

ALBUMINURIA AND GLOMERULAR FILTRATION RATE IN INDIVIDUALS WITH TYPE 1 DIABETES MELLITUS: CONTRIBUTION OF METABOLIC SYNDROME

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ABSTRACT

Background: The development of metabolic syndrome has been described in patients with type 1 diabetes mellitus as the disease progresses over time. The purpose of this study is to assess the relationship between metabolic syndrome, albuminuria, and glomerular filtration rate, as well as to determine the prevalence of metabolic syndrome, in a group of Mexican patients with type 1 diabetes mellitus. **Methods:** We conducted a cross-sectional study that included patients with type 1 diabetes mellitus who were diagnosed over 10 years ago and who are seen at the Diabetes Intensive Control Clinic of the Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran in Mexico City. The presence of metabolic syndrome was determined by using the National Cholesterol Education Program-Adult Treatment Panel III (ATP III) criteria. **Results.** A total of 81 individuals were studied. The prevalence of metabolic syndrome was 18.5% (n = 15). A higher albuminuria was found in subjects with metabolic syndrome (34.9 mg/24 hours; 8.3-169.3) than in those without metabolic syndrome (9.0 mg/24 hours; 5.0-27.0; p = 0.02). Glomerular filtration rate was lower in patients with metabolic syndrome (95.3 ml/minute; [64.9-107.2] vs. 110.2 ml/minute [88.1-120.3]; p = 0.04). After classifying the population according to the number of metabolic syndrome criteria, a progressive increase in albuminuria and a progressive decrease in glomerular filtration rate were found with each additional metabolic syndrome criterion (p = 0.008 and p = 0.032, respectively). After adjusting for age, time from diagnosis, systolic blood pressure, triglycerides, HDL-cholesterol, and treatment with angiotensin receptor blockers or angiotensin converting enzyme inhibitors, we found that age, time from diagnosis, triglycerides, and HDL-cholesterol were independent factors associated with glomerular filtration rate ($R^2 = 0.286$; p < 0.001). **Conclusions:** Metabolic syndrome was associated with a higher albuminuria and a reduction in glomerular filtration rate in patients with type 1 diabetes mellitus. Metabolic syndrome was present in 18.5% of this group of Mexican individuals with type 1 diabetes mellitus. (REV INVES CLIN. 2015;67:266-72)

Key words: Metabolic syndrome. Albuminuria. Glomerular filtration rate. Type 1 diabetes mellitus.

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INTRODUCTION

Metabolic syndrome (MS) is characterized by the clustering of cardiovascular risk factors. These include: central obesity, impaired glucose metabolism, hypertension, and dyslipidemia¹⁻⁴. In the general population and patients with type 2 diabetes (T2DM), MS is associated with adverse outcomes such as coronary artery disease and kidney disease^{5,6}.

Type 1 diabetes mellitus (T1DM) is caused by the immune-mediated destruction of pancreatic β cells. In order to obtain a good glycemic control and to reduce chronic complications, intensive treatment is required. This intensive treatment consists of the administration of multiple insulin doses or a continuous insulin infusion. Weight gain is an adverse effect of the intensive insulin regimen⁷. Some patients with T1DM are characterized by having a higher body mass index (BMI), greater insulin requirements, and they usually have a family history of T2DM. This profile is also associated with a worse metabolic control, and may confer a greater risk for developing cardiovascular disease. This phenomenon has been called “double diabetes”^{8,9}.

Central obesity is related to insulin resistance and MS. At present, these entities are more frequently found in patients with T1DM^{7,10,11}. The presence of T1DM and MS confers an increased risk not only for macrovascular disease, but also for microvascular complications, including diabetic nephropathy¹²⁻¹⁵.

In a follow-up analysis of the Diabetes Control and Complications Trial-Epidemiology of Diabetes Interventions and Complications (DCCT-EDIC) study¹⁴, the prevalence of MS increased over time in both conventional and intensive treatment groups. The prevalence of MS was 27%. Insulin resistance (estimated by glucose disposal rate) at baseline was related to an increased risk of developing both micro- and macrovascular complications. However, MS was not related to complications or to a worse glycemic control¹⁴. In the Finnish Diabetic Nephropathy Study (FinnDiane), the prevalence of MS in men and women with T1DM was 38 and 40%, respectively¹⁵. It increased with age, and was related to nephropathy and a worse glycemic control. Finally, in a prospective analysis of the Pittsburgh Epidemiology of Diabetes Complications cohort, the prevalence of MS was 21% and MS was a predictor of major complications^{8,16}.

