Chronic kidney disease and metabolic syndrome as risk factors for cardiovascular disease in a primary care program

Doença renal crônica e síndrome metabólica como fatores de risco para doença cardiovascular em um programa de atenção primária

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Abstract

Introduction: Cardiovascular disease (CVD) is especially prevalent in patients with chronic kidney disease (CKD). **Objective:** To evaluate the role of CKD and metabolic syndrome (MS), which is a cluster of risk factors for CVD, as predictors of CVD. **Methods:** Observational, cross-sectional study with a random sample aged 45 or more years extracted from the population assisted by the primary care program in Niterói city in the state of Rio de Janeiro, Brazil. CKD was diagnosed by the K/DOQI guidelines and MS, by the harmonized criteria. CVD was said to be present if the participant had one or more of the following findings: echocardiographic abnormalities, and history of myocardial infarction, stroke or heart failure. A logistic regression model was developed to analyze risk factors for CVD using CKD as the variable of primary interest. **Results:** Fifty hundred and eighty-one participants (38.2% male) with a mean age of 59.4 ± 10.2 years were analyzed. The prevalence rate of CKD was 27.9%. In participants without CKD, MS was associated with a slight but statistically significant increase in the risk for CVD (OR = 1.52, p = 0.037); in those with CKD but without MS the risk for CVD was also statistically significant and at a greater magnitude (OR = 2.42, p = 0.003); when both were present the risk for CVD was substantially higher (OR = 5.13, p < 0.001). **Conclusion:** In this study involving a population assisted by a primary care program, CKD was confirmed as an independent risk factor for CVD. The presence of MS concurrent with CKD substantially amplified the risk for CVD.

Keywords: renal insufficiency, chronic; cardiovascular diseases; metabolic syndrome X; primary health care.

Resumo

Introdução: A doença cardiovascular (DCV) é especialmente prevalente em pacientes com doença renal crônica (DRC). **Objetivo:** Avaliar o papel da DRC e da síndrome metabólica (SM), que é um conjunto de fatores de risco para DCV, como previsores de DCV. **Métodos:** Estudo observacional, transversal, com uma amostra representativa da população assistida pelo programa de atenção primária em Niterói, RJ, Brasil, incluindo pacientes com idade igual ou maior do que 45 anos. A DRC foi diagnosticada segundo o K/DOQI e a SM, pelo critério harmonizado. A DCV foi dita estar presente diante de um ou mais dos seguintes achados: anormalidades ecocardiográficas ou história de infarto do miocárdio, acidente vascular cerebral ou insuficiência cardíaca. Um modelo de regressão logística foi desenvolvido para analisar os fatores de risco cardiovasculares usando a DRC como a variável de interesse primário. **Resultados:** Foram analisados 581 participantes (38,2% homens), com idade média de 59,4 ± 10,2 anos. A taxa de prevalência da DRC foi de 27,9%. Em participantes sem DRC, a SM foi associada com um ligeiro, mas estatisticamente significativo aumento no risco cardiovascular (OR = 1,52, p = 0,04); naqueles com DRC, mas sem SM, o risco para DCV também foi estatisticamente significativo e com maior magnitude (OR = 2,42, p = 0,003); quando ambos estavam presentes, o risco para DCV foi substancialmente mais elevado (OR = 5,13, p < 0,001). **Conclusão:** Neste estudo, envolvendo uma população assistida por um programa de atenção primária, a DRC foi confirmada como um fator de risco independente para DCV. A presença da SM concomitante com a DRC ampliou substancialmente esse risco.

Palavras-chave: doença renal crônica; doenças cardiovasculares; síndrome X metabólica; atenção primária à saúde.

Introduction

The incidence of chronic kidney disease (CKD) is increasing worldwide.[1] Nowadays, the global prevalence of CKD is estimated to be around 12-14%.[1] The epidemiology of CKD in Brazil is believed to be similar to the international one, but consistent data in this regard are scarce.[2]

Cardiovascular disease (CVD) is known to be more prevalent in patients with CKD since the early stages of the disease.[1,3-5] Risk factors for cardiovascular disease in patients with CKD have been the subject of a number of studies. Traditional factors (derived from the Framingham study such as hypertension, diabetes, and smoking) and non-traditional ones (linked to the CKD itself, such as inflammation, anemia, oxidative stress, and mineral metabolism disorders) have been incriminated.[6,7]

Metabolic syndrome (MS) is a cluster of risk factors for CVD,[8,9] which are also common in CKD patients.[10] The interplay between CKD and MS as determinants of CVD has been addressed in some epidemiological studies[11-13] but the subject is still a matter of controversy.

