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PECULIARITIES OF IONOREGULATORY RENAL FUNCTION DISORDER IN CASE OF DIABETES MELLITUS

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Abstract

With the aim to study the condition of tubular mechanisms of sodium transport in case of diabetes mellitus and to evaluate their role in the development of diabetic nephropathy, ionoregulatory renal function was researched in patients with diabetes mellitus type 1. It was established, that glomerular hyperfiltration, attributive to the initial stages of diabetic nephropathy, is followed by the enhancement of filtration sodium load to the nephron and by the development of natriuresis, since the augmentation of sodium excretion by proximal tubules is associated with the disturbance of glomerulo-tubular balance and with the impairment of tubulo-tubular connection under the relative dysfunction of distal segment of the nephron. Under the condition of osmotic diuresis, caused by hyperglycemia and glucosuria, the impairment of distal transport of tubular fluid and sodium results in the inhibition of tubulo-glomerular feedback and promotes the progression of renal dysfunctions in case of diabetes mellitus.

Key words: diabetes mellitus, diabetic nephropathy, ionoregulatory renal function, tubular sodium transport

Introduction

Diabetic nephropathy (DN) is one of the most severe complications of diabetes mellitus (DM), which dramatically decreases the life quality of diabetic patients [2]. Nowadays it is considered that principal role in the development and progression of DN belongs to the untreated or insufficiently managed hyperglycemia that triggers the sequence of metabolic disorders and, as the result, leads to the disturbance of intrarenal hemodynamics, elevation of hydrostatic pressure in glomerular capillaries and hyperfiltration [1,2]. Persistent influence of hyperglycemia results in the reduction of synthesis of glucosaminoglycans, which are the ground of glomerular basement membrane structure and provide its selective permeability for proteins. These precise changes of protein excretion by urine – from microalbuminuria and to steady proteinuria, – disorders of renal filtration function with the reduction of glomerular filtration rate, are considered to be the classic clinical orientations of DN, furthered by microhematuria and cylindruria, hyposthenuria, arterial hypertension, oedema, hypochromic anemia and hypoproteinemia [2,4]. At the same time, the presence of above-mentioned symptoms signifies the irreversibility of the renal tissue structural changes and reveals already existing disorders of renal hemodynamics, but doesn't allow to predict and give a prognosis of the beginning of their development. Thus, the issues of investigation of informative pathogenetical markers of the initial stages of DN with the purpose of timely renoprotective influence become of a great importance. Meanwhile, according to numerous researchers, tubulointerstitial tissue (TIT) is involved into the pathological process earlier than glomeruli [5,6,12]. Damage of TIT causes electrolytic disturbances, which consequently aggravate renal dysfunctions [6]. Thereby, adequate assessment of kidney functional status, the early diagnostics of its disturbance in particular, provides the analysis of not only the renal glomerular apparatus, but the condition of TIT as well. Sodium excretion is one of the most important elements indicative of TIT function [13]. Regardingly, natriuresis and tubular sodium transport disturbances allow to monitor TIT function in the dynamics.

The processes of cooperative counterbalancing influence of compensatory mechanisms, which restore sodium balance and provide homeostatic regulation of fluid and electrolyte loss by the body, as well as the way of their functional adaptation to the damaging affect of hyperglycemia, osmotic diuresis and hyperfiltration, for the diabetic kidney are still unknown and need to be studied in details. Therefore, the objective of this research was to study the condition of tubular mechanisms of sodium transport in case of diabetes mellitus and to evaluate their role in the development of diabetic nephropathy.

Methods

11 patients with DM type 1 (73% of women and 27% of men), aged between 23 and 56 years old (mean age – 41,0±3,13 years), and 10 healthy individuals, who constituted the control group, participated in the study. The overwhelming majority of the enrolled patients represented age groups of 31-40 and 41-50 years (27% and 36% respectively), moreover, in 2 out of all examined patients the duration of diabetes was less than 5 years (2,2±1,85 years) before their participation in the study, in 5 participating individuals diabetes lasted for 6-10 years (8,0±0,63 years), 4 of participants had diabetes for longer than 10 years (18,3±3,66 years). The verification of the diagnosis and disease severity was based on the acting national and international regulating documents. According to the results of a complex patients' examination severe form of the disease was identified in all enrolled patients (including cases of its duration for less than 5 years). General clinical examination has revealed the initial (preclinical) stages of DN in 73% of the patients involved into the study. At the beginning of the research patients' condition was stable and didn't require additional measures, except those provided by the National medical care protocols for patients with diabetes mellitus. A complex patients' examination included methods of study of renal functioning changes as well as generally accepted clinical and laboratory-instrumental techniques. The study of kidney functional state of examined patients was performed in the conditions of spontaneous night 12-hour diuresis by clearance-method to assess vascular-glomerular apparatus, proximal and distal tubular portions of the nephron [8, 9]. Plasma and urine concentrations of sodium and potassium were detected by flame photometry on «ФПЛ-1». Urine content of creatinine was determined in the reaction with picric acid according to the Folin's method [8], its plasma level – according to the Merson's method [8] with the registration of extinction indices by photocolorimeter «КФК-2» and spectrophotometer «СФ-46». The level of 12-hour diuresis was assessed in ml/kg. Glomerular filtration rate (GFR), creatinine excretion, excretory fractions of sodium, potassium and protein, relative water reabsorption, filtrative