The aims of this study are to evaluate the association of MS with albuminuria (ALB) and glomerular filtration rate (GFR), as well as to estimate the prevalence of MS in a group of Mexican patients with T1DM.

MATERIALS AND METHODS

Study description

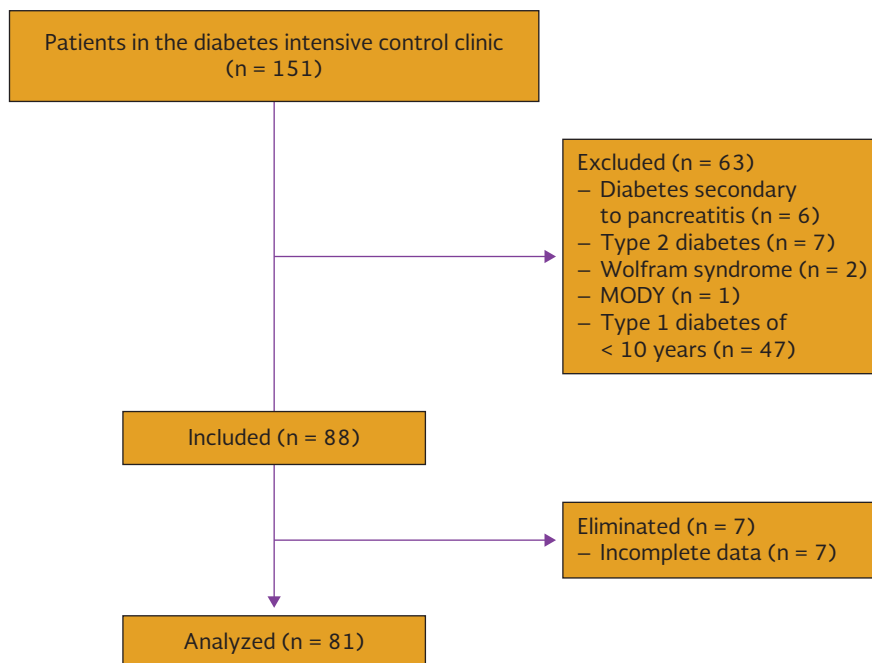
A cross-sectional study was conducted at the Diabetes Intensive Control Clinic of the Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran in Mexico City. Patients were recruited from January to August 2013, if they met the following inclusion criteria: T1DM with positive β cell antibodies, ≥ 10 years of evolution, and ≥ 18 years of age. Exclusion criteria were nephropathy secondary to rheumatologic diseases, and patients taking nephrotoxic medications on a long-term basis. Patients were not included in the study if their data was incomplete. Figure 1 shows the flow diagram of the patient selection process.

In all patients, height, weight, systolic blood pressure (SBP), and diastolic blood pressure (DBP) were measured; laboratory analyses included glucose, creatinine, glycated hemoglobin (HbA1c), total cholesterol, triglycerides, low-density lipoprotein (LDL)-cholesterol, high-density lipoprotein (HDL)-cholesterol, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and uric acid. Albuminuria (ALB) was measured using a 24-hour urine collection. The basal insulin dose, which is defined as the amount of constant long-acting insulin that is needed to maintain stable blood glucose levels in between meals and overnight, was also recorded. Body mass index was calculated as the weight in kilograms divided by height in meters squared (kg/m^2). The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula¹⁷ was used to estimate GFR.

Identification of metabolic syndrome

Individuals were divided into two groups, with and without MS. The Adult Treatment Panel III (ATP III) criteria were used¹⁸ to define MS. Body mass index was used as a surrogate of waist circumference, which has been previously validated^{18,19}. Considering that all patients had one MS criteria due to the presence of T1DM, MS was defined by the presence of at least two of the following additional criteria: hypertriglyceridemia

Figure 1. Flow diagram of the patient selection process.



≥ 150 mg/dl or use of medications, HDL-cholesterol < 40 mg/dl in men or < 50 mg/dl in women, SBP ≥ 130 and/or DBP ≥ 85 mmHg or use of anti-hypertensive medications, or BMI ≥ 30 kg/m².

