Clinical and Laboratory Profile of Patients With Type 2 Diabetes With Low Glomerular Filtration Rate and Normoalbuminuria

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The initial evidence of diabetic nephropathy in type 2 diabetic patients is the development of microalbuminuria (1). However, the UK Prospective Diabetes Study demonstrated that 51% of patients who progress to chronic renal failure had no preceding albuminuria (1).

Patients with low estimated glomerular filtration rate (eGFR) (<60 ml/min per 1.73 m^2) and normoalbuminuria presented an increased rate of cardiovascular disease (2–4) due to unknown reasons. Aggregation of conventional cardiovascular risk factors might play a role. Therefore, the aim of this study was to analyze the clinical and laboratory features of type 2 diabetic patients with low eGFR and normoalbuminuria.

RESEARCH DESIGN AND METHODS

— A cross-sectional study was performed in all consecutive normoalbuminuric type 2 diabetic patients attending the outpatient clinic at Hospital de Clinicas de Porto Alegre, Porto Alegre, Brazil, between 1999 and 2006 with eGFR >15 ml/min per 1.73 m^2. Normoalbuminuria was defined by urinary albumin excretion (UAE) values <20 μg/min, <17 mg/l (random sample), or <30 mg in 24 h (5) on at least two occasions over the preceding 6 months while on their usual antihypertensive medication. eGFR was calculated using the Modification of Diet in Renal Disease formula: $186 \times [\text{plasma creatinine (mg/dl)}^{-1.154} \times \text{age (years)}^{-0.203} \times (1.212 \text{ if black}) \times (0.742 \text{ if female})]$ (6). All patients answered a standard questionnaire and underwent physical examination and laboratory tests. Metabolic syndrome was defined according to National Cholesterol Education Program Adult Treatment Panel III criteria (7).

UAE was measured by immunoturbidimetry. Serum creatinine was measured by the Jaffé method and the lipid profile by a colorimetric method. Insulin resistance was estimated by homeostasis model assessment of insulin resistance (HOMA-IR) (8) in a subset of subjects not on insulin and with serum creatinine <1.5 mg/dl.

Fundus examination was performed by an expert ophthalmologist after mydriasis. For the purpose of this study, patients were classified only according to the presence or absence of any degree of diabetic retinopathy. The presence of coronary heart disease was evaluated by the World Health Organization questionnaire for cardiovascular disease, a 12-lead resting electrocardiogram, or a fixed and nonperfused area at myocardial scintigraphy, as previously described (9,10). The presence of cerebrovascular disease was established if a history of stroke and/or sequelae were present. Peripheral vascular disease was defined in the presence of intermittent claudication, as assessed by the World Health Organization questionnaire for cardiovascular disease and/or the absence of lower limb pulses.

Student's *t* test or the χ^2 tests and Pearson's correlations were performed. Variables with nonnormal distribution (triglycerides, UAE, and HOMA-IR) were log transformed. Multiple linear regression analysis was performed with eGFR as the dependent variable and age, sex, ACE inhibitor use, systolic blood pressure, triglycerides, and total cholesterol as independent variables. *P* values <0.05 (two tailed) were considered significant.

RESULTS

— A total of 660 normoalbuminuric type 2 diabetic patients were evaluated. Eighty-four (12.7%) had low eGFR (15–60 ml/min per 1.73 m^2), and the remaining 576 comprised the reference group (87.2%) (Table 1). The group of patients with low eGFR was older (62.9 ± 10.3 vs. 56.8 ± 9.5 years, $P < 0.001$), had more women (77.4 vs. 60.2%, $P = 0.002$), and had higher total cholesterol (222.8 ± 52.0 vs. 205.3 ± 43.9 mg/dl, $P = 0.014$), LDL cholesterol (143.0 ± 46.0 vs. 122.1 ± 40.1 mg/dl, $P = 0.028$), triglycerides (median 176 [minimum–maximum 46–842] vs. 158 [55–549] mg/dl, $P = 0.006$), and HOMA-IR (11.4 [1.6–44.7] vs. 4.84 [0.3–45], $P = 0.014$) than the reference group. Moreover, this group also presented a high proportion of patients with metabolic syndrome (81.9 vs. 70.2%, $P = 0.027$). There was no difference in the prevalence of micro- and macrovascular diabetes complications between low eGFR and reference groups (diabetic retinopathy: 28.4 vs. 31.6%, $P = 0.575$; coronary heart disease: 29.2 vs. 31.2%, $P = 0.729$; peripheral vascular disease: 33.3 vs. 24.3%, $P = 0.089$; and cerebrovascular disease: 7.7 vs. 4.4%, $P = 0.218$). The use of antihypertensive drugs (61 vs. 55%, $P = 0.120$), including ACE inhibitors (45.5 vs. 33.5%, $P = 0.132$), was also similar.

