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Original scientific paper

Hyperfiltration in Normoalbuminuric Type 1 Diabetic Patients: Relationship with Urinary Albumin Excretion Rate

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A B S T R A C T

Hyperfiltration has been documented in type 1 diabetes and may contribute to the high risk for development of albuminuria and progression of nephropathy. However, recent studies suggest that the risk of progression to albuminuria in type 1 diabetes was not increased by hyperfiltration. We investigated associations of estimated glomerular filtration rate (eGFR) and urinary albumin excretion rate (UAE) in normoalbuminuric type 1 diabetic patients. Study included 313 normoalbuminuric patients with type 1 diabetes, none showed signs of adrenal, renal, or cardiovascular diseases. GFR was estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula. Glomerular hyperfiltration was defined as eGFR ≥ 125 mL min^{-1} 1.73 m^{-2}. Renal hyperfiltration was present in 12% of the study group. Subjects with eGFR ≥ 125 mL min^{-1} 1.73 m^{-2} were younger, had shorter duration of diabetes, lower levels of total and LDL cholesterol, and higher HbA1c than subjects with an eGFR below 125 mL min^{-1} 1.73 m^{-2}. Type 1 diabetic patients with hyperfiltration also had significantly lower UAE. In a multiple logistic regression analysis, higher eGFR was associated with lower UAE. Our results indicate that normoalbuminuric type 1 diabetic patients with hyperfiltration have lower UAE than those with renal function in the normal range. Together with other recent studies this may suggest that creatinine-based estimates of GFR indicating hyperfiltration is not associated with higher UAE and subsequent development of microalbuminuria.

***Key words**: glomerular filtration rate, hyperfiltration, normoalbuminuria, type 1 diabetes*

Introduction

Long-standing type 1 diabetes is characterized by a decline in glomerular filtration rate (GFR) in contrast to general population, but in early stages of diabetes hyperfiltration is characteristic[1]. The prevalence of hyperfiltration in type 1 diabetes varies from less than 25% to more than 75%[2]. Studies in type 1 diabetes showed that primary increases in proximal tubular sodium resorption lead to glomerular hyperfiltration[3]. Glomerular hyperfiltration is usually promoted by hyperglycaemia, and reduction of blood glucose with insulin therapy returns glomerular hyperfiltration to near normal levels[4].

Hyperfiltration has been suggested as a risk factor for the development of albuminuria and progressive nephropathy, and hyperfiltration usually precedes changes in albuminuria by several years[2,5,6]. It was also suggested that hyperfiltration predicts the development of renal ultra-structural changes[2,7]. A meta-analysis of ten cohort studies of 780 normoalbuminuric patients showed that progression to micro and macroalbuminuria was significantly higher in patients with hyperfiltration at baseline[8]. In a single-centre study of 426 normoalbuminuric patients with a follow-up of 5, 10 and 15 years the risk of progression to microalbuminuria was not increased by hyperfiltration[9]. Moreover, a recent prospective study including 2,318 normoalbuminuric type 1 diabetic patients found that the distribution of estimated glomerular fil-

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tration rate (eGFR) in adults normoalbuminuric type 1 diabetic patients was not significantly different from general population[10]. In addition, type 1 diabetic patients with a higher eGFR were also no more likely to develop microalbuminuria over a median of 5.2 years of follow-up than those with normal eGFR.

The aim of this study was to explore the relationship between eGFR and urinary albumin excretion rate (UAE) in normoalbuminuric type 1 diabetic patients with normal renal function.