Diabetic nephropathy

The Kidney Disease Improving Global Outcomes (KDIGO) guidelines define chronic kidney disease as abnormalities of the kidney structure or function that have been present for 43 months and that have health implications²⁰. Chronic kidney disease is classified according to the GFR in the following categories: G1, normal or high GFR (≥ 90 ml/min); G2, mildly decreased (60–89 ml/min); G3, mildly to moderately decreased (45–59 ml/min); G3b, moderately to severely decreased (30–44 ml/min); G4, severely decreased (15–29 ml/min); and G5, < 15 ml/min. It also includes a classification for albuminuria in the following categories: A1, normal to mildly increased (< 30 mg/g); A2, moderately increased (30–300 mg/g); and A3, severely increased (> 300 mg/g).

Statistical analysis

Normally distributed data, evaluated using Shapiro-Wilk's test, are expressed as means and standard

deviation (SD), whereas variables with a non-normal distribution are reported as medians and interquartile range (IQR). Chi Square, Student's *t*, or Mann-Whitney *U* tests were used to compare the groups. Non-normal distributed variables were log transformed to approximate normality before the subsequent analyses. One-way ANOVA was used to compare ALB and GFR in the population according to the MS criteria number. Univariate correlations were estimated with Pearson coefficients, and a linear regression analysis was performed to determine the independent variables associated with GFR. This model included as independent variables age, time from diagnosis, SBP, triglycerides, HDL-cholesterol, and treatment with angiotensin receptor blockers (ARB) or angiotensin converting enzyme (ACE) inhibitors. Analyses were performed using the SPSS Statistics 19.0 software package (SPSS, Chicago, IL). A *p* value < 0.05 was considered statistically significant.

RESULTS

A total of 81 subjects with T1DM were studied. The mean age was 36.6 ± 11.3 years, 46% were women, diagnosis of T1DM was made 19.7 ± 8.4 years ago, BMI 24 ± 2.8 kg/m², and HbA1c $8.1 \pm 1.6\%$. The

Table 1. Characteristics of the study population according to the presence of metabolic syndrome

	Without metabolic syndrome (n = 66)	With metabolic syndrome (n = 15)	p
Men/women, number (%)	29 (44)/37 (56)	6 (40)/9 (60)	0.32
Age, years	36.5 ± 12.1	36.5 ± 7.6	0.72
Time from diagnosis, years	19.7 ± 8.7	19.8 ± 7.7	0.87
Glucose, mg/dl	158.3 ± 84.6	188.0 ± 93.5	0.23
Creatinine, mg/dl	0.93 ± 0.72	0.98 ± 0.26	0.25
Uric acid, mg/dl	5.6 ± 2.7	5.2 ± 2.2	0.52
ALT, U/l	20.1 ± 12.3	25.9 ± 12.3	0.05
AST, U/l	21.1 ± 13.5	23.2 ± 5.6	0.22
HbA1c, %	8.0 ± 1.6	8.8 ± 1.8	0.06
LDL-cholesterol, mg/dl	96.2 ± 25.8	90.6 ± 30.4	0.43

Variables expressed as mean ± standard deviation, median (interquartile range), or n (%). ALT: alanine aminotransferase; AST: aspartate aminotransferase; HbA1c: glycated hemoglobin; LDL: low-density lipoprotein.

Table 2. Metabolic syndrome components in the study population

	Without metabolic syndrome (n = 66)	With metabolic syndrome (n = 15)	p
BMI, kg/m ²	23.7 ± 2.6	25.3 ± 3.3	0.05
SBP, mmHg	112.9 ± 12.9	122 ± 14.2	0.02
DBP, mmHg	71.5 ± 8.5	76.6 ± 12.9	0.10
Triglycerides, mg/dl	74 (62-106)	162 (139-191)	< 0.001
HDL-cholesterol, mg/dl	55.2 ± 11.6	41.2 ± 6.8	< 0.001

Variables expressed as mean ± standard deviation or median (interquartile range).

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; HDL: high-density lipoprotein.

overall prevalence of MS in the studied population was 18.5% (n = 15).

Table 1 shows the characteristics of the study population with and without MS. The groups had no difference in age (p = 0.72) or duration of T1DM (p = 0.87). The individual elements of MS in the study population are shown in table 2. The BMI (p = 0.05), SBP (p = 0.02), ALT (p = 0.05), and triglycerides (p < 0.001) were greater in the group with MS, and HDL-cholesterol (p < 0.001) was lower, as expected.

