ARTIGO ORIGINAL

HYPERTENSION IS THE MAIN DETERMINANT BEHIND THE ASSOCIATION BETWEEN METABOLIC SYNDROME AND CHRONIC KIDNEY DISEASE IN SUBJECTS WITH DIFFERENT DEGREES OF GLUCOSE TOLERANCE

A HIPERTENSÃO É O PRINCIPAL DETERMINANTE DA ASSOCIAÇÃO ENTRE SÍNDROME METABÓLICA E DOENÇA RENAL CRÔNICA EM INDIVÍDUOS COM DIFERENTES GRAUS DE TOLERÂNCIA À GLICOSE

Alessandra Locatelli Smith, Bárbara Gastal Borges Fortes, André Dias Americo, Vanessa Piccoli, Amanda Fabbrin, Sheila Piccoli Garcia, Brunna Jaeger, Juliana Zampieri, Ennio Rocha, Alice Xavier, Gabriele Ghisleni, Luis Henrique Canani, Fernando Gerchman

ABSTRACT

Background: Chronic kidney disease (CKD) is a significant public health problem. It is still controversial if the metabolic syndrome (MS) is associated with CKD.

Methods: Cross-sectional study of individuals at high risk of developing diabetes at the endocrine outpatient clinic of Hospital de Clínicas de Porto Alegre. Fasting and 2h-plasma glucose levels, A1c, insulin, cholesterol, triglycerides, creatinine, and urinary albumin excretion were measured. MS was defined as the presence of three out of five of the following factors: hypertension, low HDL-cholesterol, high triglyceride levels, elevated plasma glucose, and high waist circumference. Glomerular filtration rate (GFR) was estimated by the Modified Diet in Renal Disease (MDRD) equation and insulin resistance was measure using the Homeostasis Model of Assessment - Insulin Resistance (HOMA-IR). Correlation analyses were performed between each MS components and the GFR.

Results: CKD was present in 20.9% of the subjects. GFR was lower in subjects with MS compared with those without MS (P =0.019). Estimated GFR decreased with the increasing number of MS criteria (mean ± SD; zero or one criterion 103.09±9.5 vs. two criteria 99.14±21.2 vs. three criteria 90.9±21.1 vs. four criteria 91.0±19.4 vs. five criteria 80.9±23.5 mL/min per 1.73m^2; P =0.053). Only systolic arterial blood pressure was related to eGFR (r = 0.280; P =0.003).

Discussion: According to our data, the previously described association between MS and decreased renal function was confirmed, mostly determined by the hypertension criterion.

Conclusion: These data suggest that the relationship between MS and CKD is driven mostly by abnormalities in blood pressure homeostasis.

Keywords: Diabetes; metabolic syndrome; chronic kidney disease

RESUMO

Introdução: A Doença Renal Crônica (DRC) é um problema de saúde pública. Ainda é controversa a existência de associação entre a presença de Síndrome Metabólica (SM) e DRC.

Métodos: Indivíduos com risco aumentado para o desenvolvimento de diabete melito acompanhados no ambulatório de Endocrinologia do Hospital de Clínicas de Porto Alegre foram analisados em um estudo transversal. Pacientes foram submetidos ao Teste de Tolerância Oral à Glicose, e hemoglobina glicada (A1c), insulina, colesterol, triglicerídeos, creatinina e excreção urinária de albumina foram medidos. A presença de SM era baseada na presença de três entre os cinco critérios a seguir: hipertensão, níveis séricos de colesterol HDL diminuídos, níveis aumentados de triglicerídeos, hiperglicemia e circunferência abdominal aumentada. A taxa de filtração glomerular (TFG) foi calculada pela equação do *Modified Diet in Renal Disease* (MDRD) e a resistência insulínica, pelo *Homeostasis Model of Assessment – Insulin Resistance* (HOMA-IR). Análises de correlação foram feitas entre cada componente da SM e a TFG.