Subjects, Materials and Methods

This study included 313 normoalbuminuric patients with diabetes mellitus type 1. Type 1 diabetes was defined as an onset of diabetes before the age of 35 years, positive autoantibodies and permanent insulin treatment initiated within 1 year of diagnosis. Subjects with insulin-treated diabetes secondary to other pathologies were excluded. The study included patients following characteristics: age of 18–65 years, minimum duration of type 1 diabetes of 1 year, no medical history of disorders of adrenal gland function, cardiovascular diseases or electrocardiogram (ECG) evidence of ischemic heart disease, absence of any systemic disease, and absence of any infections in the previous months. Patients with chronic renal disease or other chronic diseases likely to affect renal function were excluded. Patients were excluded from the study if they had taken any of the following: lipid--lowering therapy, ACE inhibitors or angiotensin II receptor blockers, medications that might affect glucose metabolism such as glucocorticoids as well as patients taking oral glucose-lowering medication. Acute and chronic inflammation was excluded on the basis of medical history, physical examination, and routine laboratory tests, including measurement of temperature and urinalysis.

All subjects were studied in the morning after an overnight fast. Basic anthropometric measurements were performed on all study subjects. UAE was measured from at least two 24-h urine samples and determined as the mean of 24-h urine collections. Patients performed collections on two consecutive days to minimize variability. Normoalbuminuria was defined as a UAE<30 mg/24h. Those with microalbuminuria (UAE≥30<300 mg/24h) and macroalbuminuria (UAE≥300 mg/24h) were excluded from the study. Serum creatinine was measured in fasting blood sample. From 2011 creatinine was measured by an enzymatic method that produced values traceable to the isotope dilution mass spectrometry (IDMS) values. We calibrated creatinine results generated before 2011 to the IDMS-traceable values obtained with the enzymatic method. Data on serum creatinine levels, age, sex and race were used to calculate the eGFR using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula, which has been shown to be accurate in determining renal function in diabetic patients with normal renal function. GFR was also estimated using the 175 Modification of Diet in Renal Disease and the Cockcroft and Gault formula. Glomerular hyperfiltration was defined as eGFR ≥ 125 mL min^{-1} 1.73 m^{-2}. Those with impaired eGFR (less than 60 mL min^{-1} 1.73 m^{-2}) were excluded from the study.

Microalbumin and HbA1c were measured spectrophotometrically by turbidimetric immuno-inhibition (Olympus AU600, Beckman-Coulter, USA). Results of HbA1c (%) are expressed in the DCCT-equivalent. Complete blood count was determined on an automatic blood counter (Advia 120, Siemens Diagnostic Solutions, USA).

The study protocol complies with the Declaration of Helsinki as well as with local institutional guidelines, and was approved by the local ethnics committees.

Data are expressed as means ± SD for normally distributed values, as median with range for non-normally distributed values, and percentage. Correlations between parameters of renal function with anthropometric and metabolic variables were determined using Spearman rho test. To investigate the relation between eGFR with UAE and other parameters data were also stratified according to levels of GFR estimated using the CKD-EPI formula and quartiles of UAE. Kruskal-Wallis test was used for calculating the significance of the trend for each variable among quartiles of UAE and among hyperfiltrating patients and those with normal renal function. Multiple logistic regression analysis was used to assess associations of eGFR with risk of higher UAE. Level of statistical significance was chosen to $\alpha = 0.05$. Statistical analysis was performed by statistical package STATA/IC ver.11.1.

Results

The characteristics of the study subjects are listed in Table 1. The average age was approximately 34 years, most were not overweight and 51% of subjects were female. Mean/median values of BMI, waist to hip ratio (WHR), systolic and diastolic blood pressure, HDL cholesterol, and triglycerides were within the normal range for patients with diabetes with slightly elevated levels of HbA1c, total and LDL cholesterol. In individuals with normoalbuminuria, the mean GFR estimated by the CKD-EPI was 106 mL min^{-1} 1.73 m^{-2}. Using the CKD--EPI formula 12% of patients had an eGFR ≥ 125 mL min^{-1} 1.73 m^{-2}. Renal function estimated using the MDRD formula was significantly lower (98 mL min^{-1} 1.73 m^{-2}) than when estimated using the CKD-EPI formula. However, the number of patients with an eGFR ≥ 125 mL min^{-1} 1.73 m^{-2} was similar to that found with the CKD-EPI formula. The mean eGFR using Cockcroft--Gault formula was 101 mL min^{-1} 1.73 m^{-2}, and 59 patients (19%) had eGFR ≥ 125 mL min^{-1} 1.73 m^{-2}, more than with others formula, which is in accordance with previous studies[10].