fraction of sodium, its absolute reabsorption (to evaluate tubular sodium transport) were calculated [8,9]. For the standardization of parameters of kidney functional status their absolute figures were recalculated per 0.1 kg of body weight or per 100 mcl of glomerular filtrate.

Numeric data has been analysed by software «Statistica for Windows», «Version 6.0». Statistical processing of the obtained data was performed with the establishment of mean value, standard errors and confidence intervals. To estimate the probability of differences in comparison of studied groups, Student's coefficient (t) was used. The difference between groups was considered to be significant at the level of P<0,05.

Results and Discussion

The assessment of carbohydrate metabolism parameters evidenced a poor compensation of the disease in the examined cohort of patients: the level of fasting glycemia was 14,77±1,38 mmol/l (2,7 times higher than corresponding index of healthy individuals), the glucosuria level – 19,50±1,39 g/l.

The analysis of changes of kidney functional state parameters in the examined patients has revealed the signs of hyperfiltration and polyuria, typical for the initial stages of DN (Table 1): 1,8-fold increased diuresis (P<0,001) as well as elevation of GFR, which exceeded the control level by 2,6 times (P<0,001), were observed, despite the absence of substantial changes of water reabsorption. Intrarenal hemodynamic reconstruction followed by the intensification of intraglomerular blood flow (hyperperfusion) and elevation of intraglomerular hydrostatic pressure (intraglomerular hypertension) are known as the ground of hyperfiltration in case of DM [1,2,4]. The level of glomerular filtration may be directly influenced by intrarenal mechanisms as well, particularly by the development of osmotic diuresis in decompensated DM due to the tubular entry of suprathreshold concentrations of osmotically active glucose, which aren't reabsorbed and resist to water absorption by osmotic gradient and, as the result, cause intensification of urination [4]. It should me mentioned, that the development of hyperfiltration in case of DM may be contributed by other mechanisms as well. Thus, hyperglycemia is followed by the increase of circulating blood volume that, in its turn, stimulates the release of atrial natriuretic hormone. The latter is able to improve the glomerular filtration and to reduce proximal sodium reabsorption, to inhibit active sodium transport by the blockage of Na^+,K^+-ATPase and decrease of succinatedehydrogenase activity. Furthermore, the kidneys themselves belong to the organs, which produce natriuretic substances. It was shown, that renal distal tubules produce natriuretic hormone urodilatin, identical to the atrial natriuretic peptide (its natriuretic activity is similar, or even higher, than of atrial hormone) [2,4].

In any case, the increase of glomerular filtration consequently leads to the elevation of filtration load of the nephron: filtration charge of sodium is found to be increased by 1,9 times (P<0,001), sodium excretion – absolute (by 3,7 times, P<0,001) as well as standardized in volume of glomerular filtrate (by 1,9 times, P<0,001) is reliably raised, that causes the loss of this electrolyte by the body considering the tendency to augmentation of urine sodium concentration (by 2,1 times, P<0,001). Evidently, the increase of sodium excretion relates to the failure of proximal segments of the nephron, expected to reabsorb from 2/3 to 3/4 of filtrated fluid and equal amount of sodium, to adapt to the overloading by hyperosmolar ultrafiltrate [3,6,7,10,11]. Thereby, the disturbance of glomerulo-tubular balance causes the flow of large volumes of hypernatrium intratubular fluid from the proximal tubules to the loop of Henle and distal segments of the nephron, that was expected to lead to the increase of distal sodium reabsorption by tubular-tubular equilibrum [6,7,14]. However, under the condition of overload by the filtrate, despite quite powerful reserve capabilities of the distal tubules and their ability to reabsorb large amounts of sodium even in case of their excessive delivery, distal sodium transport is inhibited under the intensified osmotic diuresis and proves to be unable to provide the retention of those sodium ions that avoided proximal tubular reabsorption (despite the significant intensification of absolute reabsorption – by 1,8 times as compared with the control, P<0,001, – relative sodium reabsorption is reliably lower in the enrolled patients in comparison with the corresponding control index (P<0,001)).