In the present study, we evaluate the association of CKD and/or MS with CVD in a population of primary care aged 45 or more years.

Methods

Data were derived from a database of a study evaluating the prevalence of heart failure in a population of a primary care program,[14] which was approved by the Ethics Committee of the Medical School under the number 0077.0.258.000-10.

This was an observational, cross-sectional study with a random sample aged 45 or more years extracted from the population assisted by the Family Doctor Program (FDP) of Niterói city in the state of Rio de Janeiro, Brazil, a primary health care program. Participants were selected, stratified by age and sex, in order to represent the population of the city according to the last report of demographic data by the Brazilian Institute of Geography and Statistics preceding the start of the study. By that time, the FDP covered 133,000 residents of Niterói city divided into 110 sectors and 33 service units. At first, 10 units to represent the city's administrative regions were drawn.

The calculation of sample size was based on estimates that the proportions of the population of the city with 45 years or more were: from 45 to 55 years, 69%; from 56-69 years, 14%; from 70-79 years, 10%; and above 79 years, 7%. To detect prevalence rates of about 1% (lower prevalence among the studied conditions) with a confidence of 95% and an acceptable error of 50% we found that it was needed tracing of 307 individuals from 45-55 years, 134 from 56-69 years, 80 from 70-79, and 52 with 80 or more years totaling 573 subjects. After accounting for a 10% loss, the final number of participants was found to be 632 (63 per unit).

From August 2011 to June 2012, visits were accomplished to the units in which participants underwent a blood sample collection after 8h of fasting; a fresh urine sample was obtained. By the time of the visit, an echocardiography was performed. Patients underwent a standard physical examination in which their weight, waist circumference, height and blood pressure were obtained. They also completed a questionnaire addressing issues related to heart failure, kidney disease, hypertension, diabetes, obesity, dyslipidemia, metabolic syndrome and other comorbidities, lifestyle and family history.

Blood pressure was measured with an electronic sphygmomanometer (HEM-711AC Omron Co., Japan) following VII Joint protocol.[15] Body weight was assessed by an electronic digital scale (PL80, Filizola S/A, Brazil) and height by a portable digital stadiometer (Kirchnner Wilhelm, Medizintechnik, Germany). Acuson Cypress echograph, Siemens Medical Solutions, USA or AU3 Partner, Esaote / Biosound, USA were used for the echocardiogram. Biochemical serum and urine analysis were performed with Selectra analyzer (NE Vital Scientific, Netherlands).

Serum parameters included glucose, standardized creatinine, total cholesterol, LDL-cholesterol, HDL- cholesterol, triglycerides and uric acid. Urine excretion of albumin was estimated by the albumin/creatinine ratio (mg/g).

Body mass index (BMI) was calculated as the ratio of weight (kilograms) and squared height (meters).[16] Waist circumference was measured using an inextensible tape measure, at the midpoint of the distance between the iliac crest and the last costal margin, with the participant upright and at expiration.

Subjects whose blood pressure reading was higher than 140 mmHg (systolic) or 90 mmHg (diastolic) and those who reported to be under antihypertensive

drugs were labeled as hypertensive. Participants whose fasting glucose was equal to or above 126 mg/dL, and those who reported oral use of hypoglycemic agents and/or insulin were considered diabetic.[17]

The diagnosis of metabolic syndrome was based on harmonized criteria.[8,18] Subjects who met at least three of five criteria were considered as having metabolic syndrome, namely: (i) increased waist circumference (In Latin America ≥ 90 cm for men and ≥ 80 cm for women); (ii) hypertriglyceridemia (triglycerides ≥ 150 mg/dL or use of lipid lowering drugs); (iii) low HDL-cholesterol (< 40 mg/dL in men and < 50 mg/dL in women or use of statins); (iv) systolic blood pressure ≥ 130 mmHg and/or diastolic ≥ 85 mmHg or use of antihypertensive; and (v) fasting glucose ≥ 100 mg/dl or use of anti-diabetic agents.

