0.58
GFR (mL/min/1.73 m^2)	77.75	8.5	98.61	5.87	<0.01
Creatinine (mg/dL)	0.95	0.16	0.76	0.14	<0.01
SBP (mmHg)	137.84	15.19	128.93	14.47	<0.01
DBP (mmHg)	76.07	9.48	73.82	8.66	0.06
Hypertension (%)	74.07	-	56.89	-	<0.01
BMI (kg/m^2)	32.17	5.8	30.98	4.99	0.04
HbA1C (%)	7.53	1.34	7.01	1.28	<0.01
Total cholesterol (mg/dL)	197.32	36.87	174.02	34.11	<0.01
LDL-cholesterol (mg/dL)	113.94	29.56	99.79	25.53	<0.01
Triglycerides	192.45	(132.5, 229.75)	155.62	(96.25,192)	<0.01
HDL-cholesterol	43.32	13.08	47.07	13.1	0.03
TRIG/HDL-cholesterol	5.15	3.42	3.83	2.46	<0.01
Apolipoprotein-B	88.96	19.64	81.92	19.4	<0.01
HOMA-IR	3.8	1.97	3.12	2.2	<0.01

Table 1. *Clinical-biochemical characteristics of patients in the 2 groups*

factors whose control is more difficult to achieve. Data from the literature show that despite all the findings in recent years, glycemic control, HbA1c <7%, weight control and blood pressure are rarely obtained in medical practice (16). In the first study we performed, we proved that elevated levels of apolipoprotein-B and HOMA-IR have an increased influence on the glomerular filtration rate.

Conclusion

1. The mean systolic blood pressure was statistically higher in diabetes mellitus patients with a low glomerular filtration rate compared to those with a normal glomerular filtration rate.
2. The mean diastolic blood pressure was non-statistically significantly higher in those with low glomerular filtration rate compared to those with normal glomerular filtration rate.
3. The body mass index had statistically significantly higher values in patients with low glomerular filtration rate compared to those with normal glomerular filtration rate.
4. The mean value of HbA1c was statistically significantly higher in patients with low glomerular filtration rate.
5. The mean serum cholesterol was statistically significantly higher in patients with low glomerular filtration rate compared with those with normal glomerular filtration rate, the mean serum LDL-cholesterol was statistically significantly higher in patients with dilation rate lower glomerular filtration rate compared to those with normal glomerular filtration rate, the mean triglyceride value was statistically significantly higher in patients with glomerular filtration rate and the mean HDL-cholesterol value was significantly lower in patients with low glomerular filtration rate.
6. Apolipoprotein-B had statistically significantly higher values in patients with low glomerular filtration rate compared to patients with normal filtration rate.
7. HOMA-IR, the insulin resistance index, had statistically significantly higher values in patients with a low glomerular filtration rate compared to patients with a normal glomerular filtration rate.
8. The prevalence of cardiovascular risk factors was significantly higher in patients with low rates: poor glycemic control, elevated systolic blood pressure, hypercholesterolemia, hypertriglyceridemia, elevated apolipoprotein-B levels and insulin resistance.

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Parameter	GFR 60-90 mL/min/1.73m^2 (n =118)	GFR >90 mL/min/1.73m^2 (n =126)	p-value
Poor glycemic control (HbA1c =7%)	58.47% (69)	44.44% (57)	0.04
SBP =140 mmHg	44.91% (53)	20.63% (26)	<0.01
DBP =90 mmHg	16.10% (19)	8.73% (11)	0.13
Cholesterol =200 mg/dL	44.06% (52)	22.22% (28)	<0.01
LDL-cholesterol =100 mg/dL	62.71% (74)	42.85% (54)	<0.01
Triglycerides =150 mg/dL	61.86% (73)	40.47% (51)	<0.01
HDL-cholesterol =40 mg/dL for men and =50 mg/dL for women	47.45% (56)	36.50% (46)	0.09
HOMA-IR=2.5	75.42% (89)	46.82% (59)	<0.01
Apolipoprotein B=80 mg/dL	43.22% (51)	27.77% (35)	0.01

Table 2. *Prevalence of cardiovascular risk factors and for alteration of glomerular function in the patients of the 2 groups*

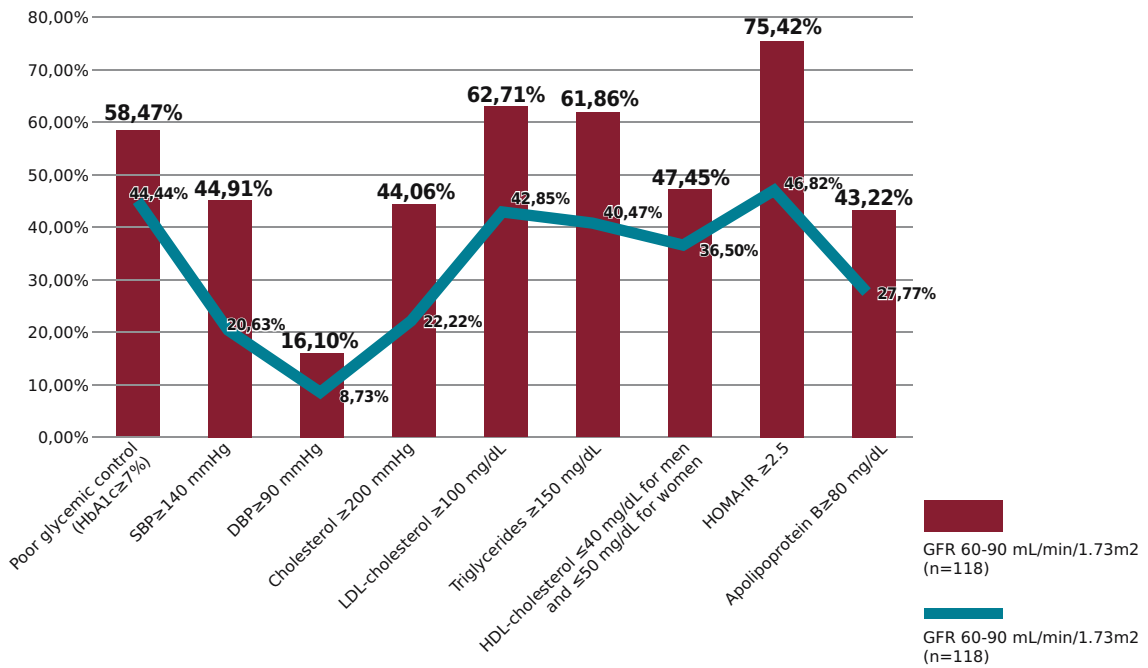

Figure 1. *Prevalence of cardiovascular risk factors in the two groups*

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