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CHARACTERISTICS OF THE LIPID PROFILE IN PATIENTS WITH DIABETES MELLITUS AND CHRONIC KIDNEY DISEASE

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Abstract

Background and aims *Diabetes mellitus (DM) is one of the leading causes of end-stage chronic kidney disease (CKD). Patients with DM and CKD have a 10 or even 20 times higher cardiovascular risk (CVR) than the general population. Lipid metabolism disorders are more frequent in these patients, dyslipidemia being aggravated by the presence of hyperglycemia and insulin resistance. The main purpose of our study was to identify possible correlations between lipid profile parameters and altered renal function in patients with DM. We have also analyzed the correlations between lipid parameters, CKD, quality of glycemic control and CVR.* ***Material and method:*** *The study was performed on 2732 patients with DM which received medical treatment and care at the Center for Diabetes Timisoara, for a 6-month period from March to October 2016, 1508 women (55.2%) and 1224 men (44.8%), mean age 63.7 ± 9.1 (33-78) years and mean diabetes duration 12.4 ± 6.8 (6-33) years. The study group included 312 patients (11.4%) with T1DM and 2420 patients (88.6%) with T2DM.* ***Results:*** *The prevalence of CKD (GFR< 60 ml/min) was 12.5%. The levels of total cholesterol (TC), triglycerides (TG) and LDLc were significantly higher in the case of patients with DM and CKD (p<0.0001).* ***Patients with CKD had twice the prevalence of ischemic heart disease and cerebrovascular disease when compared to patients without CKD. Peripheral artery disease was present in 16.9% of those with CKD and in 11% of those without CKD. Hypertension (HTN) was present in 91.8% of patients with CKD and in 67.1% of patients without CKD (GFR > 60 ml/min).*** ***Conclusion:*** *Analyzed data showed a strong correlation between CKD, dyslipidemia and CVR in patients with DM. Impaired renal function was strongly correlated with age, duration of DM and weight status of these patients.*

key words: *dyslipidemia, diabetic nephropathy, chronic kidney disease, cardiovascular risk.*

Background and aims

Diabetes mellitus (DM) is a complex metabolic disorder, characterized by chronic hyperglycemia that appears as a result of impaired insulin secretion, associated, in various degrees, with insulin resistance (IR). The prevalence of DM is continuously on the rise,

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being an extremely costly disorder from a social-economic standpoint. The global prevalence of DM is estimated to be around 8.5%, almost 415 million people being diagnosed with this disease. It is estimated that their number will reach 642 million in 2040 [1].

Patients with DM have significantly higher mortality and morbidity rates compared to the general population, mainly due to the numerous associated chronic complications [2]. Cardiovascular disease (including ischemic heart disease, cerebrovascular disease and peripheral artery disease) is the most severe macrovascular complication found in patients with DM [3].

More than one third of DM patients develop microangiopathic complications such as retinopathy, nephropathy and neuropathy [4,5]. Metabolic disorders (hyperglycemia, accumulation of advanced glycation end products, oxidative stress), as well as renal vasoactive factors (renin-angiotensin-aldosterone system and other vasoconstrictors) play a very important role in the occurrence of diabetic nephropathy (DN) [6,7]. DN, characterized by high blood pressure, proteinuria and alteration of the renal function, is the major cause for end stage chronic kidney disease (ESCKD) [8-11].

Lipid metabolism disorders (increase of LDLc particles, fasting and postprandial hypertriglyceridemia, decrease of HDLc and increase of Apo-B) are more frequent in patients with DM and CKD, dyslipidemia being aggravated by the presence of hyperglycemia and IR [12-15].

