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Tubular dysfunction and non-albuminuric renal disease in subjects with type 2 diabetes mellitus

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ABSTRACT

Introduction. Micro-albuminuria is considered an early marker of glomerular injury in patients with diabetes but it has yet to be determined whether testing for markers of tubular injury can also identify people who are at risk of progressive renal disease. **Objective.** To evaluate markers of tubular injury and renal characteristics in a sample of community treated type 2 diabetic subjects. **Material and methods.** We carry-out an assessment of a group of community diabetic patients, anthropometric measures, creatinine clearance, HbA1c, lipid profile, the mean fast serum glucose levels, albuminuria and α1-microglobulin (α1M) urine excretion were evaluated. **Results.** From 95 included patients, 45.2% had α1M urinary excretion ≥ 10 μg/gCr, 23.1% micro-albuminuria, 9.6% macro-albuminuria and 27.2% had a GFR < 60 mL/min. The most important risk factor associated with a1M excretion was fasting glucose level (OR 4.3, 95IC 1.7-11.1 p = 0.001); HbA1c ≥ 8% and age were the most important risk factors associated with GFR ≤ 60 mL/min. Most of patients had uncontrolled glucose levels and 45.1% patients with albuminuria were not receiving any drug with anti-proteinuric effects. **Conclusions.** Fasting glucose levels was the most important risk factor associated with tubular dysfunction; non-albuminuric presentation of CKD defined as GFR < 60 mL/min was frequent in our population, so is necessary to implement different strategies for surveillance in patients with type 2 diabetes aiming to delay progression to CKD.

Key words. α1-microglobulin. Diabetic nephropathy. Albuminuria.

Enfermedad renal y disfunción tubular en sujetos con diabetes mellitus-2

RESUMEN

Introducción. *La microalbuminuria se ha considerado como un marcador temprano de daño renal en pacientes con diabetes mellitus 2; sin embargo, aún no se ha determinado si estudiar marcadores de lesión tubular permita también identificar pacientes en riesgo de desarrollar enfermedad renal crónica.* ***Objetivo.*** *Evaluar marcadores de lesión tubular y las características de la enfermedad renal en una muestra de pacientes con diabetes mellitus 2.* ***Material y métodos.*** *Muestra aleatoria de pacientes con DM 2 tratados en centros de salud comunitarios del municipio de Querétaro. Se realizó un cuestionario, mediciones antropométricas y de presión arterial, así como determinaciones bioquímicas de laboratorio y determinación de albúmina y α1M en muestra de orina al azar.* ***Resultados.*** *Se incluyeron 95 pacientes, 45.2% tuvo excreción urinaria de α1M ≥ 10 μg/gCr, 23.1% micro-albuminuria, 9.6% macro-albuminuria y 27.2% tuvo TFG ≤ 60 mL/min. El valor de glucosa en ayuno fue el factor de riesgo más importante asociado a mayor excreción de α1M. La HbA1c ≥ 8% y la edad fueron los más importantes factores de riesgo asociados a TFG ≤ 60mL/min. La mayoría de los pacientes presentaba descontrol crónico de la glucosa y 45.1% de pacientes con albuminuria no se encontraban recibiendo ningún tratamiento anti-proteinúrico.* ***Conclusiones.*** *El nivel de glucosa sérico fue el factor de riesgo más importante asociado a mayor excreción de α1M, la frecuencia de pacientes con TFG ≤ 60 mL/min sin albuminuria es elevada en nuestro medio. Es necesario implementar diferentes estrategias encaminadas al diagnóstico y tratamiento oportuno en pacientes con DM 2.*

Palabras clave. *α1-microglobulina. Nefropatía diabética. Albuminuria.*

INTRODUCTION

Diabetic nephropathy is one of the most important causes of chronic kidney disease (CKD) in Mexico;[1] the ability to predict which patients with diabetes will progress to CKD would permit targeted treatment with more aggressive therapies at an earlier stage and enable new therapies to be

tested. Micro-albuminuria is considered an early marker of glomerular injury in patients with diabetes but it has yet to be determined whether testing for markers of tubular injury can also identify people who are at risk of progressive renal disease.[2]