Apparently, activation of intrarenal RAAS, induced by natriuresis, is followed by the release of aldosterone, which, while leaving not restored the ability of the kidneys to reabsorb the large volumes of the fluid, tends to normalize distal sodium transport improving the potassium secretion simultaneously [4,6]: according to the ratio of sodium and potassium concentrations in the urine of examined patients, the excretion of the latter one prevails – ratio coefficient of urine concentrations of sodium and potassium in patients with DM type 1 3,3-folds exceeds the level of healthy individuals (P<0,001), accompanied by the reliable decline of potassium concentration in the

urine examined patients (by 1,5 times, P<0,01). Hence, besides the loss of proportionality between the filtrated sodium fraction and its proximal reabsorption, impairment of glomerulo-tubular and tubulo-tubular balance, DM appeared to be accompanied by the inhibition of the tubulo-glomerular feedback mechanism, resulted from hyperglycemia on one side and glucosuria – on the other one. The extenuation of renal response on the excessive delivery of tubular fluid with high sodium content to the macula densa and the absence of adequate normalizing renal reactions are the consequences of decreased activity of above-mentioned renal mechanism of homeostasis autoregulation.

It should be taken into consideration, that the study of kidney functional activity was performed in patients with DM type 1, known to require the replacement therapy by insulin medications, which, as it has been demonstrated recently, may effect the kidneys directly not depending on its influence on hyperglycemia [2]. It has been stated, that even under stable hyperglycemia, insulin infusion itself can lead to the reduction of intraglomerular pressure and glomerular filtration and cause antinatriuresis. Absence of stabilizating effect of insulin-therapy upon the parameters of intraglomerular hemodynamics in the examined patients again emphasizes the leading pathogenetical role of the osmotic diuresis in disorganization of the processes of renal filtration and tubular ions transport.

Conclusions

Glomerular hyperfiltration, attributive to the initial stages of diabetic nephropathy, is followed by the enhancement of filtration sodium load to the nephron and by the development of natriuresis, since the augmentation of sodium excretion by proximal tubules is associated with the disturbance of glomerulo-tubular balance and with the impairment of tubulo-tubular connection under the relative dysfunction of distal segment of the nephron. Under the condition of osmotic diuresis, caused by hyperglycemia and glucosuria, the impairment of distal transport of tubular fluid and sodium results in the inhibition of tubulo-glomerular feedback and promotes the progression of renal dysfunctions in case of diabetes mellitus.

Conflict of Interest

The authors declare that there are no conflicts of interest.

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Table 1: Characteristics of ionoregulatory renal function in patients with diabetes mellitus type 1 (x±Sx)

Indices	Group, number of examined patients	
	Healthy individuals, n=10	**DM type 1, n=11**
Diuresis, ml/kg per 12 hours	8,87±0,14	15,75±0,52 P<0,001
Glomerular filtration rate, ml/min	120,60±1,72	236,39±5,32 P<0,001
Water reabsorption, %	89,77±0,20	90,75±0,22 P<0,01
Urine concentration of sodium ions, mmol/l	49,50±2,47	105,68±8,45 P<0,001
Excretion of sodium ions, mmol/kg per 12 hours	0,44±0,02	1,64±0,10 P<0,001
Excretion of sodium ions, mcmol/100 ml of glomerular filtrate	0,36±0,02	0,70±0,05 P<0,001
Filtration fraction of sodium ions, mmol/min	17,07±0,28	32,33±0,81 P<0,001
Absolute reabsorption of sodium ions, mmol/min	16,46±0,28	30,06±0,87 P<0,001
Relative reabsorption of sodium ions, %	96,44±0,16	92,88±0,56 P<0,001
Concentration index of sodium ions, un.	0,35±0,02	0,78±0,07 P<0,001
Ratio coefficient of urine concentrations of sodium and potassium, un.	1,91±0,23	6,39±0,89 P<0,001
Urine concentration of potassium ions, mmol/l	28,50±2,67	18,64±2,06 P<0,01
Excretion of potassium ions, mmol/kg per 12 hours	0,25±0,03	0,30±0,04 P>0,3

P – statistically significant difference in comparison with healthy individuals; n – number of patients