Resultados: DRC esteve presente em 20,9% dos indivíduos. Níveis diminuídos de TFG foram observados em pacientes com SM comparados com aqueles sem SM (P=0,019). TFG diminuiu com o aumento no número de critérios para SM (média±DP; 0 e 1 critério 103,09±9,5; vs. 2 critérios 99,14±21,2; vs. 3 critérios 90,9±21,1; vs. 4 critérios 91,0±19,4; vs. 5 critérios 80,9±23,3 ml/min; P=0,053). Apenas pressão arterial sistólica mostrou-se relacionada com a TFG (r=0,280; P=0,003).

Discussão: Nosso trabalho confirmou a associação entre a presença de Síndrome Metabólica e TFG diminuída descrita previamente por outros estudos, tendo, neste presente estudo, a hipertensão como o principal determinante desta relação.

Conclusão: Nossos achados sugerem que a relação existente entre a presença de SM e o desenvolvimento de DRC é determinada principalmente por anormalidades na homeostase pressórica.

Palavras-chave: Diabete melito; síndrome metabólica; doença renal crônica

Chronic kidney disease (CKD) is a significant public health problem in the United States, affecting 20 million adults (1). CKD causes not only renal failure and related complications, but it also has been associated with increased cardiovascular morbidity and mortality (1).

Metabolic syndrome (MS), which is characterized by abdominal obesity, hypertriglyceride-

mia, low HDL-cholesterol levels, high blood pressure, and hyperglycemia, is a common problem in the United States (2). People with MS are at high risk for cardiovascular disease, which is associated with CKD (3,4). However, whether MS is independently associated with CKD remains unknown (5,6).

Several studies have addressed this issue with contradictory results. In the 9-year prospective Atherosclerosis Risk in Communities study and in the Third National Health and Nutrition Examination Survey, central obesity and MS were associated with the development of CKD (3,7,8), whereas in a sample of young apparently healthy males studied by Tomaszewski et al, MS was associated with hyperfiltration (9).

Based on these contradictory results, a study involving a population with different aspects of MS provides a unique opportunity to understand the relationship between this problem and CKD. Therefore, the objective of the present study was to determine the relationship between MS, insulin resistance, and renal function in Brazilian subjects with different degrees of glucose tolerance, as well as to analyze if the relationship between MS and renal function is determined by the MS components.

METHODS

Subjects

The present study included patients seen at the endocrine and diabetes outpatient clinic of Hospital de Clínicas de Porto Alegre who were at high risk of developing diabetes according to the recommendations of the American Diabetes Association for screening of the disease. These individuals did not have previous history of diabetes.

For this particular analysis, subjects were excluded if they were being treated with medications known to affect glucose tolerance (e.g., glucocorticoids) or had a history of kidney disease (e.g., chronic glomerulonephritis). Drug treatment for hypertension was interrupted one week before the study procedures in those on anti-hypertensive therapy (N =55). The study was approved by the Institutional Review Board of Hospital de Clínicas de Porto Alegre, and all participants provided written informed consent.

Study procedures and assays

Height (cm) and weight (kg) were measured in barefoot subjects wearing light clothes and BMI as weight (kg)/height² (m) was calculated. Waist circumference was measured at the level of the umbilicus to the nearest tenth of a centimeter in men and at the natural waistline in women. While the participant was seated, blood pressure was measured in the right arm three times by auscultation, and the mean of the last two measurements was used to estimate systolic and diastolic arterial blood pressure. A standard 75 g oral glucose tolerance test (OGTT) was performed in the morning after a 12-hour overnight fast. Blood samples for measurements of glucose were collected prior to and 120 minutes after glucose oral ingestion. A baseline blood sample was also collected for triglycerides, total and HDL- cholesterol, A1c, insulin, and traceable creatinine measurements. Insulin resistance was assessed using the homeostasis model assessment (HOMA) (fasting insulin (μU/l) x fasting glucose (mmol/l)/22.5) (10).

Participants were instructed to collect a 24-hour urine sample and record the collection start and end times, with the end time being in the morning of the clinical visit. Urine was kept at low temperature (4°C) until brought to the clinical visit. Subjects avoided intense physical activity during the collection period and urinary collection was postponed in case of fever, urinary tract infection, or menstruation.