The low molecular weight protein (LMWP) α1-microglobulin (α1M) is a glycoprotein with a molecular weight of 26-31 κDa, the unbound form is filtered freely through the renal glomerular basement membrane and reabsorbed by the proximal tubular cells, hence, any proximal tubular cell dysfunction results in increased quantities of α1M in the urine;[3] α1M has been used as marker of tubular dysfunction in patients with type 2 diabetes mellitus[4] and other nephropathies.[5]

Table 1. Prevalence of tubular proteinuria, microalbuminuria, macroalbuminuria, and GFR < 60 mL/min/1.73 m^2 SC in subjects with T2DM.

	Prevalence, n (%)
α1M excretion (TP)	38/84 (45.2)
Non-albuminuric DN	16/26 (61.6)
Microalbuminuria	22/95 (23.1)
Macroalbuminuria	9/95 (9.4)
GFR < 60 mL/min/1.73 m^2 SC MDRD	26/95 (27.2)

α1M: α1-microglobulin. TP: tubular proteinuria. GFR: glomerular filtration rate. MDRD: modification diet in renal disease equation.

The presence of markers of tubular dysfunction in subjects with T2DM in México is currently unknown and the aim of the current study was to determine the urinary excretion of α1M in this population as well as to describe the clinical characteristics of diabetic nephropathy in this group of patients.

RESEARCH DESIGN AND METHODS

Study population and sample collection

The study was done with subjects attending communitarian clinics (Centros de Salud) located in Querétaro city. This study was approved by the Bioethics Committee of the University of Querétaro Medical School (FM-UAQ) and informed consent was obtained of each participant; the information was collected using a probabilistic sampling procedure with diabetic participants. We included subjects aged > 20 years old and those with uncontrolled hypertension, current urinary tract infection and pregnant women were excluded.

A questionnaire was used to obtain information on demographic and socioeconomic aspects, family health history, and personal medical history. Diabetes was defined as either fasting glucose level ≥ 126 mg/dL plus HbA1c ≥ 6.5% or use of oral hypoglycemic medication or insulin. Blood pressure measurements were obtained with an aneroid sphyg-

Table 2. Clinical and laboratory characteristics of participants with T2DM according to urinary α1M excretion.

	α1M < 10 (μg/gCr) n = 46	α1M > 10 (μg/gCr) n = 38	p
Age	48.7 ± 11.1	56.0 ± 12.0	0.005
Time from diagnosis	6.7 ± 6.8	7.2 ± 5.9	NS
Males (%)	12.7	37.8	0.006
Smokers (%)	25.5	35.1	NS
Hypertension (%)	44.6	37.8	NS
BMI	30.7 ± 5.7	28.3 ± 5.1	0.05
SBP (mmHg)	125 ± 19	129 ± 19	NS
Albuminuria (%)	28.2	34.2	NS
AUE (g/gCr)	0.5	2.7	0.07
Glucose (mg/dL)	167 ± 60	227 ± 78	0.0001
HbA1c (%)	8.7 ± 2.7	9.2 ± 2.7	NS
Urea (mg/dL)	34.6 ± 12.8	36.5 ± 10.8	NS
Creatinine (mg/dL)	0.92 ± 0.2	0.98 ± 0.2	NS
GFR (mL/min/1.73 m^2 SC)	76.2 ± 20	75.4 ± 19.2	NS
Uric acid (mg/dL)	4.7 ± 1.3	5.7 ± 2.5	0.02
Cholesterol (mg/dL)	228 ± 54	224 ± 50	NS
Triglycerides (mg/dL)	289 ± 234	388 ± 272	0.006

α1M: α1-microglobulin. SBP: systolic blood pressure. AUE: albumin urinary excretion. GFR: glomerular filtration rate.

Table 3. Risk factors associated with α1M urinary excretion > 10 μg/grCr.

