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THE RELATIONSHIP BETWEEN THE RATES OF URINARY ALBUMIN EXCRETION AND GLOMERULAR FILTRATION IN TYPE 1 DIABETES MELLITUS PATIENTS

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Summary. *Background/Aim: Albuminuria is recognized as an early marker of diabetic nephropathy, but glomerular hyperfiltration appears prior to its development. The aim of this study was to assess relationship between the rates of urinary albumin excretion and glomerular filtration in different diabetic kidney disease stages of type 1 diabetes mellitus.*
Methods: According to urinary albumin excretion rate and serum creatinine, seventy patients with type 1 diabetes mellitus were classified into normoalbuminuric (NA), microalbuminuric (MiA), macroalbuminuric (MaA) and chronic renal failure (CRF) group. Their results were compared with those of 23 healthy volunteers. Plasma clearance of ^{99m}Tc-DTPA was used to estimate glomerular filtration rate.
Results: Mean clearance value of ^{99m}Tc-DTPA was recorded as increased in NA group ($p<0.005$), unchanged in MiA group and decreased in both MaA and CRF groups ($p<0.0001$). The relationship analysis established a significant correlation between albumin excretion rate and glomerular filtration rate only in MaA group ($r = –0.588$, $p=0.008$).
Conclusion: Related to urinary albumin excretion, glomerular filtration rate alteration appears in the earlier stage and represents a more reliable indicator of renal function impairment in diabetic kidney disease.

Key words: *Type 1 diabetes mellitus, urinary albumin excretion rate, glomerular filtration rate*

Introduction

The diabetic kidney disease is characterized by the occurrence of primary lesions at glomeruli level (1-5). In clinical practice, the severity of renal dysfunction is widely estimated by the increase in urinary albumin excretion (AER) and the decrease in glomerular filtration rate (GFR). Albuminuria, as a marker for diabetic nephropathy, is commonly used to determine the stage of the kidney disease (6,7). On the other hand, hyperfiltration as a transient disorder of glomerular function at the early stage of the kidney disease may appear prior to albuminuria (8,9). Some of hemodynamic factors are reported to play an important role in both albuminuria and hyperfiltration genesis (10,11). In addition, the occurrence of these glomerular disorders was proposed to be mediated by the same compound, nitric oxide, whose enhanced biosynthesis has been shown to be followed by vasodilatation, the increase in the rate of glomerular filtration and filter permeability for albumin molecules (12,13). With advancement of structural lesions there is a gradual fall of GFR associated with further increase in AER (2,14).

This study was carried out in order to assess the relationship between urinary albumin excretion rate and glomerular filtration rate in different kidney disease stages of type 1 diabetes mellitus patients.

Subjects and Methods

Subjects

Seventy patients with type 1 diabetes mellitus of duration longer than five years were included in the study. Patients' characteristics are displayed in table 1. According to the rate of urinary albumin excretion and serum creatinine they are classified into following groups: 1. normoalbuminuria, n=24, AER<20μg/min; 2. microalbuminuria, n=14, AER 20–200μg/min; 3. macroalbuminuria, n=19, AER>200μg/min; and 4. chronic renal failure, n=13, serum creatinine >130μmol/l. Patients' results were compared with those of 23 healthy volunteers.

Measurement of urinary albumin excretion rate

Proteinuria was detected by using the dipstick test and, then measured in 24 h collections by biuret method.

In negative test samples differentiation between normoalbuminuria (AER<40mg/l) and microalbuminuria was assessed qualitatively by Micro-Bumintest (Bayer Diagnostik, Munch Germany), and after that the latter one was quantified by immunoturbidimetric method using "Ames " DCA 2000 analyzer.

Table 1. Patients' characteristics

	Control	NA	MiA	MaA	CRF
n	23	24	14	19	13
Gender (%) f/m	73.9/26.1	62.5/37.5	64.3/35.7	57.9/42.1	61.5/38.5
Age (years)	42.4±11.3	39.2±7.8	38.1±12.0	46.5±12.5[d]	48.3±13.0[d]
Diabetes duration (years)	-	12.4±6.5	14.0±6.7	18.1±5.0[c]	20.3±6.4[c,e]
Blood glucose (mmol/l)	4.12±1.06	12.7±4.9[a]	15.3±5.2[a]	12.0±3.6[b]	14.7±4.2[a]

NA, normoalbuminuria; MiA, microalbuminuria; MaA, macroalbuminuria; CRF, chronic renal failure. Vs. control: [a]P<0.0001, [b]P<0.005; vs. NA: [c]P<0.005, [d]P<0.05; vs. MiA: [e]P<0.05.