Characteristics of study subjects with and without renal hyperfiltration are displayed in Table 2. Subjects with eGFR ≥ 125 mL min^{-1} 1.73 m^{-2} were younger, had shorter duration of diabetes, lower levels of total and LDL cholesterol, and higher HbA1c than subjects with

TABLE 1
CLINICAL AND METABOLIC CHARACTERISTICS OF ALL PATIENTS

Variable	Value
Age (years)	34 (18–65)
Duration of diabetes (years)	12 (1–42)
Body mass index (kg/m^2)	24 (15–37)
Waist to hip ratio	0.81±0.07
HbA1c (%)	7.43±1.63
Systolic blood pressure (mmHg)	120 (79–180)
Diastolic blood pressure (mmHg)	80 (50–100)
Total cholesterol (mmol/L)	5.0±0.8
LDL cholesterol (mmol/L)	2.8±0.7
HDL cholesterol (mmol/L)	1.7±0.4
Triglycerides (mmol/L)	0.91 (0.3–4.1)
Serum creatinine (μmol/L)	71±14
CKD-EPI (mL min^{-1} 1.73 m^{-2})	106±16
MDRD (mL min^{-1} 1.73 m^{-2})	98±20
Cockcroft-Gault (mL min^{-1} 1.73 m^{-2})	101±28
Urinary albumin excretion (mg/24h)	11.0 (1.7–29.8)

CKD-EPI – Chronic Kidney Disease Epidemiology Collaboration, MDRD – Modification of Diet in Renal Disease.

an estimated GFR below 125 mL min^{-1} 1.73 m^{-2}. However, blood pressure, HDL cholesterol, triglycerides, BMI and WHR were similar among those with and without hyperfiltration. In addition, hyperfiltration status did not significantly differ between males and females (11.4 vs. 13.0 %), or between smokers and non-smokers (11.8 vs. 12.7 %). Surprisingly, UAE was significantly lower in subjects with eGFR ≥ 125 mL min^{-1} 1.73 m^{-2}, than in subjects with eGFR 60–124 mL min^{-1} 1.73 m^{-2}.

TABLE 3
SPEARMAN CORRELATION ANALYSIS OF ASSOCIATIONS OF RENAL PARAMETERS WITH METABOLIC AND ANTHROPOMETRIC VARIABLES

Variable	UAE	Serum creatinine	eGFR
Age	0.07	0.02	–0.60*
Duration of diabetes	0.14*	0.00	–0.29*
Body mass index	–0.02	0.15*	–0.10
Waist to hip ratio	0.01	0.39*	0.01
HbA1c	0.06	–0.14*	0.15*
Total cholesterol	0.02	–0.01	–0.21*
LDL cholesterol	0.03	0.08	–0.18*
HDL cholesterol	–0.13*	–0.19*	–0.17*
Triglycerides	0.11*	0.07	0.06
Systolic blood pressure	0.09	0.11*	–0.08
Diastolic blood pressure	0.23*	0.08	–0.01

*p<0.05, UAE – urinary albumin excretion rate, eGFR – estimated glomerular filtration rate.