	OR	IC 95	p
Glucose > 200	4.3	1.7-11.1	0.001
TGL > 250 mg/dL	4.2	1.5-11.6	0.005
Male	3.8	1.3-11.4	0.01
Age > 50 years	2.8	1.1-6.9	0.02
HbA1c > 8%	2.0	1.02-4.0	0.05
Albuminuria	1.5	0.6-3.7	0.48

TGL: triglycerides.

momanometer after 5 min resting in sitting position; hypertension was defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or current use of antihypertensive medication.

Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared.

Laboratory and measures of kidney function

Blood samples were taken after ≥ 8 h fasting during the same visit; the analytical measurements of the biochemical variables were done at the core laboratory of the FM-UAQ by standard technique. GFR was estimated using the modification of diet in renal disease equation (MDRD).

Spot urine samples for albumin and α1-microglobulin analysis were collected in sterile -plastic containers, and stored frozen at -80 °C until their analysis. Albumin and a1M were creatinine adjusted. The α1M determinations were done with the Alpco Immunoassays Kit ELISA[33] according to the manufacturer instructions. Albuminuria was considered abnormal with a ratio > 0.3 g/gCr and those patients with a ratio < 0.3 g/gCr were considered as non-albuminuric; tubular proteinuria was defined as a ratio α1M/creatinine > 10 μg/gCr.

Statistical analysis

For descriptive statistics mean ± standard deviation, median or percentages as appropriate were calculated. Comparisons between groups for continuous variables were done by t-Student analysis and nominal variables were compared by χ^2. For variables correlated with α1M and GFR levels a multiple linear regression analysis and contingency tables with Odds Ratio were used. A p value < 0.05 was considered as statistically significant. The data were analyzed using the SPSS 16.0 program.

Table 4. Comparison of the clinical characteristics of population with and without GFR < 60 mL/min.

	GFR < 60, n = 26	GFR > 60, n = 69	p
Age (yrs)	58.1 ± 10	50.5 ± 12.5	0.007
Time from diagnosis (yrs)	9.0 ± 8.5	7.1 ± 6.7	0.1
Hypertension (%)	52.0	36.2	0.05
TAS (mmHg)	135 ± 25	125 ± 18	0.03
α1M ≥ 10 μg/g (%)	40	45.1	0.3
Albuminuria (%)	38.4	30.4	0.10
HbA1c (%)	10.6 ± 2.2	8.3 ± 2.7	0.001
HbA1c ≥ 8 (%)	84.2	47.4	0.004

GFR (mL/min/1.73 m^2 SC): glomerular filtration rate. TAS: systolic blood pressure. α1M: α1-microglobulin.

Table 5. Risk factors associated with GFR < 60 mL/mL.

	OR	IC 95	p
HbA1c > 8%	5.9	1.5-22	0.007
Age > 50 years	2.8	1.02-7.5	0.05
Time from diagnosis > 10	2.0	0.7-5.2	0.19
Hypertension	1.7	0.7-4.3	0.2
Albuminuria	1.4	0.5-3.6	0.5
α1M > 10 μg/g	1.0	0.5-3.7	0.8

α1M: α1-microglobulin.

RESULTS

A total of 95 subjects with T2DM were included; the mean age was 52.6 ± 12.5 yrs and 76.9% of participants were females, the mean BMI was 29.9 ± 5.4, and most of patients were taking an oral hypoglycemic agent: 68.3% with regimens containing glyburide/metformin and 21.1% metformin alone. The median time from diagnosis was 7.6 ± 7.2 years, and the prevalence of tubular proteinuria, non-albuminuric diabetic nephropathy, microalbuminuria, macroalbuminuria, and GFR ≤ 60 mL/minare shown in table 1.

