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ROLE OF DYSLIPIDEMIA IN THE DEVELOPMENT AND PROGRESSION OF DIABETIC NEPHROPATHY

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Abstract

With the aim to study the dynamics and interconnection between nephropathic and dyslipidemic disorders in case of diabetes mellitus type 2, in addition to the assessment of carbohydrate metabolism and glomerular filtration rate blood spectrum of lipids was evaluated in patients with diabetes mellitus type 2 of various severity. It was established, that the progression of diabetes mellitus is associated with the development of diabetic nephropathy, whose morphological substrate is diffuse glomerulosclerosis, and one of the leading etiological factors is dyslipidemia. The degree of reduction in glomerular filtration rate as well as changes of atherogenic dyslipidemia triad indices – hypercholesterolemia, hypertriglyceridemia, hyperlipoproteinemia – progress depending on the severity of diabetes, have mutually aggravating effect related to the number of functioning nephrons and the capacity of renal compensatory adaptation processes.

Keywords: diabetes mellitus, diabetic nephropathy, dyslipidemia.

Introduction

Despite the diversity of etiologic factors causative for chronic kidney disease (CKD), most renopathies, regardless of primary renal disease, have a relatively universal mechanism of progression, whereas morphologic changes in the kidneys under renal failure, eventually, come to prevalence of fibroplastic processes, an expansion of extracellular matrix with the replacement of functioning nephrons by the connective tissue, a limitation of functional ability of the kidneys and loss of nephrons. Thus, the morphological substrate of CKD is glomerulosclerosis, whose development is contributed by the numerous growth factors, cytokines, heat shock proteins, etc. The role of lipid metabolism disturbances (dyslipidemias) in the progression of CKD is undisputable as well [1, 2].

Common features of dyslipidemias, associated with increased levels of cholesterol, triglycerides, low density lipoprotein and low plasma content of high density lipoproteins [3, 4], differ significantly in various categories of patients with CKD depending on the stage of the process [5, 6]. Thereby, nephrotic syndrome is manifested by the increase of total cholesterol (TC) and low density lipoproteins (LDL), hypertriglyceridemia, while the level of high density lipoproteins (HDL) in these patients is mostly normal. The most typical disorder of lipid metabolism in patients with CKD without nephrotic syndrome is the elevation of serum concentration of triglycerides (TG) and reduction of HDL [1, 7, 8].

The issue of a pathogenetic role of dyslipidemias in the development of renal dysfunction is paid a special attention in diabetes type 2, when in addition to glucose toxicity the dysfunction of adipocytes and insulin resistance initiate a cascade of hemodynamic, neurohormonal, immunoinflammatory, pro-coagulating reactions, underlying the atherosclerotic vascular lesions of various locations, intrarenal atherosclerosis in particular [9, 10]. However, current views on the contribution of certain factors to the formation of numerous micro- and macrovascular complications of diabetes are rather fragmented than comprehensive and, therefore, require certain generalization. Predicted enhancement of the number of this cohort of patients, pathogenic multifactorial character of diabetic nephropathy determine the need for a detailed study of the mechanisms of renal disease chronization in diabetes mellitus (DM), search for triggers and markers of failure of renal adaptive processes and their transition into tubulo- and glomerulopathies.

The objective of this research was to study the dynamics and interconnection between nephropathic and dyslipidemic disorders in patients with DM type 2 of various severity.

Materials and Methods

25 patients with DM type 2 (16 women and 9 men – 64% and 36% respectively), aged between 34 and 66 years (mean age – 53,4±1,72 years), and 10 healthy individuals, who constituted the control group, participated in the study.

The verification of the diagnosis and disease severity was based on the acting national and international regulating documents. According to the results of a comprehensive patients' examination moderate severity of DM was identified in 10 (40%) of enrolled patients (mean duration of DM – 6,5±0,93 years), severe form of the disease was observed in 15 (60%) of examined patients (mean duration of DM – 10,6±1,15 years).

