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PECULIARITIES OF EXCRETORY RENAL FUNCTION IN THE EARLY PERIOD OF ALLOXAN-INDUCED EXPERIMENTAL DIABETES

T. M. Boychuk[1], O. A. Olenovych[1], A. I. Gozhenko[2]

[1]Higher State Educational Establishment of Ukraine «Bukovinian State Medical University», Chernivtsi, Ukraine
[2]State Enterprise «Ukrainian Scientific Research Institute of Transport Medicine of Ministry of Health of Ukraine», Odesa, Ukraine
Address for correspondence: olenovych.olga@bsmu.edu.ua.

Summary. Boychuk T. M., Olenovych O. A., Gozhenko A. I. **PECULIARITIES OF EXCRETORY RENAL FUNCTION IN THE EARLY PERIOD OF ALLOXAN-INDUCED EXPERIMENTAL DIABETES.** The article presents data concerning the peculiarities of excretory renal function on 11th day after the administration of diabetogenic dose of alloxan (160 mg/kg) to white non-linear matured male rats. It is established, that 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.
Key words: experimental diabetes mellitus, alloxan, diabetic nephropathy, excretory renal function.

Реферат. Бойчук Т. М., Оленович О. А., Гоженко А. І. **ОСОБЕННОСТИ ЭКСКРЕТОРНОЙ ФУНКЦИИ ПОЧЕК В РАННИЙ ПЕРИОД АЛЛОКСАН-ИНДУЦИРОВАННОГО ЭКСПЕРИМЕНТАЛЬНОГО ДИАБЕТА.** В статье представлены данные относительно особенностей экскреторной функции почек на 11-е сутки после введения нелинейным половозрелым самцам белых крыс диабетогенной дозы аллоксана (160 мг/кг). Установлено, что гипердинамичекси-гиперперфузионный тип функционирования почек на 11-е сутки с момента введения диабетогенного вещества является следствием мобилизации адаптационных, резервных почечных механизмов, которые регулируют приспособление почек к системному и локальному влиянию гипергликемии. Характер и динамика развития нарушений экскреторной деятельности почек свидетельствуют о преимущественно функциональном происхождении ренальных нарушений на 11-е сутки экспериментального диабета в отсутствие значимых структурных изменений канальцевого аппарата почек.
Ключевые слова: экспериментальный сахарный диабет, аллоксан, диабетическая нефропатия, экскреторная функция почек.

Реферат. Бойчук Т. М., Оленович О. А., Гоженко А. І. **ОСОБЛИВОСТІ ЕКСКРЕТОРНОЇ ФУНКЦІЇ НИРОК У РАННІЙ ПЕРІОД АЛОКСАН-ІНДУКОВАНОГО ЕКСПЕРИМЕНТАЛЬНОГО ДІАБЕТУ.** У статті наведені дані щодо особливостей екскреторної функції нирок на 11-у добу після введення нелінійним статевозрілим самцям білих щурів діабетогенної дози алоксану (160 мг/кг). Встановлено, що гіпердинамічно-гіперперфузійний тип функціонування нирок на 11-у добу з моменту введення діабетогенної речовини є наслідком мобілізації адаптаційних, резервних ниркових механізмів, що регулюють пристосування нирок до системного та локального впливу гіперглікемії. Характер та динаміка розвитку порушень екскреторної діяльності нирок засвідчують переважно функціональне походження ренальних розладів на 11 добу експериментального діабету за відсутності значущих структурних змін канальцевого апарату нирок.
Ключові слова: експериментальний цукровий діабет, алоксан, діабетична нефропатія, екскреторна функція нирок.