Associations of renal parameters with anthropometric and metabolic variables are presented in Table 3. UAE was significantly associated with duration of diabetes, HDL cholesterol, triglycerides and diastolic blood pressure, with diastolic blood pressure showing the strongest correlation (r=0.23). In addition, serum creatinine was significantly associated with BMI, WHR, HbA1c, HDL cholesterol and systolic blood pressure, with WHR showing the strongest correlation (r=0.39). Estimated

TABLE 2
CLINICAL AND METABOLIC CHARACTERISTICS OF PATIENTS DEPENDING ON LEVEL OF eGFR (ESTIMATED WITH THE CKD-EPI FORMULA)

Variable	eGFR 60–89	eGFR 90–124 mL min^{-1} 1.73 m^{-2}	eGFR ≥125	p
N	55/313	220/313	38/313	
Sex (m/f)	19/36	116/104	17/21	0.04
Age (years)	45 (19–60)	35 (19–65)	22 (18–34)	<0.001
Duration of diabetes (years)	16 (2–42)	12 (1–42)	7 (1–25)	<0.001
Body mass index (kg/m^2)	24 (17–33)	24 (17–37)	24 (15–34)	0.4
Waist to hip ratio	0.81±0.07	0.81±0.06	0.81±0.06	0.7
HbA1c (%)	7.1±1.2	7.3±1.6	8.4±1.9	0.002
Systolic blood pressure (mmHg)	120 (79–170)	120 (90–180)	120 (90–140)	0.3
Diastolic blood pressure (mmHg)	80 (65–110)	80 (60–110)	80 (50–90)	0.7
Total cholesterol (mmol/L)	5.1±0.7	5.0±0.9	4.6±0.7	0.02
LDL cholesterol (mmol/L)	2.9±0.7	2.8±0.7	2.4±0.7	0.006
HDL cholesterol (mmol/L)	1.8±0.4	1.6±0.3	1.6±0.3	0.1
Triglycerides (mmol/L)	0.91 (0.4–2.5)	0.8 (0.3–4.1)	0.95 (0.4–4.1)	0.3
Serum creatinine (μmol/L)	86±14	70±11	56±10	<0.001
Urinary albumin excretion (mg/24h)	13.7 (1.7–29.4)	10.8 (2.2–29.8)	7.0 (2.7–29.8)	<0.001

TABLE 4
QUARTILES OF URINARY ALBUMIN EXCRETION RATE

	1st quartile <6.8 mg/24h	2nd quartile 6.8–10.9	3rd quartile 11.0–16.7	4th quartile >16.7 mg/24h	p for trend
CKD–EPI	110±16	106±14	103±15	105±18	0.08
MDRD	103±22	96±18	94±17	97±23	0.06
Cockcroft-Gault	110±34	99±26	100±23	96±25	0.08

CKD-EPI – Chronic Kidney Disease Epidemiology Collaboration, MDRD – Modification of Diet in Renal Disease

TABLE 5
MULTIVARIATE LOGISTIC REGRESSION ANALYSIS OF eGFR WITH DEVELOPMENT OF HIGHER URINARY ALBUMIN EXCRETION RATE

Independent variable	Model A	Model B
CKD-EPI	0.98 (0.97-0.99)*	0.98 (0.96–1.00)
MDRD	0.99 (0.97–1.00)	0.98 (0.97–1.00)
Cockcroft-Gault	0.99 (0.98–0.99)*	0.98 (0.97–0.99)*

Data are OR (95% CI) from separate models. Model A crude, model B adjusted for age, sex, duration of diabetes, BMI.
*p<0.05. CKD-EPI – Chronic Kidney Disease Epidemiology Collaboration, MDRD – Modification of Diet in Renal Disease.

GFR using CKD-EPI formula significantly correlated with even 6 parameters (age, duration of diabetes, HbA1c, total, LDL and HDL cholesterol). The magnitude of these associations were strongest for age and duration of diabetes (r= –0.60, and –0.29, respectively, all p<0.001).

Relationship between eGFR among those in the 2nd, 3rd and 4th quartiles of UAE compared to those in quartile 1 are presented in table 4. Stratifying eGFR for degree of UAE trends across quartiles for GFR estimated by CKD-EPI, MDRD and Cockcroft-Gault formula were not statistically significant, but subjects in the 1st quartile of UAE had elevated eGFR levels compared to subjects in 2nd, 3rd and 4th quartiles.