Plasma glucose was measured using the hexokinase method; cholesterol and triglycerides were determined by means of an enzymatic method; creatinine was defined by Jaffé reaction (Advia 1800; Siemens Healthcare Diagnostics, Tarrytown, NY); insulin by a chemiluminescent method (Advia Centaur; Siemens Healthcare Diagnostics); and A1c by the high performance liquid chromatography (HPLC) method (Tosoh Plus HbA1c; Tosoh Corporation, Tokyo, Japan).

Classification of metabolic syndrome

Based on the Joint Scientific Statement of different medical societies, the MS was defined as the presence of three out of the five criteria described below: high waist circumference ($\geq$80 cm for women and $\geq$94 cm for men); elevated triglyceride levels ($\geq$150 mg/dL) or drug treatment for elevated triglycerides levels; reduced HDL-cholesterol (<40 mmHg for men and <50 mmHg for women) or treatment for reduced HDL-cholesterol levels; elevated blood pressure (systolic $\geq$130 mmHg or diastolic $\geq$85 mmHg) or antihypertensive drug treatment; and high plasma glucose (fasting plasma glucose >100 mg/dL and/or a 2h-plasma glucose level $\geq$140 mg/dL) (11).

Classification of glucose tolerance

Based on fasting and 2h-plasma glucose concentrations, subjects were categorized according to the American Diabetes Association criteria as having normal glucose tolerance (NGT: fasting plasma glucose [FPG] <100 mg/dL and 2h-plasma glucose level <140 mg/dL); impaired fasting glucose (IFG; FPG 100-125 mg/dL and 2h-plasma glucose level <140 mg/dL), or impaired glucose tolerance (IGT; FPG <100 mg/dL and 2h-plasma glucose level 140-199

mg/dL) and diabetes (FPG ≥126 mg/dl and/or 2-h PG ≥200 mg/dl) (12). Subjects with IFG and/or IGT were considered to have impaired glucose metabolism (IGM) and comprised 11 (10.2%) individuals with isolated IFG, 17 (15.7%) with isolated IGT, and 25 (23.1%) with both IFG and IGT.

Glomerular filtration estimation and chronic kidney disease classification

Glomerular filtration rate (GFR) was estimated by the abbreviated Modified Diet in Renal Disease (MDRD) equation (mL/min per 1.73 m^2 of body surface area): 175 x (serum creatinine)$^{-1.154}$ x (age)$^{-0.203}$ x (0.742 if female) x (1.212 if African descent) (1,13). CKD was defined as an estimated GFR <60 mL/min per 1.73 m^2. Subjects with CKD were grouped according to the following criteria: CKD stage 1 if GFR >90 mL/min per 1.73 m^2 and an abnormal urinary albumin excretion (UAE; random urine sample >17 mg/l) (14), or proteinuria or hematuria on urinalysis; CKD stage 2 if 60 mL/min < GFR >89 mL/min per 1.73m^2 and an abnormal UAE (random urine sample >17 mg/l), proteinuria or hematuria on urinalysis; CKD stage 3 if 30 mL/min <GFR >59 mL/min per 1.73m^2; CKD stage 4 if 15 mL/min <GFR <30 mL/min per 1.73m^2 and CKD stage 5 if GFR <15 mL/min per 1.73m^2 (1).

Data analysis and statistical methods

Data are presented as mean ± standard deviation (SD), median (P25-P75), unless otherwise specified. To compare demographic, clinical, and laboratory data, the chi-square test, independent-samples t test and one-way ANOVA were used as appropriate. Variables with a non-normal distribution were log transformed to achieve a normal distribution before analysis for comparison between groups. Correlations between the variables were assessed using Pearson's correlation coefficient for normally distributed variables and Spearman's correlation coefficient when at least one of the variables in the analysis had a skewed distribution.

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS, version 18.0 for Windows, Chicago, IL). A two-sided P value <0.05 was considered significant.

