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ASSOCIATION ANALYSIS OF DYSLIPIDEMIA AND PROGRESSION OF DIABETIC KIDNEY DISEASE

Bohomazova A. A., Olenovych O. A.

Higher State Educational Establishment of Ukraine
«Bukovinian State Medical University»,
Department of Clinical Immunology, Allergology and Endocrinology,
Chernivtsi

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Summary. It was established, that morphological substrate of diabetic nephropathy 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.

Резюме. Установлено, что морфологическим субстратом диабетической нефропатии является диффузный гломерулосклероз, а одним из ведущих этиологических факторов является дислипидемия. Степень снижения скорости клубочковой фильтрации, а также изменения показателей атерогенной триады дислипидемии – гиперхолестеринемии, гипертриглицеридемии, гиперлипопротеинемии – прогрессируют в зависимости от тяжести диабета, оказывают взаимоотягощающее влияние.

Introduction. The role of lipid metabolism disturbances (dyslipidemias) in the progression of CKD is undisputable [5]. Common features of dyslipidemias, associated with increased levels of cholesterol, triglycerides, low density lipoprotein and low plasma content of high density lipoproteins [2, 10], differ significantly in various categories of patients with CKD depending on the stage of the process. 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 [1, 3]. 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.

Material 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. 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).

All the patients underwent standard general clinical and laboratory-instrumental examinations. Glucose blood concentration was determined by glucose oxidase method

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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) [7].

The data obtained were statistically analyzed by means of «Statistica for Windows» software, «Version 8,0». Correlation analysis was performed by determining the nonparametric Spearman rank correlation coefficient (R) [9].

Results. 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. 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 ($R=-0,90$; $P<0,05$). 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 [4], 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 ($R=0,64$; $P<0,05$) changes to a reliable medium negative correlation between GFR and GC in patients with severe DM ($R=-0,46$; $P<0,05$).

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.

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 [5, 6]. 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. [8]. Thereby, lipoproteins, deposited in the cell basement membrane, bind negatively charged glycosaminoglycans, increasing membrane permeability for macromolecules. Simultaneously, the production of

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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 [5]. 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 [8].

Conclusion. 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.

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