At the moment of enrolment into the investigation the majority of DM type 2 patients belonged to the age group 51-60 years (64%); the share of representatives of age groups 31-40 and 61-70 years was significant as well (16% each), moreover in 5 (20%) of the enrolled patients the duration of diabetes was less than 5 years (3,2±0,80 years), in 11 participating individuals diabetes lasted for 6-10 years (7,8±0,42 years), 9 of the participants suffered from diabetes longer than 10 years (13,6±0,87 years).

At the moment of enrolment into the investigation patients' condition was stable and didn't require additional measures, except those provided by the National medical care protocols for patients with diabetes mellitus. All the enrolled patients have been trying to keep to diet recommendations and received hypoglycemic therapy – oral hypoglycemic agents (36% of individuals), combined hypoglycemic therapy (48% of patients), insulin preparations (16% of diabetics).

All the patients underwent standard general clinical and laboratory-instrumental examinations. Glucose blood concentration was determined by glucose oxidase method before and 2 hours after meal (pre- and postprandial glycemia) to assess carbohydrate metabolism. Detection of glycated haemoglobin (HbA_{1C}) was used as an informative criterion of continuous glycemic control. Blood spectrum of lipids was evaluated according to the level of general cholesterol (GC), triglycerides (TG), high density lipoproteins (HDL), low density lipoproteins (LDL). Glomerular filtration rate (GFR) was assessed by endogenous creatinine clearance according to CKD-EPI formula (Chronic Kidney Disease Epidemiology Collaboration, 2009; 2011) [11].

The data obtained were statistically analyzed by means of «Statistica for Windows» software, «Version 8,0». Statistical processing of the obtained data was performed with detection of mean values, standard errors, confidence intervals. Analysis of the normality of quantities distribution in randomized variables was performed with the determination of skewness and kurtosis coefficients using the Shapiro-Wilkie criteria [12, 13]. To estimate the probability of differences in

comparison of the studied groups, Student's coefficient (t) was used in case of normal distribution for the equality of general dispersions of compared variables, and nonparametric Mann-Whitney rank test in the absence of normal statistical distribution [13]. Correlation analysis was performed by determining the nonparametric Spearman rank correlation coefficient (R) [12].

Results and discussion

The analysis of carbohydrate metabolism parameters evidenced a poor compensation of the disease in patients of the examined cohort (table 1): average daily glycemia level was 12,02±0,60 mmol/L (2,3 times higher than the corresponding index in healthy individuals, P<0,001), glycosuria level was 9,34±0,64 g/L, and the relative content of HbA_{1C} was significantly increased in patients with diabetes to 10,30±0,36% (by 2,1 times (P<0,001)).

According to the obtained findings, DM was associated with a significant two-fold reduction of GFR as compared to those in healthy individuals (P<0,001), accompanied by microalbuminuria 42,29±5,63 mg/dL in 56% of patients with diabetes (table 2).

Signs of dyslipidemia in the examined patients were characterized by hypercholesterolemia, hypertriglyceridemia, hyperlipoproteinemia. Thus, in 28% of diabetic patients a significant increase of GC blood level was observed, exceeding the control parameter by 23% (P<0,05) in case of moderate diabetes, by 34% (P<0,01) – in severe DM. Hypertriglyceridemia was found in 96% of enrolled patients (24 diabetics), TG blood content in the examined patients was found to be twice higher than corresponding control index in both – moderate and severe DM (P<0,001). The development of hyperlipoproteinemia in patients with type concerned mainly LDL: increased serum LDL concentration was observed in 18 (72%) patients – in 90% of moderate DM cases (by 1,5 times higher than in controls, P<0,001) and in 60% of cases of severe diabetes (by 1,6 times higher than in controls, P<0,001). However, a significant elevation of HDL concentrations was detected only in severe diabetics (by 34%, P<0,01) and was absent in patients with moderate severity of diabetes. Revealed findings are proved by existing literature data: patients with microalbuminuria usually demonstrate increased blood levels of very low density lipoproteins (VLDL), LDL and TG. The level of HDL in patients with microalbuminuria is known to be lower than in patients with normoalbuminuria. In addition to changes of lipoproteins quantity the decrease of LDL particles diameter is observed as well in patients with diabetic nephropathy as compared to those without nephropathy. All of the above mentioned abnormalities in lipoprotein metabolism are more noticeable in case of increased albuminuria and renal dysfunction. In diabetic patients with nephrotic syndrome the type of dyslipoproteyinemia differs in comparison with that in patients without diabetes [1, 7]. Experimental animal studies have also demonstrated the damaging effect of hyperlipidemia on tubulointerstitium [1, 14], affected in diabetic nephropathy, and known as a predictor of renal dysfunction [1, 14].