The pathogenesis of dyslipidemia in DM is complex. Insulin mediates the uptake of free fatty acids (FFA) by fatty tissue and skeletal muscle. Thus, IR increases the levels of free FFA released by the liver, determining an increase in the production and concentration of VLDL and the appearance of hypertriglyceridemia. Insulin deficiency and/or IR, present in different degrees in patients with DM contribute to the quantitative and qualitative changes occurring in all lipoprotein (LP) fractions. Hypertriglyceridemia (HTG) is the most frequent pathogenic occurrence. The pathogenetic mechanisms involved in HTG are: the decrease of lipoprotein lipase (LPL) action, which reduces chylomicron and VLDL particles catabolism and lowers the VLDL to LDL conversion rate, the stimulation of adipocyte hormone-sensitive lipase, resulting in an increase in the hepatic influx of FFAs by stimulating the synthesis of VLDL and apo B100, an increase in the activity of cholesteryl ester transfer protein (CETP) which is responsible for the compositional abnormalities encountered in the VLDL particles. Postprandial hyperlipidemia, having both an exogenous and endogenous source, is the result of an imbalance between excessive dietary fat intake (with increased chylomicron generation), on one hand, and increased VLDL synthesis paired with a decrease in LPL activity on the other [16]. The small and dense LDLc particles penetrate the artery wall having a high glycation and oxidation susceptibility which leads to atherosclerosis. IR can also increase the hepatic overproduction of lipoproteins (LP) containing Apo-B, and implicitly lead to the increase of hepatic concentration of VLDLc [17,18].

Dyslipidemia is a frequent complication of CKD, thus contributing to the increase of cardiovascular risk (CVR) in these patients. In patients with ESCKD, LDLc and HDLc particles undergo a series of oxidizing processes that generate low density LP and lead to an increase in the oxidized sub-fraction of LDLc. In the case of nephrotic syndrome (NS) the lipid profile is intensely atherogenic, with an increase of total cholesterol (TC), triglycerides (TG), LDLc and lipoprotein A (LPA), as well as a decrease of HDLc [19,20].

Dyslipidemia alters the endothelium of the glomerular capillaries and the mesangial cells. The mesangial cells express receptors for both oxidized LDL and LDL, whose activation determines the proliferation of mesangial cells, a thickening of the glomerular basal membrane and the expansion of the mesangium through matrix accumulation, increases the production of chemokines (macrophage chemotactic protein 1 – MCP-1), cytokines (IL-6) and growth factors. MCP-1 increases the macrophage recruitment process. Once infiltrated in the renal glomerulus the macrophages become foam cells that release cytokines. Oxidized LDL increases the adhesion of monocytes to glomerular endothelial cells, thus favorizing the infiltration of monocytes and the affection of tubular epithelial cells. Hypercholesterolemia and hypertriglyceridemia are associated with podocite injury, which, secondarily, causes mesangial sclerosis. Oxidized LDL induces the apoptosis of podocytes and nephron loss (a key component of the glomerular filtering barrier), with an increase of albumin diffusion into the podocyte monolayers [21-24].

The main aim of this study was to investigate the correlation between the fractions of the lipidic metabolism and the alteration of the renal function in patients with DM. We have also analyzed the correlations between lipid profile parameters, CKD, glycemic control and the CVR.

Material and method

Study description

This study included 2732 patients with DM which were treated in the Timisoara Center of Diabetes, for a 6-month period from March to October 2016, of which 1508 were women (55.2%) and 1224 were men (44.8%). Mean age was 63.7 ± 9.1 (33-78) years and mean DM duration was 12.4 ± 6.8 (6-33) years. In regard to the types of DM, 312 patients (11.4%) had T1DM and 2420 patients (88.6%) had T2DM.

Studied parameters

The following parameters were evaluated: gender, age (years), weight status: body mass index (BMI) expressed in kg/m^2, abdominal circumference (AC) expressed in cm. We have also collected data related to family history, alcohol consumption, smoking habits and hypertension (HTN).

The quality of the glycemic control was quantified through the value of HbA1c (%).

We have assessed the presences of microvascular, macrovascular and neuropathic complications in all the patients included in the present study. Diabetic retinopathy (DR) was established based on an ophthalmoscopic exam.

The glomerular filtration rate (GFR) was calculated and expressed in ml/min, by using the Modification of Diet in Renal Disease (MDRD) equation. A decrease in GFR < 60 $ml/min/1,73m^2$, sets the diagnosis of CKD, regardless of the urinary albumin.

The lipid profile was calculated by dosing TC (mg/dl), HDLc (mg/dl) and TG (mg/dl) levels. LDLc (mg/dl) was calculated using the Friedewald formula: TC-(TG/5)-HDLc (mg/dl) when TG levels are lower than 400 mg/dl and measured directly in the case of TG values of over 400 mg/dl.

Statistical analysis

Data was collected and analyzed using SPSS v.17 software suite (SPSS Inc. Chicago, IL, USA) and is presented as mean ± standard deviations (for continuous variables with Gaussian distribution), or percentages (categorical variables). Continuous variable distributions were tested for normality using Shapiro-Wilk test and for equality of variances, with Levene's test.