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 [1, 2, 3]. This is a clinical diagnosis historically based on the detection of proteinuria in diabetic patients, confirming a long existence of kidney damage with already irreversible changes [1, 4]. To emphasize the impact of diabetes on the renal parenchyma at earlier stages of the disease, unaccompanied by clinical manifestations of kidney damage, in 2007, the National Kidney Foundation and Dialysis Outcomes Quality Initiative offered the introduction of the concept of «diabetic kidney disease» (DKD),

reflecting the nonproteinuric stage of chronic kidney disease in case of DM [1, 4], focusing on the limitation of an association of diabetic kidney damage with proteinuria only [10].

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 [5, 6]. 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 [7].

Instead, recent scientific information has led to a reassessment of the micro/macroalbuminuria meaning in the context of the pathogenesis of DKD. Thus, microalbuminuria does not always reflect the presence of DKD [1, 4, 7]. Nowadays, it is apparent that the presence of only albuminuria does not give grounds for a precise diagnosis of DKD. 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 [2, 7]. 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 [7].

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) [8].

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 features of the excretory renal function in the early period of experimental diabetes mellitus.

Materials and Methods. The experiments were carried out on 20 white non-linear mature male rats, with 0,18–0,20 kg of body weight, kept under identical standard vivarium, lighting and temperature conditions, with free access to water and food, and adapted to the conditions of the experiment one week before its beginning. For modeling of the experimental DM 10 animals were administered alloxan solution (Alloxan monohydrate, «Acros Organics», Belgium) intraperitoneally in the dose of 160 mg/kg after the preceding 12-hour deprivation of food with preserved access to water *ad libitum*; 10 animals served as control group. 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 of renal vascular-glomerular apparatus, the animals were loaded with water in the volume of 5% of body weight, urine was collected for 2 hours, and euthanasia was performed by decapitation under the slight diethyl ether anesthesia. Removed right after decapitation, the kidneys were exempted from the capsule and weighted with further calculation of the organ mass index (relative weight of the kidney per 100 g of the animal body weight). Glucose concentration was determined in the blood of experimental animals using portable glucometer One Touch Ultra (LifeScan, USA). Glucose content in urine samples was determined by enzymatic colorimetric method using the standard diagnostic set of reagents Liquick Cor-GLUCOSE (Poland). 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 [9, 10].

The research was carried out following the requirements of the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes (86/609EEC) and the Order by the Ministry of Health of Ukraine №690 dated September 23, 2009 «On Measures for the Further Improvement of Organizational Norms for the Use of Experimental Animals».

The obtained data were statistically processed with detection of mean values, standard errors. To estimate the probability of differences in comparison with 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, by means of «Statistica for Windows» software, «Version 8,0» [11].

Results and Discussion. As the results of the investigation demonstrated, blood glucose concentration in rats with 11-day-long alloxan-induced diabetes significantly exceeded the value of the appropriate index in the control group rats – by 2,2 times ($p<0,001$) (Fig. 1), expectedly followed by the development of glucosuria (Fig. 2), that evidences the adequacy of the used experimental model.

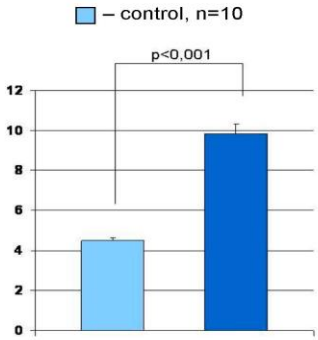

Fig.1. **Glycemia level in rats with 11-day-long alloxan diabetes, mmol/L**

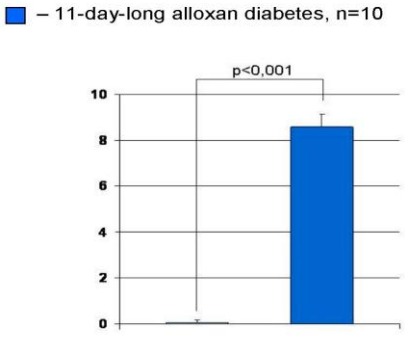

Fig.2. Glucosuria level in rats with 11-day-long alloxan diabetes, mmol/L

* assessment of intergroup differences was carried out using the parametric Student's coefficient (t); p – reliability of differences of the indices as compared to control.