In logistic regression analysis, lower estimated GFR calculated using CKD-EPI and Cockroft-Gault formula was significantly associated with risk of higher UAE (OR=0.98–0.99) (Table 5, Model A). However, after adjustment for age, sex, duration of diabetes and BMI only eGFR assessed by Cockcroft-Gault was associated with higher UAE in our normoalbuminuric subjects (Table 5, Model B).

Discussion

Hyperfiltration has been suggested as a risk factor for the development of albuminuria and progressive nephropathy, and hyperfiltration usually precedes changes in albuminuria by several years[2,5,6]. However, recent studies suggest that the risk of progression to albuminuria in type 1 diabetes was not increased by hyperfiltration[6,9–11]. In support to this data, we showed that elevated eGFR in normoalbuminuric type 1 diabetic patients is not associated with higher UAE. Moreover, in logistic regression analysis higher eGFR tended to be associated with lower UAE. In addition, mean values of UAE of 7 mg/24h in our hyperfiltrating patients is not an early predictive factor for the delopment of albuminuria[12,13]. Taken together with other studies[9,10], it seems that creatinine-based estimates of GFR is not associated with higher UAE and subsequent development of microalbuminuria.

The prevalence of hyperfiltration in type 1 diabetes varies from less than 25% to more than 75%[2,14], and those subjects display increased mortality independent of presence or severity of albuminuria[15]. It is more often in patients with newly diagnosed diabetes, which is rapidly normalized by intensive insulin treatment[16]. Prevalence of hyperfiltration in our subjects was only 12%, probably because creatinine-based methods tend to underestimate GFR in the hyperfiltration range[2]. However, recent prospective study including 2,318 initially normoalbuminuric type 1 diabetic patients found that the distribution of eGFR in adults normoalbuminuric type 1 diabetic patients was not significantly different from general population[10].

It has been argued that in type 1 diabetes uncontrolled hyperglycemia is the most important determinant of hyperfiltration, and subsequent progressive kidney disease[2,8]. Moreover, it was showed that hyperglycemia is associated with higher GFR in hyperfiltering type 1 diabetic patients, with no change in GFR in normofiltering diabetics or in normal control subjects[17]. However, early hyperfiltration can be reversed by insulin therapy and better glucoregulation[16,18]. In contrast, persistent hyperfiltration may persist for years and may not be associated with glycemic control assessed by HbA1c[2]. In our study mean HbA1c levels (7.4%) was significantly lower than in most previous studies. Glycaemic control was associated with eGFR, such that subjects with higher levels of HbA1c had higher eGFR. In addition, poor glycemic control was associated with an increased incidence of microalbuminuria[10,19], and lower A1c with returning to normoalbuminuria from microalbuminuria[20,21]. In our study, hyperfiltrating subjects had significantly higher HbA1c levels, but lower UAE. It is possible that reduction of plasma glucose levels in our patients caused GFR to become normal in initially hyperfiltrating patients, which is previously observed[4,16].

It was shown that the incidence of microalbuminuria was also associated with serum lipids[22,23]. Serum lipids were associated with eGFR and UAE in our subjects. However, those subjects with eGFR ≥ 125 mL min^{-1} 1.73 m^{-2} had significantly lower levels of total and LDL cholesterol. It is possible that better lipid profile in our hyperfiltrating subjects may be explanation of the lack of association between hyperfiltration and higher UAE observed by us.