In order to assess the significance of the differences between groups, t-student (means, Gaussian populations), Mann-Whitney U (not-Gaussian populations), and chi-square with Yates correction (proportions) tests were used.

A p value <0.05 was considered the threshold for statistical significance.

Results

Prevalence of CKD among the patients in our study was of 12.5% (342 patients). As related to gender, CKD prevalence was higher in women than in men: 231 women (15.3%) vs. 111 men (9.1%) (Figure 1).

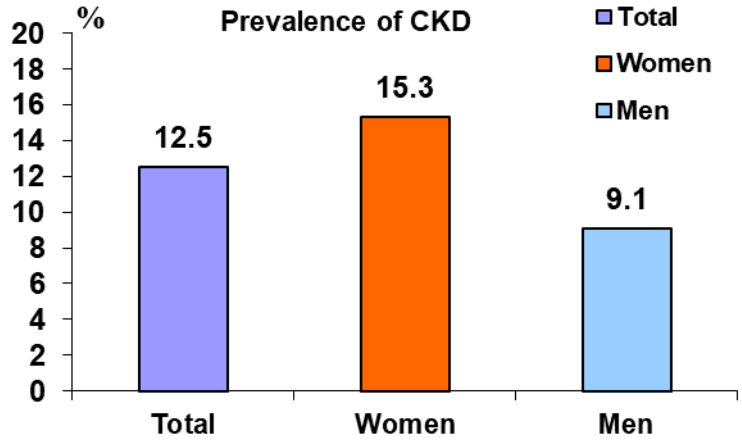

Figure 1. *The prevalence of CKD by gender, at the patients in our study.*

Table 1. The main parameters investigated of the patients included in the study according to gender.

Parameter (Mean value)	Total	Women	Men	p
Age (years)	63.7 ± 9.1	65.8 ± 11.2	61.6 ± 8.7	p< 0.0001
BMI (Kg/m^2)	29.4 ± 5.1	30 ± 5.5	28.7 ± 4.7	p< 0.0001
DM duration (years)	12.4 ± 6.8	13.4 ± 8.1	11.4 ± 6.2	p< 0.0001
HbA1c (%)	8.8 ± 1.8	8.7 ± 1.8	8.9 ± 1.9	p=0.0049
TC (mg/dl)	195.5 ± 51.7	200 ± 51.9	190.9 ± 48.7	p< 0.0001
TG (mg/dl)	187.6 ± 99.8	183.4 ± 97.5	191.3 ± 102.6	p=0.0389
HDLc (mg/dl)	44.3 ± 10.2	46.7 ± 10.8	41.9 ± 9.6	p< 0.0001
LDLc (mg/dl)	114 ± 43.4	117 ± 51.1	111 ±36.8	p=0.0006
Uric Acid (mg/dl)	5.3 ± 1.9	5.1 ± 2.1	5.5 ± 1.8	p< 0.0001
Serum Cr (mg/dl)	1 ± 0.7	0.9 ± 0.6	1.1 ± 0.9	p< 0.0001
GFR (ml/min)	80.7 ± 26.1	74.7 ± 24.5	86.7 ± 27	p< 0.0001

Regarding the prevalence of CKD according to the type of DM, we have found that the prevalence of CKD was two times higher in the case of T2DM, compared to T1DM: 13.4%, respectively 5.8%. This may be explained by the

longer duration of DM in the case of patients with T2DM.

Table 1 shows the main parameters of the patients included in the study, according to gender (Table 1).

Statistically significant differences were observed in the case of all researched parameters, with GFR significantly lower in women (p< 0.0001). Moreover, we have concluded that the mean values of TC and LDLc have been statistically higher in women (Table 1).

To establish the potential correlations between the lipid profile of the patients included in the study and presence of CKD, we have made a comparison between the main parameters, on value intervals for the GFR (Table 2).

Table 2. Comparison between the main parameters of the research, by GFR value (ml/min).