On the 11th day of the alloxan-induced hyperglycemia, an increase of the kidney weight was observed: the absolute weight of the kidneys of the experimental animals was found to be 21,1% higher than the index of that of the controls ($p<0,05$), accompanied by a reliable increase of kidney mass index of rats with mentioned duration of diabetes – by 35,4% in comparison with the corresponding control index ($p<0,02$) (Fig. 3). Noted changes of kidney mass indices of the alloxan-diabetic rats are, probably, related not only to the decline of animals' body weight in the dynamics of diabetes, but to blood flow disorders in the kidneys, the increase of the intravascular volume of the fluid, hyperperfusion of the kidneys.

The development of hyperperfusion and intraglomerular hypertension in every separate nephron leads to the total hyperfiltration in the whole organ [2, 6, 12]. The analysis of the effect of experimental insulindependent hyperglycemia on the excretory function of the kidneys (Table) has revealed that signs of hyperfiltration, typical for the initial stages of DN [13], 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 ($p<0,01$)).

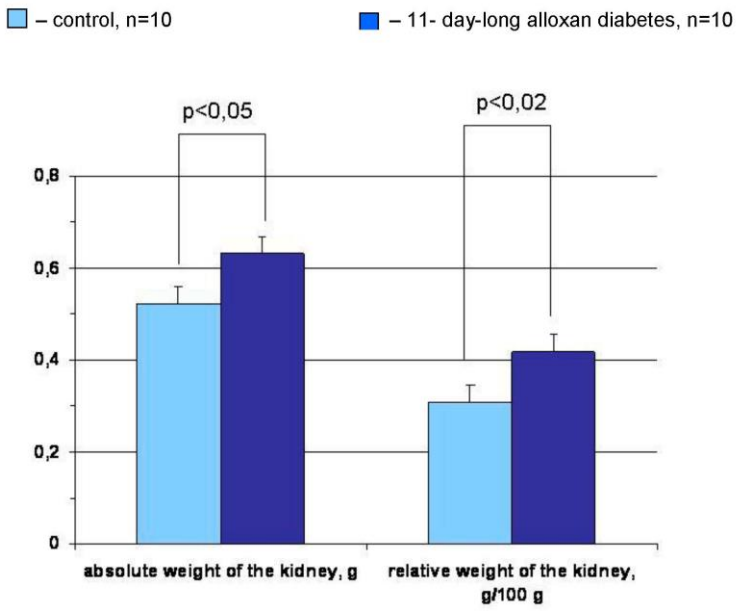

Fig.3. **Kidney mass indices in rats with 11-day-long alloxan diabetes**

* assessment of intergroup differences was carried out using the nonparametric Mann-Whitney criterion;
p – reliability of differences of the indices as compared to control.

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 remained higher than that of the control by 24,5% ($p<0,001$), that is probably related to reduction of animals body weight 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% in animals of this group ($p<0,05$)).

However, 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 ($p>0,2$), probably due to a significant intensification of relative water reabsorption in the tubular portions of the nephron (by 1,6% in comparison with control ($p<0,05$)).

Consequently it can be assumed that the causes of the latter are related to the disturbances of the processes of obligatory reabsorption of ions and water in proximal tubules of the nephron and the thin segment of Henle's loop, or its facultative reabsorption (osmotically free water) in the distal segment of the nephron and the collecting duct under the regulatory influence of the antidiuretic hormone (ADH) [12].