A larger percentage of individuals in the group with MS received antihyperlipidemic agents, ARBs or ACE inhibitors, and acetylsalicylic acid (ASA). The use of metformin and basal insulin dose were similar in both groups. The overall adherence to treatment, reported by the participants, was > 80%. These data are shown in table 3.

Metabolic syndrome, albuminuria, and glomerular filtration rate

Albuminuria was higher in subjects with MS compared to those without MS (34.9 [8.3-169.3] vs. 9.0 [5.0-27.0] mg/24 hour; p = 0.01) (Fig. 2). In addition, GFR was significantly lower in the group with MS (95.3 [64.9-107.2] vs. 110.2 [88.1-120.3] ml/min; p = 0.04) (Fig. 3). When stratifying the population by the number of MS criteria present, a progressive increase in ALB and a progressive decrease in GFR were found with the addition of each MS criterion (p = 0.008 and p = 0.032, respectively).

When categorizing GFR and albuminuria according to the KDIGO classification, a higher number of patients with MS were in stages A2 and A3 for albuminuria compared with the group without MS (53.4 vs. 23.8%, respectively; p = 0.016). No difference was observed

Table 3. Treatment received by the study population

	Without metabolic syndrome (n = 66)	With metabolic syndrome (n = 15)	p
Antihyperlipidemic drugs, n (%)	26 (40)	10 (66.7)	0.057
ARB or ACE inhibitors, n (%)	21 (32.3)	9 (60)	0.046
ASA, n (%)	12 (18.5)	6 (40)	0.077
Basal insulin dose, U/kg	0.42 ± 0.19	0.50 ± 0.19	0.19
Metformin use, number (%)	30 (46.9)	7 (46.7)	0.60

Variables expressed as n (%) or mean ± standard deviation.

ARB: angiotensin receptor blocker; ACE: angiotensin converting enzyme; ASA: acetylsalicylic acid.

when establishing the GFR stage in patients with and without MS ($p = 0.306$). However, the majority (73.4%) of the individuals without MS were in stage G1 and a significant proportion (40%) of individuals with MS were in categories G2 and G3.

Independent contribution of metabolic syndrome to glomerular filtration rate

In the univariate analyses, a significant correlation between GFR and the following parameters was found: age ($r = -0.389$), time from diagnosis ($r = -0.383$), SBP ($r = -0.243$), triglycerides ($r = -0.237$), and HDL-cholesterol ($r = -0.220$). These factors, in addition to the treatment with ARBs or ACE inhibitors, were included as independent variables in the multiple linear regression model. The dependent variable was GFR. Age, time of diagnosis, triglycerides, and HDL-cholesterol remained significantly related to GFR ($R^2 = 0.286$; $p < 0.001$).

In contrast, in univariate analyses, albuminuria was only associated with glycated hemoglobin concentration ($r = 0.315$). Therefore, a multiple lineal regression model could not be performed.

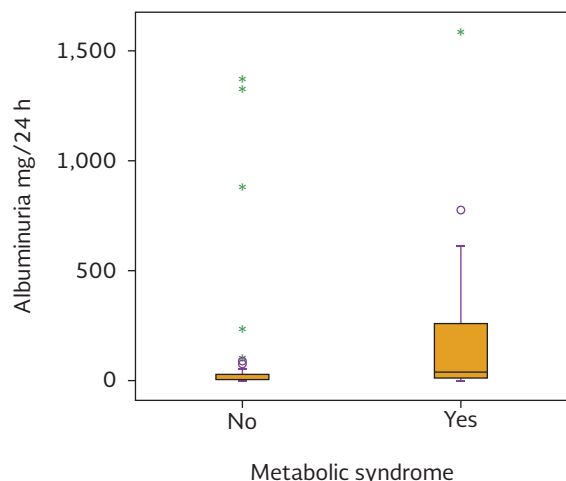
DISCUSSION

This study demonstrated that the presence of MS in individuals with T1DM is related to a higher ALB and lower GFR. A progressive increase in ALB and a decrease in GFR could be observed when MS criteria were added. Furthermore, the individual MS elements had a significant and independent association with GFR. The prevalence of MS in this population of T1DM patients was 18.5%.