GFR group (ml/min)	< 30	30-60	60-90	> 90	p (ANOVA)
No (%)	55 (2)	287 (10.5)	1188 (43.5)	1202 (44)	
Age (years)	64.3±10.3	64.4±10.8	63.8±9.1	62.3±8.9	p<0.0001
BMI (Kg/m^2)	31.7±7.6	29.5±5.1	28.9±4.8	27.8±4.2	p<0.0001
DM duration (years)	14.6±8.1	13.2±7.6	11.5±5.7	11.9±5.9	p<0.0001
HbA1c (%)	9.1±±2.1	8.5±1.4	8.8±1.6	8.8±1.8	p=0.0168
TC (mg/dl)	216.1±63.4	202.4±54.8	180.6±43.6	182.9±46.5	p<0.0001
TG (mg/dl)	193.4±103.1	198.5±105.3	180.9±86.8	177.6±83.4	p=0.0027
HDLc (mg/dl)	43.4±9.3	43.8±9.8	44.7±11.1	45.3±11.6	p=0.1312
LDLc (mg/dl)	134±53.6	118.9±48.7	100±32.5	96.8±28.2	p<0.0001
Uric Acid (mg/dl)	5.4±1.9	5.3±1.8	5.2±1.8	5.3±1.7	p=0.4755

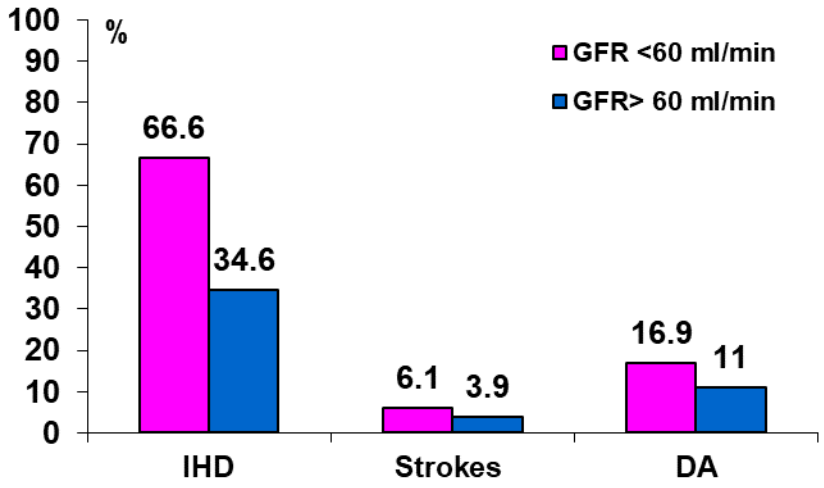

Figure 2. *Presence of macroangiopathic complications, as related to the GFR value (ml/min).*

We have noticed that age, DM duration and the BMI of patients with a GFR value lower than 60 ml/min were significantly higher than those of patients with GFR > 60 ml/min ($p<0.0001$). Moreover, lipid profile parameters: serum TC, serum TG and serum LDLc were significantly higher in the case of diabetic patients with CKD ($p<0.0001$).

In order to assess the CVR, we have investigated the presence of macrovascular complications in the patients included in the study: ischemic heart disease (IHD), strokes, as well as the presence of peripheral artery disease (PAD). These complications have been analyzed according to the the GFR values (Figure 2).

The prevalence of IHD and strokes was almost twice increased in patients with CKD, compared to patients without CKD (Figure 2).

DA was present in 16.9% of patients with CKD and in 11% of those without CKD.

HTN prevalence was of 91.8% in patients with CKD (GFR< 60 ml/min) and of 67.1% in patients without CKD (GFR > 60 ml/min) (Figure 3).

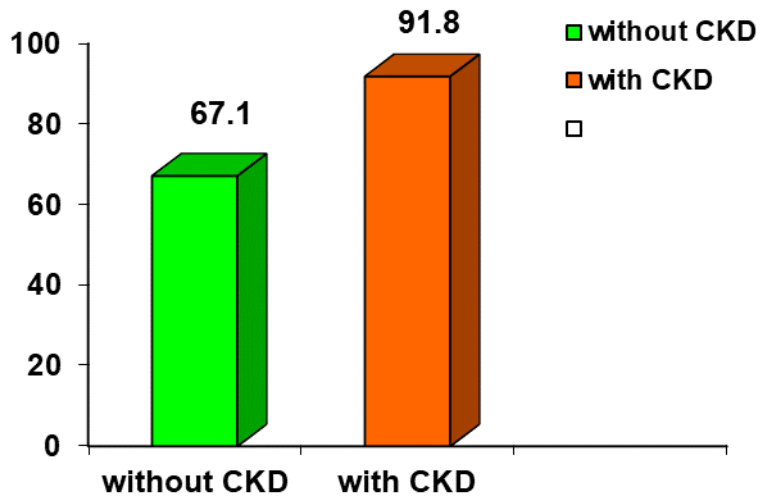

Figure 3. *The prevalence of hypertension in patients included in the study.*

Discussions

DN is the main cause of ESCKD. In the same time, patients with T2DM and CKD have a much higher rate of mortality compared to patients without DN.