Measurement of glomerular filtration rate

The filtration rate was evaluated by measuring ^{99m}Tc-DTPA clearance (15) with one blood sample method (16). After an intravenous injection of 1.85 MBq/kg/BW ^{99m}Tc-DTPA, the volume of distribution was calculated from the activities of dose applied and 3 h blood sample. Both one minute measurements were carried out in a well detector (Biogamma II, "Beckman", USA). Individual clearance rates were expressed as normalized on 1.73m^2 of the body surface.

Statistical analysis

Group values of parameters are expressed as mean ±SD, while the incidence rates were presented in percentages. Comparisons between groups were performed by Student's t test. Patients were considered to have hyper or hypofiltration when their ^{99m}Tc-DTPA clearance values were out of the control mean ±2SDs. Pearson' correlation coefficient was performed to determine the relationship between parameters studied. p<0.05 indicated statistical significance.

Results

The measurement of AER showed a significantly higher value of 1.390±0.940 g/24 h in MaA group when compared to MiA group value of 0.155±0.100 g/24 h (Fig. 1). However, AER of 1.310±1.470 g/24 h in CRF group did not differ significantly from that of MaA group. Within both groups, MaA and CRF, a wide range of individual values variations was recorded. The tested relationship between AER and blood glucose showed a significant correlation only in MaA group (r=0.557, p=0.010).

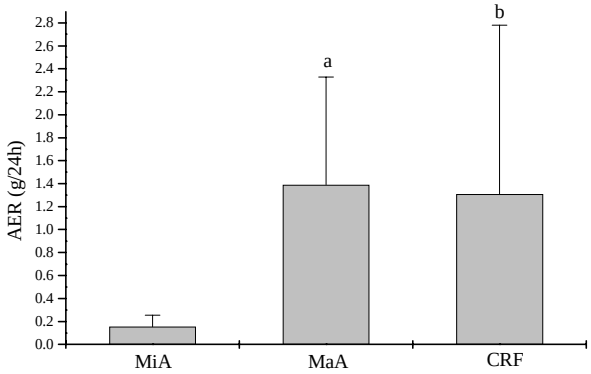

Fig. 1. Urinary albumin excretion rate in type 1 diabetes mellitus patients. Vs. MiA: [a]p<0.0001, [b]p<0.05.

Clearance values of ^{99m}Tc-DTPA, presented in Fig. 2, point to a significantly increased mean value of 136±15 ml/min/1.73m^2 in NA group in comparison with control value of 121±9 ml/min/1.73m^2, while such significance was not found in MiA group. In MaA and CRF group a remarkable decrease to 81.8±12.4 ml/min/1.73m^2 and further fall to 30.0±12.9 ml/min/1.73m^2, respectively was observed. The analysis of individual clearance values established the increase in 45.8% and normal range values in the rest of NA group patients. Out of 14 MiA patients, one had increased, 10 normal and 3 lowered clearance values, while the decrease was present in all MaA and CRF patients. In NA group ^{99m}Tc-DTPA clearance was found to correlate significantly with diabetes mellitus duration (r= –0.511, p=0.011).

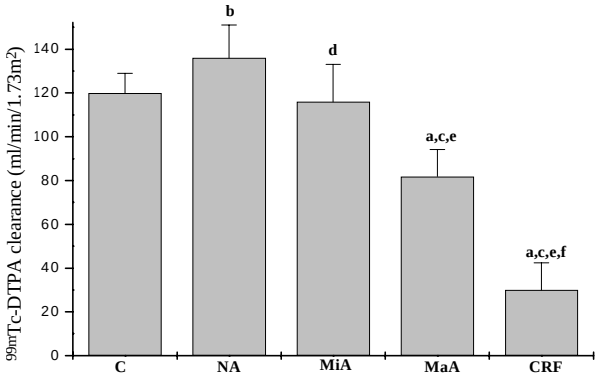

Fig. 2. ^{99m}Tc-DTPA clearance values in type 1 diabetes mellitus patients. Vs. control: [a]p<0.0001, [b]p<0.005; vs. NA: [c]p<0.0001, [d]p<0.005; vs. MiA: [e]p<0.0001; vs. MaA: [f]p<0.0001.