The relationship between MS and the risk of chronic kidney disease and/or ALB has been previously described²¹. In a study performed in Australia, individuals with T1DM and MS required significantly higher insulin doses, had longer duration of diabetes, and had more macrovascular and microvascular complications²². Similarly, the FinnDiane study found that MS in patients with T1DM was related to a worse glycemic control and diabetic nephropathy¹⁵. In the Pittsburgh Epidemiology of Diabetes Complications Study, MS predicted major complications in T1DM¹⁶. Finally, in the Metascreen survey, MS was an independent indicator of the presence of nephropathy in T1DM²³. Our study provides confirmatory data in a Mexican population with T1DM. In contrast, in a subsequent analysis of the DCCT study, the presence of MS was a poor predictor of macro and microvascular complications. Likewise, the Fremantle Diabetes Study concluded that the presence of MS has a limited prognostic value for cardiovascular death in patients with T1DM¹³.

The effect of the addition of MS elements on ALB levels may be explained by the interrelationship of these elements linked by a common factor that is insulin resistance²⁴. In previous studies, including the DCCT, higher insulin resistance at baseline was related to increased subsequent risk of both micro- and macrovascular complications^{14,25}. The DCCT has proven that intensive glycemic control in patients with T1DM is strongly related to significant clinical benefits¹². The adverse effects of trying to achieve a better glycemic control by increasing insulin doses include a greater risk of hypoglycemia, development of obesity, and MS. However, the benefits of improved glycemic control appear to outweigh the risks related to the development of the MS⁹. In fact, in the DCCT study, even though the intensive treatment was related to a

Figure 2. Box plot graph showing albuminuria according to the presence of metabolic syndrome, $p = 0.02$.

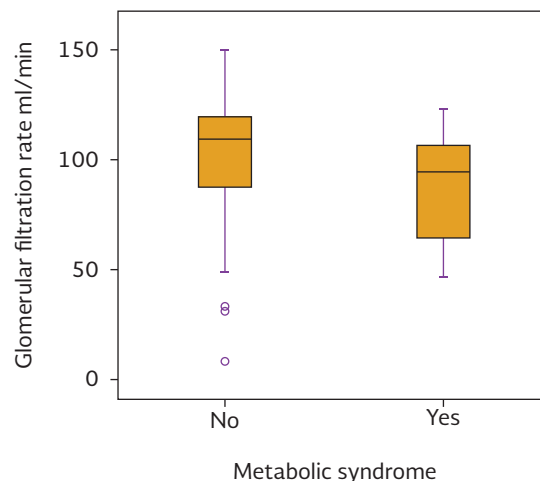


higher subsequent prevalence of MS, subjects with MS appeared to have a better glycemic control¹⁴. In this study, individuals with MS had a worse glycemic control. Differences in the amount of basal insulin used between the groups were not found. A high proportion of patients were taking metformin as an adjunct therapy to reduce insulin requirements and weight gain²⁶. However, the proportion of patients using metformin in the groups with and without MS was similar.

The prevalence of MS found in this study is lower compared to previous reports, including the DCCT (22%) and FinnDiane (39%) studies. An important factor to take into consideration is that the individuals included in this report were selected from the Diabetes Intensive Control Clinic, which is composed of patients who attend the clinic at least once a month, perform daily self-monitoring of glucose, and have a good adherence to treatment. In addition, the population in this clinic is young. These factors may have decreased the prevalence of MS and diabetes complications in this study.

Limitations of this report include the small and highly selected sample. As mentioned before, insulin resistance may have an independent relationship with diabetic nephropathy, and quantification could not be done. In addition, glomerular filtration rate was not estimated by measuring creatinine in a 24-hour urine collection. However, the CKD-EPI equation that has been previously validated¹⁷ was used. Due to the cross-sectional

Figure 3. Box plot graph showing glomerular filtration rate estimated by the Chronic Kidney Disease Epidemiology Collaboration equation according to the presence of metabolic syndrome, $p = 0.04$.



design, we did not analyze the changes of variables associated with the development of nephropathy such as glycated hemoglobin, weight, hypertension, and dyslipidemia, among others. Finally, causality between the MS and diabetic nephropathy cannot be established. Nevertheless, a slower renal function decline in T2DM patients when the elements of MS were adequately treated has been previously described²⁷.

In conclusion, the presence of MS is related to ALB and GFR in individuals with T1DM. A higher ALB level and lower GFR in individuals with MS was found, and there was a significant deterioration of both parameters when elements of MS were added.

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