RESULTS

Subjects' characteristics

Our sample comprised 110 subjects. Of these, 23 (20.1%) were males and 87 (79.1%) were females. The clinical and laboratory characteristics are summarized in table 1. Subjects were subdivided according to the presence or absence of MS. These two groups did not differ in terms of sex distribution, ethnicity, A1c, UAE, and total cholesterol, but systolic and diastolic arterial blood pressures, BMI, waist circumference, fasting and 2h-plasma glucose levels, and HOMA-IR were higher in subjects with MS than in those without the syndrome. As expected, HDL plasma levels where lower in the patients with MS compared with those without it (table 1).

CKD was present in 20.9% of subjects, with 10.0% being classified as CKD stage 1, 7.3% CKD stage 2, and 3.6% CKD stage 3. There were no subjects classified as CKD stages 4 and 5.

Table 1 - Demographic, clinical, and laboratory characteristics of subjects with and without metabolic syndrome.
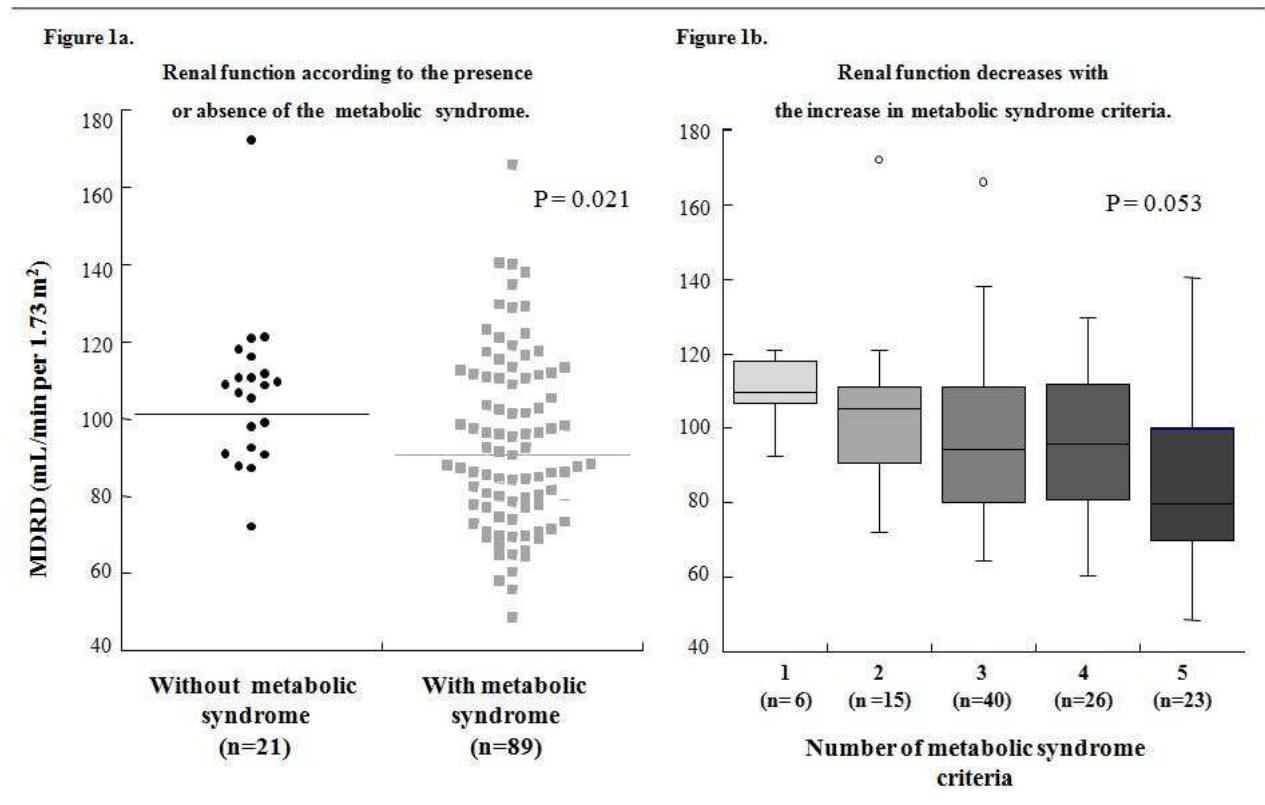
	Without metabolic syndrome (N = 21)	With metabolic syndrome (N = 89)	P
Age (years)	48.0 ± 11.5	53.7 ± 11.0	0.030
Female sex – n (%)	16 (76.2)	71(79.8)	0.716
No-African descent - n (%)	17 (17.1)	82(83.9)	0.124
Diastolic blood pressure (mmHg)	79.7 ± 13.0	87.0 ± 13.9	0.025
Systolic blood pressure (mmHg)	124.1 ± 16.3	144.7 (25.0)	< 0.001
BMI (kg/m^2)	28.7 ± 5.5	32.4 ± 7.1	0.024
Waist circumference (cm)	96.3 ± 13.8	106.3 ± 13.0	0.002
Fasting plasma glucose (mg/dL)	94 ± 10.7	116.03 ± 42.8	< 0.001
2h-plasma glucose (mg/dL)	116.6 ± 47.0	185.4 ± 81.9	< 0.001
A1c (%)	6.0 ± 0.5	6.4 ± 1.3	0.070
24h UAE (mg/24h)	1.0 (0-6.2)	4.6 (0-14.4)	0.372
Random sample UAE (mg/L)	3.0 (1.0-8.1)	3.8 (1.0-8.9)	0.616
MDRD (mL/min per 1.73 m^2)	100.3 ± 18.5	88.4 ± 21.5	0.019
Creatinine (mg/dL)	0.72 ± 0.12	0.78 ± 0.18	0.292
Total cholesterol (mg/dL)	206.5 ± 46.0	203.3 ± 42.6	0.917
LDL-cholesterol (mg/dL)	129.1 ± 45.7	124.8 ± 38.1	0.863
HDL-cholesterol (mg/dL)	57.4 ± 11.4	49.6 ± 15.4	0.752
Triglycerides (mg/dL)	93.0 (65.5-136.5)	135 (100-178)	0.003
HOMA-IR	1.69 (1.07-2.48)	3.32 (1.97-4.91)	< 0.001