Sodium-dependent water reabsorption in the proximal tubules of the kidneys in case of alloxan-induced experimental diabetes occurs against the background of a tubular overload of the kidney with glucose, which secondary-active transport through the tubular wall is provided at the expense of the driving force of energy-consuming sodium reabsorption with the participation of proteins-carriers (sodium-dependent co-transporters) [12]. The activity of the latter is determined not as much by the concentration of glucose in the blood and, accordingly, in the filtrate, as by the intensity of the filtration. Hence, an increase of GFR in case of 11-day-long alloxan diabetes, is probably accompanied by an exceedance of productivity threshold of proteins-transporters [6]. The development of glucosuria against the background of hyperfiltration can disrupt the proximal sodium transport and, accordingly, limit the reabsorption of sodium-dependent water in the proximal tubules of the kidney.

The intensification of reabsorption of osmotically free (sodium-free) water is determined by the volume of fluid entering the collecting duct, by osmotic gradient between the intra- and transtubular fluid, by the osmotic permeability of the tubular epithelium, and by the absorption of urea and ions [14, 15].

Table 1

Characteristics of excretory renal function in rats with 11-day-long alloxan-induced diabetes under the conditions of induced water diuresis (x±Sx)

Indices	Groups, number of animals	
	Control group, n=10	11-day-long alloxan diabetes, n=10
Diuresis, ml/2 hours	3,24±0,11	3,56±0,16 p>0,2
Urine concentration of creatinine, mmol/L	0,95±0,04	1,57±0,17 p<0,001
Plasma concentration of creatinine, μmol/L	66,50±1,14	82,80±6,62 p<0,001
Glomerular filtration rate, μl/min	387,43±25,23	559,29±42,54 p<0,01
Concentration index of endogenous creatinine, un.	14,34±0,78	19,31±1,89 p<0,05
Relative water reabsorption, %	92,86±0,35	94,38±0,51 p<0,05
Urine concentration of protein, g/L	0,066±0,001	0,107±0,004 p<0,001
Protein excretion, mg/2 hours	0,214±0,007	0,379±0,015 p<0,001
Standardized protein excretion, mg/ 100 μL of glomerular filtrate	0,057±0,003	0,072±0,007 p<0,001

Note: assessment of intergroup differences was carried out using the nonparametric Mann-Whitney criterion; p – reliability of differences of the indices as compared to control.

Under conditions of osmotic diuresis, common for diabetes, it is glucose resulting from insulin insufficiency is considered to enter the proximal tubule in quantities exceeding the reabsorption capacity of the kidneys, is capable of retaining water in the lumen of the collecting tube, preventing its reabsorption by an osmotic gradient [6]. On the other hand, the condition of hyperhydration, created in our research by the induction of water diuresis, is predicted to be followed by the suppression of sodium-free water reabsorption to the interstitium of the renal medulla and the elevation of its clearance. Instead, tubular reabsorption of water on the 11th day after the induction of alloxan diabetes is increasing, being, perhaps, stipulated by the change of tubular wall permeability for water with preserved adequate ADH secretion and by the augmentation of the renal medulla osmolarity, providing the osmotic gradient between the interstitium and the lumen of the collecting duct [12, 16]. Therefore, one more factor that can influence the intensity of sodium-free water reabsorption is the presence of other substances in the liquid of the distal segment and the collecting duct, whose reabsorption may alter their content in the collecting duct during the urine flow and determine the osmotic gradient with the renal medulla (such as sodium, urea, etc.) [14, 15], indirectly certifying the tubular component of hyperfiltration [17].

Simultaneously the protein content in urine of experimental animals on 11th after administration of alloxan significantly 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 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) [18], 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. This is accordant to the meta-analysis of 10 studies results, which proves that it is initial hyperfiltration which increases the risk of microalbuminuria and macroalbuminuria twice as much [19, 20, 21]. In addition, as it is reported in certain literature data, hyperfiltration may be associated with an excessive albumin excretion even in people without hyperglycemia [8]. Thereby, an overloading phenomenon develops for transport reabsorption systems in proximal tubules accompanied by their intactness.

Conclusions. Thus, glomerular hyperfiltration, revealed in the early period of alloxan-induced diabetes, is not only a marker, but also a risk factor for 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.

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