In 84 subjects we have determination for α1M, of them 38 (45.2%) had α1M > 10 μg/gCr; the median in males [16.8 IC 95 (5.0-31.5)] was significantly higher than in females [6.3 IC 95 (2.6-17.4)]. Subjects with α1M ≥ 10 μg/gCr were older (56 ± 11 *vs.* 48 ± 11 years, p = 0.002), and had higher fasting glucose levels (227 ± 78 *vs.* 166 ± 60 mg/dL, p = 0.00); the percentage of subjects with albuminuria was similar comparing α1M excretion< 10 μg *vs.* > 10 μg (28.2 *vs.* 34.2% p = NS), and other clinical characteristics in both groups are shown in table 2.

In multivariate analysis the most important risk factors associated with higher α1M excretion were fasting serum glucose, gender and age > 50 years old (Table 3). There was a significant correlation between fasting glucose levels with α1M excretion (r = 0.27, p = 0.01). Subjects ≥ 50 years with abnormal α1M excretion had less GFR when was compared with those with normal values of α1M (65.7 ± 13 *vs.* 72.4 ± 14 mL/min, p = 0.04).

Urinary albumin excretion (UAE) was determined in 95 subjects, 64 (67.3%) without albuminuria (normo-albuminuria), 22 (23.1%) micro-albuminuria, and 9 (9.6%) macro-albuminuria; 14 (45.1%) patients with albuminuria were not receiving any drug with antiproteinuric effects. The most important factors associated with albuminuria were age, time from diagnosis and systolic blood pressure; participants with albuminuria have a higher α1M excretion (35 ± 45 *vs.* 17 ± 30 p = 0.03), and there was no difference in GFR between non-albuminuric and albuminuric subjects.

Subjects with HbA1c > 7% had significantly higher UAE (4.2 ± 17 *vs.* 0.4 ± 1.1 p = 0.04) and those subjects with hypertension have higher UAE compared with normotensive subjects.

In this study, 26 (27.2%) patients had GFR < 60 mL/min, 61.6% of them without albuminuria (Table 4), the most important risk factors associated with GFR ≤ 60 mL/min in this population of diabetic patients were HbA1c and age (Table 5).

Fifty nine patients were not taking drugs for high blood pressure, however we detected 8 subjects (13.5%) in this group with blood pressure > 140/90 mmHg, and 7 (11.8%) with systolic blood pressure > 140 mmHg.

DISCUSSION

The use of markers of tubular dysfunction may confer additional diagnostic and prognostic information in patients with diabetic nephropathy. This is the first study on urinary α1-microglobulin excretion as marker of tubular dysfunction in type 2 diabetic subjects in México. Fasting hyperglycemia and male gender were the most important risk factors associated with higher urinary α1M excretion and we showed that tubular proteinuria as well as non-albuminuric CKD in T2DM subjects was highly prevalent in this group of patients; however, is unknown if these findings associated with tubular dysfunction can lead to GFR decline in this population.

The finding that hyperglycemia is associated with higher excretion of α1M is of interest because hyperglycemia triggers the generation of free radicals and promote apoptosis in tubular cells,[6] this mechanisms are associated in the pathogenesis of diabetic nephropathy; previous studies have demonstrated that acute hyperglycemia is an independent risk factor for acute tubular necrosis in patients with established diabetic nephropathy and cardiac surgery.[7] Male gender has been considered as a risk factor associated with development of albuminuria[8] and according to this study also with development of tubular injury.

Hong, *et al.*,[4] found that higher α1M urinary excretion was related to duration, control of diabetes and albuminuria, and that in some patients (as we found in our study) one was present in the absence of the other. Lim, *et al.*,[9] found that in non-albuminuric diabetic patients α1M and zinc-α(2)-glycoprotein were the most abundant urinary proteins and Petrica, *et al.*,[10] showed that in some patients α1M excretion precedes the onset of albuminuria. Conway, *et al.*,[11] showed that tubular injury in people with T2DM may contribute to the decline in kidney function; but measuring the urinary concentration of KIM-1 (kidney injury molecule-1) and Gpnmb (glycoprotein non-metastatic melanoma B) does not confer additional prognostic information.