Data expressed as absolute number (%), mean ± SD or median (P25-75) BMI =body mass index, HOMA-IR =homeostasis model of insulin resistance, MDRD =modification diet in renal disease, UAE =urinary albumin excretion

Glomerular filtration rate estimation according to the presence of metabolic syndrome

In order to determine differences in renal function according to the presence or absence of MS, estimated glomerular filtration rate (eGFR) was calculated using the MDRD equation and compared between these two groups. eGFR was lower in subjects with MS than in those without the syndrome (Figure 1a; P =0.019).

To better examine the association between decreased renal function and MS, we additionally analyzed eGFR according to the number of MS criteria (Figure 1b). eGFR decreased with the increasing number of MS criteria (mean ± SD; zero or one criterion 103.09±9.5 vs. two criteria 99.14±21.2 vs. three criteria 90.9±1.1 vs. four criteria 91.0±19.4 vs. five criteria 80.9±23.5 mL/min per 1.73m^2; P =0.053). As eGFR observed in the presence of three and four criteria for MS was similar, we also performed this comparison grouping together subjects with three and four criteria, and this association was statistically significant (P =0.025).

Figure 1a.

Renal function according to the presence or absence of the metabolic syndrome.

P = 0.021

Without metabolic syndrome (n=21)

With metabolic syndrome (n=89)

Figure 1b.

Renal function decreases with the increase in metabolic syndrome criteria.

P = 0.053

Number of metabolic syndrome criteria

Impact of each metabolic syndrome component on renal function

To better understand the contribution of each MS criterion to that association, we divided our sample according to the presence or absence of each component. While eGFR was significantly lower in those with hypertension than in those with normal blood pressure (88.3±21.1 vs. 99.0±20.5 mL/min per 1.73 m^2; p = 0.026) and lower in those with hyperglycemia (87.6±20.6 vs. 98.6±19.7 mL/min per 1.73m^2, P =0.010), eGFR was similar in those with hypertriglyceridemia (87.4±22.5 vs. 92.4±19.9 mL/min per 1.73m^2; P =0.221), low HDL (91.9±19.1 vs. 85.6±22.3 mL/min per 1.73 m^2; P =0.556), and high waist circumference (90.8±21.4 vs. 96.6±9.7 mL/min per 1.73m^2; P =0.550) than in those without each one of these components (Figure 2).