The results of correlation analysis of the studied parameters are suggestive of a positive and statistically significant correlation found between GFR and the degree of glycosuria in patients with moderate DM (R=0,54; P<0,05), moreover mentioned correlation was lost in patients with severe form of diabetes. Causing the development of osmotic diuresis, glucosuria consequently influences the intensity of filtration in the kidneys. Therefore, the progression of diabetic nephropathy with the reduction of GFR is accompanied by the decrease of filtration load of the nephrons by glucose (despite high hyperglycemia level), limiting its impact on the tubular reabsorptive ability and the mechanism of tubular-glomerular feedback. Hence, absence of correlation between the intensity of filtration in the kidneys and the level of glycosuria under the severe course of diabetes, obviously evidences the progression of diabetic glomerulosclerosis.

Furthermore, correlation analysis of the studied parameters has revealed strong statistically significant negative correlation between GFR and microalbuminuria level in patients with DM of moderate severity (R=-0,90; P<0,05), which is probably related to the limiting influence of the colloid-osmotic (oncotic) pressure of proteins, that overload glomerular filter under long-term renal hyperperfusion and high filtration pressure, and cause glomerular-tubular imbalance between filtration and the ability to reabsorb a protein with its further excretion with urine. Considering the fact that a reduced strength and reverse direction on the mentioned correlation in patients with severe diabetes (R=0,34; P<0,05), accompanied by the progressive reduction of GFR, is indicative of the toxic effect of excessive entry of a protein on proximal tubule of the nephron with the loss of its reabsorptive ability for a protein, the development of tubulointerstitial inflammation and fibrosis [15] and, probably, may serve an indirect marker of diabetic nephropathy progression.

Moderate statistically significant positive correlation between GFR and GC blood level in patients with moderate DM (R=0,64; P<0,05) enables to suggest that that excessive glomerular filtration load by cholesterol molecules, «overload» of the mesangium by macromolecules causes the development of adaptive response of the functioning nephrons with further compensatory intensification of intraglomerular blood

flow (their hyperperfusion), temporary elevation of glomerular filtration in them. However, afterwards the permeability of glomerular membrane for the complexes of large molecular lipoproteins caused by the loss of its size- and charge-related selectivity, occlusion of the glomerular capillaries by cholesterol deposits, etc. promotes the progression of diabetic glomerulosclerosis, inevitably leading to the inhibition of renal filtration capacity. A reliable medium negative correlation between GFR and GC in patients with severe DM (R=-0,46; P<0,05) serves as it's confirmation.

At the same time, moderate negative correlation (R=-0,39; P<0,05) between GFR and blood level of LDL in patients with moderate DM was absent in case of severe form of the disease, when progressive sclerotic changes in the kidneys are accompanied by considerable restriction of filtration for various micro- and macromolecules from blood plasma. However, a positive medium correlation between GFR and TG level (R=0,46; P<0,05) was found in that case. Probably the latter, similarly to the action of cholesterol, induces compensatory hyperperfusion of the functioning nephrons proportionally to the growing number of the lost ones, worsening, eventually, the degree of glomerulosclerosis.