Bhavsar, *et al.*,[12] in 286 subjects with high risk to develop CKD (18.2% with T2DM) found that higher NGAL (neutrophil gelatinase-associated lipocalin), but not KIM-1 levels were associated with

incident CKD stage 3, however, another study[13] found that higher levels of urinary KIM-1, but not NGAL, may predict future CKD risk independent of the presence of albuminuria. Other tubular markers used to detect early CKD progression are Tamm-Horsfall protein, haptoglobin, L-FABP (Liver-fatty acid binding protein), tenascin and urinary CD14 mononuclear cells.[14]

There are no established treatments for tubular dysfunction in T2DM, treatment with IECAs/ARBs is ineffective but pioglitazone[15] and pentoxyfilline[16] have shown some positive benefits. The role of lipid control on progression of renal injury is a controversial topic that requires further studies in our population;[17] however, Perkins, *et al.,* found that triglycerides levels < 145 mg/dl was a predictor of regression to normoalbuminuria.[18]

Few studies in México have evaluated the renal characteristics of patients with T2DM, Cueto-Manzano, *et al.,*[19] found in 756 patients that 71% had no albuminuria,19% had microalbuminuria, and 10% had macroalbuminuria. Leza-Torres, *et al.,*[20] found microalbuminuria in 85.7% (n = 301) T2DM patients with a mean GFR of 83.3 ± 32 mL/min however, the methodology in the measurements for albumin excretion was not described and this makes difficult to explain the high prevalence found in this study. López-Arce, *et al.*,[21] in 86 normotensive T2DM subjects, found microalbuminuria in 19 (22%) and this finding was related with time from diagnosis and higher HbA1c.

Many studies have shown that development of albuminuria in T2DM patients is a risk factor for progression to CKD, cardiovascular disease and mortality but results are still controversial about the prognostic value of tubular markers in these patients.[22]

Some recent reports do not support the classical notion that increased albumin excretion inexorably precedes GFR decline in T2DM diabetic patients. According to the UKPDS (United Kingdom Prospective Diabetes Study) the percentage of patients with decreased renal function without albuminuria was 11%.[23] The study NHANES III (National Health and Nutrition Examination Survey) reports that 13% of T2DM subjects had GFR < 60 mL/min, and 36% of them had no albuminuria.[24] In our sample, 16/26 (61.6%) patients with GFR < 60 mL/mL were normoalbuminuric, this is worrisome because measurement of microalbuminuria is the standard test to detect diabetic nephropathy in earlier stages, and this means that current strategies for screening and treatment of renal disease in patients with T2DM that implicitly assume that the underlying disease process is uniformly associated with albuminuria must change.

Decrease in GFR in subjects with type 2 diabetes have been associated with increases in carotid intimal-medial thickness, carotid stiffness, and increases in the intra-renal arterial resistance index.[25] This has led to the suggestion that the decline in GFR in patients with non-albuminuric renal disease is in part due to generalized arteriosclerosis.[26] However, is likely that in our population the important grade and chronicity of uncontrolled glucose have a role in early development of low GFR.

A lack of optimal metabolic control in our patients is evident, similar findings have been confirmed in other studies done in México and is likely that this situation play a role in the high prevalence of renal disease in type 2 diabetic patients.[27]

All subjects were seen in communitarian centers and had one monthly visit to the family doctor, so 26.9% subjects with hypertension were not taking medication or had uncontrolled high blood pressure, also none of our patients had at least one visit to the ophthalmologist to evaluate retinopathy, this implies the necessity to improve the educational programs for primary care physicians in the diagnosis and treatment of diabetes and hypertension.

There are some limitations in this study like the small sample of patients, the measurement of just one marker of tubular injury, and the transversal design of the study with no follow-up of the patients.

In conclusion, α1M is a marker of tubular dysfunction in diabetic patients and fasting hyperglycemia was the most important risk factor associated with α1M urinary excretion, so we hypothesize that acute hyperglycemia may be associated with direct and clinical tubule-interstitial damage. Many patients with T2DM develop GFR < 60 mL/min with no albumin excretion; in this population α1M excretion was not associated with GFR < 60 mL/min, but a closer follow-up of this population is necessary.

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