Figure 2. Renal function according to the presence or absence of each metabolic syndrome criterion.
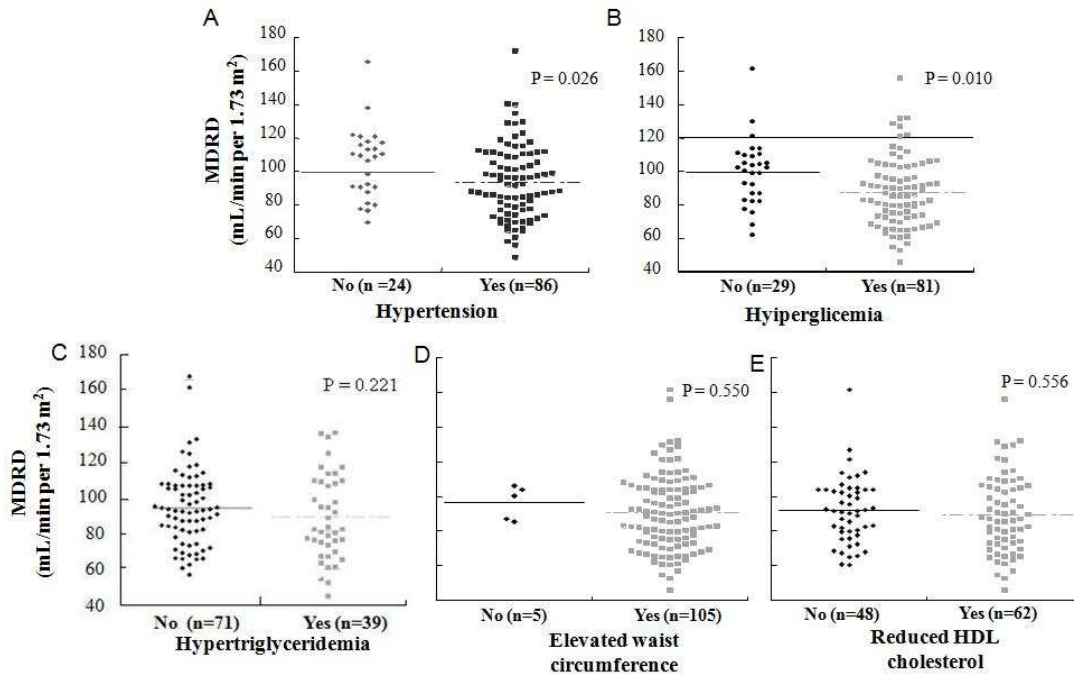
We also performed correlation analysis to better understand the association between each MS component and renal function (table 2). While systolic arterial blood pressure was negatively correlated with eGFR and A1c presented a borderline negative correlation, BMI, waist circumference, diastolic arterial blood pressure, fasting and 2h-plasma glucose levels, triglycerides, HDL-cholesterol and HOMA-IR were not.

Table 2 - Associations of renal function estimated by MDRD including anthropometry, arterial blood pressures, glycemic control, lipid profile, and insulin resistance.

	All Subjects (N =110)	
Independent Variable	r	P
BMI	0.079	0.397
Waist circumference	0.071	0.453
Systolic blood pressure	-0.280	0.003
Diastolic blood pressure	-0.144	0.134
Fasting plasma glucose	-0.103	0.269
2h-plasma glucose	-0.038	0.687
Triglycerides	-0.089	0.338
HDL-cholesterol	-0.014	0.885
HOMA-IR	0.070	0.468
A1c	-0.185	0.067

Data expressed as absolute number (%), mean ± SD or median (P25-75)
BMI = body mass index, HOMA-IR = homeostasis model of insulin resistance, MDRD = modification diet in renal disease

DISCUSSION

The present study assessed the relationship between MS and renal function in subjects with different degrees of glucose tolerance. We demonstrated that MS is significantly associated with decreased renal function estimated using the MDRD equation. In addition, we found that eGFR progressively decreased with a higher number of MS components.