The regression analysis revealed a significant correlation between AER and GFR only in MaA group (Fig. 3), whereas this relation was missing in other studied groups.

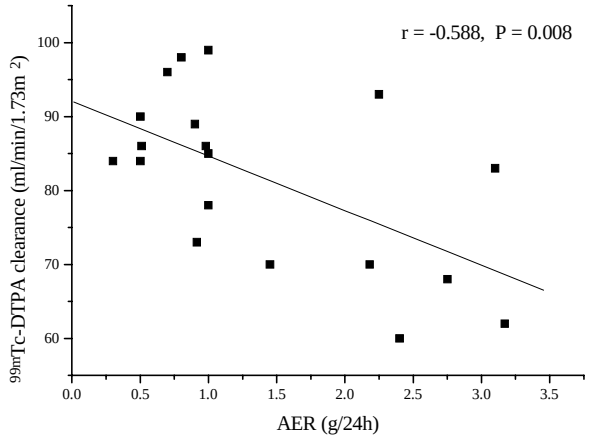

Fig. 3. The relationship between AER and ^{99m}Tc-DTPA clearance in macroalbuminuric type 1 diabetes mellitus patients.

Discussion

The results of this study showed an increasing trend of albumin excretion rate with the progression of the kidney disease in type 1 diabetes mellitus patients before the renal failure stage was reached. Considering the rate of glomerular filtration, a high incidence of hyperfiltration in normoalbuminuric, predominantly normal rate in microalbuminuric, and the reduction in all macroalbuminuric patients were revealed. The analysis of the relationship between AER and GFR demonstrated a significant correlation only in the group with macroproteinuria.

Previous studies of insulin-dependent diabetic patients resulted in different findings of AER and GFR, separately, as well as regarding their relationship. This is emphasized particularly in the early stage of the kidney disease. In some reports a positive correlation between the increase of AER and GFR was established (9,13), but it was missing in others (5,17). Such a difference originated probably from multifactorial pathogenesis of albuminuria and hyperfiltration, as well as various degree risk factors involved in the progression of the kidney disease. There is a strong interaction among biochemical, hemodynamic and structural injuring factors in the complex pathogenetic mechanisms. Some of factors are included in both glomerular function disorders, while others are specific for each of them.

High blood glucose concentration seems to be a trigger of the pathological sequences (5,18,19). In the present study macroalbuminuria was found to correlate significantly with glucose level. Considering other metabolic disturbances, increased nitric oxide generation is reported to induce glomerular vasodilatation, which increases glomerular filtration rate and transglomerular passage of albumin (12,13). The increase in glomerular mRNA for connective tissue growth factor has been shown to correlate with both GFR and AER, while the only significant correlation of mRNA for type IV collagen has been related to AER (4). Altered synthesis of heparan sulfate is suggested to affect glomerular filter charge-selectivity that contributes to albuminuria appearance (20). Moreover, albuminuria itself has been proposed to exert renal injuring effect through degradation of reabsorbed proteins (21).

Hemodynamic changes, manifested as vasodilatation associated with increased blood flow, result in the increase of intraglomerular pressure, which is involved in hyperfiltration and albuminuria development (10,11). The pathogenetic effect of hyperfiltration is recognized to be nephron damage with subsequent decline in renal function (22,23). In addition, it has been supposed to be a prerequisite for the development of initial microalbuminuria (6). Recent follow-up studies of normoalbuminuric and microalbuminuric patients demonstrated a remarkable GFR reduction of baseline values (5,9) only in hyperfiltrating patients, that was associated either with a significant AER increase (9) or without it (5).

Structural lesions of glomeruli are found linked tightly to AER and GFR alteration grade. The early development of glomerular hyperfiltration, apart from other factors, is attributed to the increased filtration surface (1). On the other hand, advanced basement membrane thickening, mesangial and matrix expansion (4,5) are accompanied by the fall of GFR and further elevation in AER (1,2,14). The results of our study evidenced a significant correlation between marked GFR decrease and AER increase in macroalbuminuric patients.