Numerous studies have revealed the fact that dyslipidemia is a major risk factor for the appearance of CKD. An observational study that included 1428 patients tracked for a period of time between 5 and 6 years, with a GFR > 70 ml/min, has proven that patients with TC values equal to or higher than 350 mg/dl have had a greater decline of the renal function compared to the patients with TC values lower than 250 mg/dl. This fact has been observed both in patients with DM (RR 2.4, 95%CI 1.1-5.2), as well as in patients without DM (RR 4, 95%CI, 1.3-12.5) [25,26]. More studies that included patients with HTN and an initially normal renal function, have been indicated that systolic blood pressure (SBP) and the mean value of TC are major risk factors in the development of CKD (GFR < 60 ml/min) [27-29].

Ravid et al. have proven in a prospective study on 574 T2DM patients with normal renal function that high TC values have been associated with a significantly higher incidence of microalbuminuria, as well as with major cardiovascular events [30].

Samuelsson et al. have proven that there is a strong correlation between the values of TG and

Apo B on one hand and the progression rate of CKD on the other [31]. Muntner et al. have shown that people with low HDLc values and high TG values have an increased risk of renal function alteration. All the participants in the study (12728 participants in the Atherosclerosis Risk in Communities Study) had initial creatinine levels lower than 2 mg/dl in men and lower than 1.8 mg/dl in women. The results have indicated that the level of plasma TG is an independent risk factor for CKD, a fact that was also confirmed by another prospective study that included 297 patients with T1DM [32].

It appears that the major risk factors for the appearance and progression of DN are the increase in the excretion rate of urinary albumin, male gender, age, presence of DR, as well as the high values of TC and HbA1c [33]. In patients with TG values between 150-199 mg/dl, the RR associated with the appearance of DN was of 3.2 and of 3 in those with TG values equal to or higher than 200 mg/dl [34,35].

Generally, diabetic patients with peritoneal dialysis have a more atherogenic lipid profile, with higher values of small and dense LDLc particles, Apo B, oxidized LDLc, TG, Lp(a) and lower HDLc values. This aspect can be explained by the glucose content of the patient that undergoes peritoneal dialysis, with a higher absorption of glucose through the peritoneal membrane. Numerous studies have shown that the prevalence of dyslipidemia is very frequent in patients with renal transplant. Approximately 80% of those patients have TC values of over 200 mg/dl and 90% have LDLc values higher than 100 mg/dl [36].

In the Early Treatment Diabetic Retinopathy Study (ETDRS), that included 2226 patients with DM (934 patients with T1DM and 1292 patients with T2DM) and diabetic retinopathy, the estimated 5 years incidence of ESCKD requiring dialysis or renal transplant was of 10.2% for patients with T1DM and 9.8% for patients with T2DM [37].

The World Health Organization Multinational Study of Vascular Diseases in Diabetes (WHO MSVDD) also highlighted the fact that the level of serum TG is strongly correlated with the alteration of the renal function in patients with T2DM [38]. A study conducted in China that included patients with T2DM without renal alteration has shown a strong correlation between HDLc levels and the urinary albumin excretion rate [39].

Overall, there are various and extremely different results related to the association of different types of dyslipidemia and the stages of CKD.

Conclusions

An extremely atherogenic diabetic dyslipidemia is strongly correlated with the appearance and progression of DN, as well as with a high CVR.

The prevalence of IHD and strokes was two times higher in the case of patients with CKD. All the parameters of the lipid profile were statistically significant higher in diabetic patients with CKD.

The decline of the renal function is strongly correlated with age, DM duration and the body weight status of these patients.

To prevent alteration of renal function and delay of these severe complications requires a multifactorial and interdisciplinary approach, a sustained and individualized diet and intensive therapies.

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