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Euro Nephrology 2019: Pathophysiology of proteinuria in the early period of Alloxan-induced experimental diabetes- Olenovych Olha- Bukovinian State Medical University

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Introduction:
Diabetes mellitus (DM) has been and remains a global problem today resulting in disability, working incapacity and untimely death. Diabetic nephropathy (DN) is one of the most severe complications of DM, which dramatically decreases the quality and duration of life of diabetic patients. This is a clinical diagnosis historically based, primarily, on the detection of proteinuria in diabetic patients, confirming a long existence of kidney damage with already practically irreversible changes.
Until recently proteinuria was considered to be the evidence of the degree of glomerular destruction in case of diabetes. Microalbuminuria was suggested to be associated with stable renal function, but with a high risk of developing macroalbuminuria and renal failure in the future. Meanwhile, macroalbuminuria was considered to be associated with a progressive decrease of glomerular filtration rate, an increase of systemic blood pressure and a high risk of renal failure in early terms.

Instead, recent scientific information has led to a reassessment of the micro/macroalbuminuria meaning in the context of the pathogenesis of diabetic kidney disease (DKD). Thus, microalbuminuria does not always reflect the presence of DKD. Nowadays, it is apparent that the presence of only albuminuria does not give grounds for a precise diagnosis of DKD, especially concerning the degree of renal damage. Moreover, antihypertensive therapy is known to reduce the level of albuminuria. Furthermore, there are partial evidences that a short-term withdrawal of therapy may lead to an increase of albuminuria to its initial level before the beginning of treatment. At the same time, there is a significant number of patients with both types of DM and microalbuminuria spontaneously returning to normoalbuminuria. Despite this fact, microalbuminuria is not considered to be a specific marker for diabetic kidney damage only and is widely used as a predictor of chronic renal disease (CRD) in people without diabetes.
Meanwhile, hyperfiltration is well-known to precede albuminuria markedly in case of DM and to be associated with a high risk of rapid progression of chronic renal failure (CRF).
Considering the multifactoriality of renal impairment mechanisms in case of DM and the importance of their identification at the initial stages of the disease, the objective of this research was to clarify the peculiarities of proteinuria in the early period of experimental diabetes mellitus.

Material and Methods: The experiments were carried out on 20 white non-linear mature male rats. Experimental modeling of DM was performed by the intraperitoneal administration of Alloxan monohydrate to 10 animals in diabetogenic dose of 160 mg/kg after the preceding 12-hour deprivation of food with preserved access to water ad libitum. On 11th day after the administration of diabetogenic substance all the experimental animals were withdrawn from the experiment. With the purpose to study the function kidney state, the animals were loaded with water in the volume of 5% of body weight, placed into individual cages for 2 hours to collect urine samples. Further analysis of urine samples, as well as blood plasma, collected at the moment of decapitation of animals, enabled the evaluation of kidney functional state by the clearance method.

Results: It is known, that the development of hyperperfusion and intraglomerular hypertension in every separate nephron leads to the total hyperfiltration in the whole organ. The analysis of the effect of experimental insulin dependent hyperglycemia on the excretory function of the kidneys has revealed that signs of hyperfiltration, typical for the initial stages of DN, have been observed on 11th day after the induction of alloxane diabetes – glomerular filtration rate (GFR) was found to be almost twice higher than that of the control (by 1,9 times, $P<0,01$).

As a result of hyperfiltration, there was an increase of creatinine excretion – its concentration in the urine of animals with alloxane DM significantly exceeded the corresponding index of intact animals (by 1,7 times, $P<0,001$). At the same time, the plasma creatinine level in animals of this group was higher than that of the control by 24,5% ($P<0,001$), that is probably related to reduction of animals body weight (primarily muscles) as the result of absolute insulin insufficiency induced by Alloxan. Whereas, the calculation of the concentration index of endogenous creatinine confirms the tendency to its excessive urinary excretion in the early period of the experimental DM (creatinine clearance increased by 34,7% ($P<0,05$) in animals of this group).

We find it interesting, that the intensification of glomerular filtration processes and raised filtration load of the nephrons in experimental animals on 11th day of the research was not accompanied by a reliable increase of urine volume, probably due to a significant intensification of relative water reabsorption in the tubular portions of the nephron (by 1,6% in comparison with control ($P<0,05$)).

The protein content in urine of experimental animals on 11th after administration of Alloxan reliably 1,6-folds exceeded the control values ($P<0,001$). The significant augmentation of protein excretion – by 77,1% ($P<0,001$) – was observed as well, including that standardized in 100 µL of glomerular filtrate – by

26,3% (P<0,001). Developing against the background of marked renal hyperfiltration, with the mobilization of all the functioning nephrons at the maximum of the functional renal reserve (due to the induction of water diuresis), the total protein loss, observed in the early period of the experimental DM, resulted mainly from an increase of GFR with raised filtration loading of the nephron and exceeding of «reabsorption threshold».

Thereby, the increase of protein filtration with further overloading phenomenon develops for transport reabsorption systems in proximal tubules accompanied by their intactness at this stage of DM. Depending on the hyperfiltration rate, protein overload, in its turn, promotes further damage of the nephrons.

Conclusions: Thus, glomerular hyperfiltration, revealed in the early period of Alloxan-induced diabetes, is not only a marker, but also a risk factor for progression of renal dysfunctions in case of hyperglycemia. However, the hyperdynamically-hyperperfusing type of renal function on 11th day after the administration of diabetogenic substance results from the mobilization of adaptive, reserve renal mechanisms regulating the adaptation of the kidneys to the systemic and local effects of hyperglycemia. The character and dynamics of disorders of the excretory renal function evidences mainly the functional origin of renal disorders on the 11th day of experimental diabetes in the absence of significant structural changes in the tubular apparatus of the kidneys.

Keywords: Experimental Diabetes, Proteinuria, *Alloxan*.