To understand the contribution of MS components in decreasing renal function, we analyzed how renal function differs by the presence or absence of each one of them. While hypertension and hyperglycemia were significantly associated with lower eGFR, waist circumference, triglycerides, and HDL were not.

Several epidemiological studies have shown that MS is a risk factor for CKD and end-stage renal disease as replicated in the present study (3,7,8). To our knowledge, this is the first study exploring this issue based on the Joint Scientific Statement, which harmonizes the definition of MS among different medical societies

(11). As opposed to these studies, we were not able to show that all MS components were related to eGFR. Indeed, eGFR was significantly lower in the presence of MS with hyperglycemia and hypertension. To confirm these findings, we analyzed how different MS components were related to eGFR using correlation analysis. According to that, systolic arterial blood pressure was the only factor significantly correlated with eGFR, whereas A1c had a borderline correlation and BMI, diastolic arterial blood pressure, plasma glucose levels, triglycerides, and HDL-cholesterol were not associated with eGFR. In addition, we analyzed whether insulin resistance, estimated by HOMA-IR, was related to eGFR, since this phenomenon has been shown to have a main role in the development of MS and could, consequently, be the main mechanism involved in this relationship (6). Although subjects with MS were more insulin resistant than subjects without the syndrome, we were not able to observe a correlation between insulin resistance and decreased eGFR, suggesting again that MS itself is not associated with a synergistic risk for CKD. Therefore, our findings suggest that the possible association between MS and decreased renal function is mostly driven by abnormalities in blood pressure homeostasis, namely high systolic arterial blood pressure.

Other studies have found similar results, showing the great impact of hypertension on the development of CKD in patients with MS (7,15,16). In the 3-year prospective Tehran Lipid and Glucose Study with 4,607 non-diabetic adult subjects without CKD at baseline, the increased risk for developing CKD was no longer significant when hypertensive subjects were excluded from the analysis (15). In the ARIC study the increased risk for developing CKD in the 9-year follow-up of 10,000 non-diabetic American adults was about halved, although still significant, after adjustment for subsequent development of diabetes and hypertension (7).

The differences of our results compared to those found by others might be explained by the use of the National Cholesterol Educational Program (NCEP) criteria for the diagnosis of MS (2,3,17). According to the NCEP definition of MS, the central obesity criterion is defined by a higher waist circumference than the current definition. In our study, only five subjects had normal waist circumference based on the new definition of MS what makes the power to detect differences between subjects with and without MS too limited in this context.

Our study has some potential limitations. Firstly, the MDRD equation was used to estimate GFR. This equation was built and validated based on the study population of the MDRD study, which included predominantly subjects with CKD (13). It has been shown that its estimation of renal function is underestimated in subjects with normal or mild abnormal renal function, which is the prevailing population of the present study. Therefore, assuming that the presence of MS is associated with diminished renal function and that renal function was underestimated in subjects without MS, we believe that using more accurate methods to directly assess GFR, such as inulin clearance or radioisotope methods, the difference in renal function would be higher between these two groups. Secondly, the cross-sectional study design makes it difficult to infer causality between MS and changes in renal function. Therefore, while showing the association between the presence of MS and decreased eGFR, our study did not address which mechanisms of MS are behind this process.

In conclusion, the presence of MS is associated with decreased eGFR and, consequently, increased risk for CKD in a population including predominantly subjects with less advanced degrees of CKD and/or normal eGFR. In addition, there is a graded relationship between the number of MS components and decreased renal function. Among the MS criteria related to decreased eGFR, high systolic arterial blood pressure showed a significant correlation, whereas hyperglycemia showed a borderline association, suggesting a possible but less important role in the development of CKD. Since abnormal blood pressure homeostasis was the most important factor related to decreased eGFR in subjects with MS, strict blood pressure control might prevent the future development or progression of CKD in these subjects. Such findings need to be confirmed by future clinical trials.

Grants and Support

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