The identified correlations of the indices of atherogenic dyslipidemia triad and GFR in the examined patients suggest to consider dyslipidemia as a factor of formation of renal dysfunctions in case of DM. Influencing on the progression of renal damage through the development of intrarenal atherosclerosis or through toxic effect of lipids on the nephron structures, dyslipidemia leads to the lesions in the endothelium of glomerular capillaries and tubulointerstitium [1, 7, 14]. Hyperlipidemia stimulates the activation of mesangial cells, that have receptors to LDL, bind and oxidize them, and leads to the stimulation of cell proliferation and an increase of the number of macrophages, extracellular matrix components, to the generation of reactive oxygen species, etc. [16, 17]. Thereby, lipoproteins, deposited in the cell basement membrane, bind negatively charged glycosaminoglycans, increasing membrane permeability for macromolecules. Simultaneously, the production of protective proteoglycans and collagenolytic enzymes regulating the formation of mesangial matrix, is lowered, the phagocytic abilities of mesangiocytes are weakened, the mesangium comes to be «overloaded» by macromolecules [1]. As a result of this process filtered lipoproteins are deposited in the renal tubules and initiate tubulointerstitial processes. In response to the alteration, tubular epithelium improves the expression of adhesion molecules, synthesis of endothelin and other cytokines, promoting inflammation and tubulointerstitial sclerosis [17].

Conclusions

The progression of diabetes mellitus is associated with the development of diabetic nephropathy, whose morphological substrate is diffuse glomerulosclerosis, and one of the leading etiological factors is dyslipidemia. The degree of reduction in glomerular filtration rate as well as changes of atherogenic dyslipidemia triad indices – hypercholesterolemia, hypertriglyceridemia, hyperlipoproteinemia – progress depending on the severity of diabetes, have mutually aggravating effect related to the number of functioning nephrons and the capacity of renal compensatory adaptation processes.

Conflict of Interest

The authors declare that there are no conflicts of interest.

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Table 1: Carbohydrate metabolism indices in the studied groups (X±Sx)

Indices	Group, number of examined patients		
	Healthy individuals, n=10	Patients with DM type 2, n=25	
		moderate severity, n=10	*severe form, n=15*
Fasting glycemia, mmol/L	4,43±0,25	12,55±1,24 p<0,001	11,72±0,60 p<0,001 p_1=1,0
Postprandial glycemia, mmol/L	6,14±0,30	13,65±1,48 p<0,001	11,43±0,69 p<0,001 p_1>0,1
Average daily glycemia, mmol/L	5,29±0,19	12,67±1,21 p<0,001	11,59±0,60 p<0,001 p_1>0,3
HbA_{1C}, %	4,95±0,17	10,12±0,59 p<0,001	10,42±0,47 p<0,001 p_1>0,6

P – statistically significant difference in comparison with healthy individuals;
P_1 – statistically significant difference between the indices of patients with moderate and severe course of DM.

Table 2: Characteristics of the studied indices in patients with DM type 2 (X±Sx)

Indices	Group, number of examined patients		
	Healthy individuals, n=10	Patients with DM type 2, n=25	
		moderate severity, n=10	*severe form, n=15*
Glomerular filtration rate, ml/min./1,73 m^2	125,41±1,22	67,11±9,09 p<0,001	63,13±4,28 p<0,001 p_1>0,6
Blood concentration of general cholesterol, mmol/L	4,44±0,22	5,46±0,35 p<0,05	5,95±0,35 p<0,01 p_1>0,3
Blood concentration of triglycerides, mg/dL	138,19±15,02	285,60±30,73 p<0,001	292,30±19,26 p<0,001 p_1>0,4
Blood concentration of high density lipoproteins, mmol/L	1,27±0,05	1,37±0,06 p>0,1	1,70±0,11 p<0,01 p_1>0,06
Blood concentration of low density lipoproteins, mmol/L	2,04±0,09	3,16±0,15 p<0,001	3,20±0,22 p<0,001 p_1>0,8

P – statistically significant difference in comparison with healthy individuals;
P_1 – statistically significant difference between the indices of patients with moderate and severe course of DM.