The lack of correlation between AER and GFR in microalbuminuric patients obtained in this, as well as in other studies (5,17) may be attributed to several factors. One of them is earlier appearance of hyperfiltration related to albuminuria in our patients. Another reason may be a different glomerular function status within the same AER range. Namely, microalbuminuric patients are reported to have a high incidence of hyperfiltration (5,8,24), or predominantly unchanged rate (25,26), but some of them had hypofiltration (5). In the present study, beside the vast majority with normal GFR, patients with hypofiltration or hyperfiltration were observed, too. The absence of correlation may originate from overlapping of structural lesions grades among different stages of the kidney disease. Although, glomerulopathy has usually a progressive course, morphometric measurements showed quite advanced glomerular lesions associated with GFR decrease in some microalbuminuric and even normoalbuminuric patients (3,5,27). Poor correlation between AER and GFR in microalbuminuric patients obtained in the current survey, as well as in another reports (5,17) could be also impute to insufficient number of patients studied, so it is necessary to perform prospective investigations on a greater number of patients.

Taking into the consideration function state in different stages of the kidney disease, our study showed altered GFR in patients with normal ranged AER. If hyperfiltration is considered as a transient phase, normal GFR in our microalbuminuric and some normoalbuminuric patients could be supposed to represent the very beginning of renal function regression. This speculation

is supported by the finding of significant negative correlation between GFR and diabetes mellitus duration in normoalbuminuric patients. In overt diabetic nephropathy an overall decrease of glomerular filtration rate is present at the same time with proportional enhancement of albumin filtering. However, when progression to the renal failure stage is achieved further huge drop of GFR, but only negligible AER increase is evidenced due to total occlusion of a significant proportion of glomeruli (28). Although albuminuria is claimed to be a marker of nephropathy progression (6), at this stage it fails to reflect appropriately glomerular function and could not be used as its valuable parameter.

Related to albuminuria, the results of this study favor the glomerular filtration rate estimation to define kidney disease stages in diabetes mellitus patients. The radionuclide clearance measurement is a sensitive method, able to determine quantitatively hyperfiltration at an early stage of the kidney disease. Early detection of supranormal glomerular filtration may be important for the beginning of ACE inhibitors treatment in order to prevent diabetic nephropathy. When diabetic nephropathy is developed, decreased clearance values provide more reliable information on the severity of renal function impairment.

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ODNOS IZMEĐU BRZINE URINARNE EKSKRECIJE ALBUMINA I JAČINE GLOMERULSKE FILTRACIJE KOD BOLESNIKA SA TIPOM 1 DIJABETES MELITUSA

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Kratak sadržaj: *Cilj ove studije je bio da se ispita odnos između brzine urinarne ekskrecije albumina i jačine glomerulske filtracije u različitim stadijumima dijabetesne bubrežne bolesti kod bolesnika sa tipom 1 dijabetes melitus-a.*
Prema brzini urinarne ekskrecije albumina i nivou serumskog kreatinina, sedamdeset bolesnika sa tipom 1 dijabetes melitus-a raspoređeno je u grupu sa normoalbuminurijom, mikroalbuminurijom, makroalbuminurijom i hroničnom bubrežnom slabošću, dok je kontrolnu grupu činilo 23 zdravih ispitanika. Jačina glomerulske filtracije procenjivana je plazmatskim klirensom ^{99m}Tc-DTPA .
Srednja vrednost klirensa ^{99m}Tc-DTPA bila je značajno povišena u bolesnika sa normoalbuminurijom ($p<0,005$), neizmenjena u bolesnika sa mikroalbuminurijom i snižena u bolesnika sa makroalbuminurijom i bubrežnom insuficijenciom ($p<0,0001$). Statistički značajna korelacija između ekskrecije albumina urinom i glomerulske filtracije dokazana je samo u makroalbuminuriji ($r=–0,588$ $p=0,008$).
Dobijeni rezultati su pokazali da se poremećaj glomerulske filtracije javlja pre povećanja ekskrecije albumina urinom i da predstavlja pouzdaniji indikator renalnog funkcionog oštećenja u dijabetesnoj bubrežnoj bolesti.

Ključne reči: *Dijabetes melitus tip 1, brzina urinarne ekskrecije albumina, jačina glomerulske filtracije*