In a univariate analysis, eGFR corre-

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Abbreviations: eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; HOMA-IR, homeostasis model assessment of insulin resistance; UAE, urinary albumin excretion.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Clinical and laboratory characteristics according to eGFR in normoalbuminuric type 2 diabetic patients*

	eGFR		
	>60 ml/min per 1.73 m^2	15–60 ml/min per 1.73 m^2	*P*
n	576	84	—
Female subjects	444 (77.4)	51 (60.2)	0.002
Age (years)	56.8 ± 9.5	62.9 ± 10.3	<0.001
Diabetes duration (years)	9.3 ± 7.1	10.1 ± 7.0	0.318
BMI (kg/m^2)	28.9 ± 5.2	29.0 ± 5.4	0.841
Male waist circumference (m)	0.98 ± 0.11	0.100 ± 0.65	0.449
Female waist circumference (m)	0.95 ± 0.12	0.98 ± 0.12	0.348
Obesity	518 (90.9)	75 (89.7)	0.375
Smoking	97 (16.4)	9 (11.4)	0.474
Systolic blood pressure (mmHg)	130.0 ± 22.2	146.0 ± 23.7	0.069
Diastolic blood pressure (mmHg)	86.0 ± 12.3	87.0 ± 16.9	1.000
Hypertension	334 (58.7)	56 (67.5)	0.140
HOMA-IR*	4.84 (0.3–45)	11.4 (1.6–44.7)	0.015
A1C (%)	7.07 ± 2.18	6.74 ± 2.35	0.259
Fasting plasma glucose (mg/dl)	175 ± 70.2	164 ± 76.7	0.521
Cholesterol (mg/dl)			
Total	205.3 ± 43.9	222.8 ± 52.0	0.014
HDL	46.4 ± 11.9	44.9 ± 10.6	0.288
LDL	122.1 ± 40.1	143.0 ± 46.0	0.028
Triglycerides (mg/dl)	158 (55–549)	176 (47–842)	0.006
UAE rate (mg/l)	4 (0.1–28.5)	2.35 (1–17)	0.181
Creatinine (mg/dl)	0.9 (0.5–1.2)	1.22 (0.98–2.6)	—
eGFR (ml/min per 1.73 m^2)	88.0 (60.7–186.5)	54.2 (31.3–59.7)	—
Metabolic syndrome	403 (70.2)	68 (81.9)	0.027

Data are means ± SD, median (minimum–maximum), or *n* (%) unless otherwise indicated. *$n = 101$.

lated negatively with age ($r = -0.288$, $P < 0.001$), systolic blood pressure ($r = -0.131$, $P = 0.008$), total cholesterol ($r = -0.130$, $P = 0.007$), and triglycerides ($r = -0.131$, $P = 0.001$). In a multivariate linear regression analysis, only triglycerides and age remained significantly associated with eGFR ($R^2_a = 0.187$, $P < 0.001$). In another model, the blood pressure and triglycerides were replaced by the presence of metabolic syndrome, and it remained significantly associated with eGFR ($R^2_a = 0.144$, $P < 0.001$). The same analysis was performed only with patients not on ACE inhibitors, and similar results were found (data not shown).

CONCLUSIONS — The prevalence of patients with low eGFR in this sample of type 2 diabetic patients was high (13%) and was associated with high triglyceride levels and the presence of metabolic syndrome, after adjusting for sex and age.

There are few reports analyzing the characteristics of type 2 diabetic patients with low glomerular filtration rate (GFR) and normal UAE. De Cosmo et al. (11) observed that cigarette smoking was associated with a low GFR in male patients with type 2 diabetes. In the present study, the proportion of smokers was similar in both groups. The predominance of females in the low eGFR group is in concordance with other authors (12), suggesting that female sex is a risk factor for low GFR despite normal UAE.

The mechanism of the decreased GFR in this group of normoalbuminuric type 2 diabetic patients is still unknown. There are no biopsy data for this group of patients; however, in autopsy series of patients with ischemic nephropathy, the decreased eGFR was associated with metabolic syndrome (13). The high levels of serum triglycerides and the presence of metabolic syndrome found suggest that renal microvascular atherosclerotic disease leading to decreased renal plasma flow could be a possible explanation for low eGFR. Accordingly, triglycerides have been consistently considered an independent risk factor for both vascular disease and diabetic nephropathy (14). However, those with diabetic nephropathy have heterogeneous renal lesions (15), and nondiabetic nephropathies could coexist (16,17).

In conclusion, the presence of low eGFR in normoalbuminuric type 2 diabetic patients was associated with high levels of triglycerides or the presence of metabolic syndrome. Therefore, assessment of renal function in type 2 diabetic patients should include eGFR in addition to UAE measurement, mainly in the presence of metabolic syndrome.

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