Since we investigated adult type 1 diabetic patients, it is also possible that hyperfiltration in type 1 diabetes is a childhood or early adult phenomenon[20]. In subjects with longer duration of diabetes, progression to higher UAE was associated with a GFR below 100 mL min^{-1} 1.73 m^{-2} [24,25]. We were unable to assess the effect of hyperfiltration occurring and resolving very soon after diabetes onset because the majority of our patients have over 5 years duration of diabetes. It is possible that renal hyperfiltration has an impact on higher UAE in early duration of diabetes, and our patients with longer duration of diabetes and initially hyperfiltration may have returned to normal filtration levels. Moreover, our patients were investigated years after exposure to pubertal hormonal changes, which are thought to increase hyperfiltration[21]. Additionally, there is a normal physiological decline in GFR associated with ageing. However, in previous prospective studies observing the increase of UAE in hyperfiltrating patients, the baseline UAE did not differ or were higher according to hyperfiltration status[6,13,21,26,27]. Moreover, lower baseline UAE was predictive of regression of microalbuminuria[28]. In addition, higher UAE values in the normoalbuminuric range were predictors of progression to microalbuminuria or proteinuria[13,29,30].

The present study has a number of potential limitations. First, our study was cross-sectional, which limited our ability to infer a causal relation between hyperfiltration and risk for the development of microalbuminuria. Second, our analyses were based on measurement of eGFR and UAE on two consecutive days that may not reflect the relation over time. Third, creatinine-based formula used to estimate GFR is not the »gold standard« procedure and tend to underestimate GFR in the hyperfiltration range, while Cockcroft-Gault formula overestimates the actual renal function.

In summary, our results indicate that normoalbuminuric type 1 diabetic patients with hyperfiltration have lower UAE than those with renal function in the normal range. Together with other recent studies this may suggest that creatinine-based estimates of GFR indicating hyperfiltration is not associated with higher UAE and subsequent development of microalbuminuria. However, future studies will need to address the independent role of hyperfiltration in the evolution of albuminuria in type 1 diabetes.

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UTJECAJ HIPERFILTRACIJE NA RAZINU ALBUMINA U URINU U NORMOALBUMINURIČNIH BOLESNIKA S TIPOM 1 ŠEĆERNE BOLESTI

S A Ž E T A K

Glomerularna hiperfiltracija je česta kod bolesnika s tipom 1 šećerne bolesti i dugi niz godina je prepoznata kao rizični čimbenik razvoja mikro- i makroalbuminurije te nefropatije. Međutim, novije prospektivne studije na velikom broju ispitanika s tipom 1 šećerne bolesti nisu potvrdile da hiperfiltracija doprinosi razvoju mikroalbuminurije. Istraživali smo povezanost glomerularne filtracije (GF) i razine albumina u urinu u normoalbuminuričnih bolesnika s tipom 1 šećerne bolesti. U istraživanje je uključeno 313 bolesnika s tipom 1 šećerne bolesti koji nisu imali poremećaj funkcije nadbubrežne žlijezde, bubrežnu insuficijenciju ili kardiovaskularnu bolest. GF je izračunata prema Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formuli. Glomerularna hiperfiltracija je definirana kao vrijednost GF ≥ 125 mL min^{-1} 1,73 m^{-2}. Glomerularna hiperfiltracija je bila prisutna u 12% ispitanika. Ispitanici s GF ≥ 125 mL min^{-1} 1,73 m^{-2} bili su mlađi, imali su kraće trajanje šećerne bolesti, nižu razinu ukupnog i LDL kolesterola te višu razinu HbA1c u odnosu na ispitanike s GF <125 mL min^{-1} 1,73 m^{-2}. Bolesnici s glomerularnom hiperfiltracijom su imali statistički značano nižu razinu albumina u urinu. Multiplom logističkom regresijom viša vrijednost GF bila je povezana s nižom razinom albumina u urinu. Rezultati našeg istraživanja ukazuju da je serumskim kreatininom izračunata glomerularna hiperfiltracija povezana s nižom razinom albumina u urinu u normoalbuminuričnih bolesnika s tipom 1 šećerne bolesti. Rezultati našeg istraživanja su u skladu s rezultatima novijih istraživanja koji ukazuju da glomerularna hiperfiltracija nije rizični čimbenik kasnijeg razvoja mikroalbuminurije u bolesnika s tipom 1 šećerne bolesti.