Smoking was defined as the use of at least 100 cigarettes (5 packs) in life and/or currently smoking;[19] CKD was defined by the criteria of the K/DOQI;[20] GFR estimation was based on serum creatinine using CKD-EPI equations without adjustment for race;[21] hyperuricemia as serum uric acid ≥ 6.0 mg/dL in women and ≥ 7.0 mg/dL in men;[22] and heart failure, by the III Guidelines of the Brazilian Cardiology Society for chronic heart failure.[23]

CVD was said to be present if the participant had one or more of the following findings: echocardiographic abnormalities (systolic dysfunction, diastolic dysfunction or left ventricular hypertrophy, LVH),[24] and self-reported history of myocardial infarction, stroke or heart failure.

CKD-/MS+ (Participants were grouped as: 1. Without both, CKD and MS (CKD-/MS-); 2. Without CKD but with MS (CKD-/MS+); 3. With CKD but without MS (CKD+/MS); and 4. With both conditions (CKD+/ MS+).

For the present analysis, only subjects who had determinations of serum creatinine, urine creatinine, and urine albumin as well as all the parameters required for the diagnosis of MS were included.

Statistical analysis

Continuous variables were expressed as mean ± S.D. in case of normal distribution or as median and range otherwise. Categorical variables were expressed as frequencies. Comparisons between groups were performed by the *t*-test or the Mann-Whitney test as appropriate. Frequencies were compared using the Chi-square test.

A logistic regression model was developed to analyze risk factors for cardiovascular disease using CKD as the variable of primary interest.

The software SPSS, version 18.0 for Windows (IBM, Chicago, IL, USA), was used for statistical analysis.

Results

The starting sample was composed of 632 individuals. After application of the inclusion criteria, the final sample comprised 581 individuals. The general characteristics of the whole population and of each group are shown in Table 1.

The general prevalence of CKD was 27.9% (162 cases) with 159 (96.9%) belonging to stages 1, 2 and 3 (26.5, 35.8 and 34.6%, respectively). In CKD patients, CVD was present in 109 cases (68.5%). Its prevalence rate tended to increase according to the stages of CKD: 44.2% in stage 1, 78.6% in stage 2, 74.5% in stage 3, and 100% in stages 4 and 5. Patients with CKD, in comparison to the ones without CKD, had a higher frequency of: LVH (40.9% *vs.* 27.6%, $p = 0.002$), systolic dysfunction (8.8 *vs.* 3.1%, $p = 0.004$), diastolic dysfunction (42.4% *vs.* 19.9%, $p < 0.001$), history of myocardial infarction (7.4% *vs.* 3.3%, $p = 0.03$), and stroke (7.4% *vs.* 2.9%, $p = 0.01$). One hundred and two CKD patients (63.0%) also had a concomitant diagnosis of MS.

The whole prevalence rate of MS in the sample was 57.8% (336 cases). Affected parameters for the diagnosis of MS in participants with MS were: waist circumference 92.9%; blood pressure 85.7%; glucose 78.9%; HDL-C 58.3%; and triglycerides 50.3%.

Regarding the use of medications, we found that the use of fibrates was higher in the group CKD-/MS+ when compared to the CKD-/MS- group. The use of calcium channel blockers DHP was higher in the CKD+/SM+ group in relation to the others. Central alpha-agonists and antiarrhythmic drugs other than digitalis and beta-blockers were also more frequently used in the CKD+/SM+ but only when compared to CKD-/MS- group. In addition, the use of thiazide and loop diuretics, RAAS inhibitors, statins, and aspirin was higher in groups with MS than in the ones without MS.

Among all participants, 285 (49.6%) were found to be positive for the presence of CVD. The frequency of CVD in each group was: CKD-/MS-36.6%, CKD-/MS+ 46.8%, CKD+/MS- 58.3%, and CKD+/MS+

Table 1 General characteristics of the population

	All	CKD-/MS-	CKD-/MS+	CKD+/MS-	CKD+/MS+
N	581	185 (31.8)	234 (40.3)*	60 (10.3)*¥	102 (17.6)*¥§
Male	222 (38.2)	69 (37.3)	93 (39.7)	25 (41.7)	35 (34.3)
Age, years	59.35 ± 10.16	56.49 ± 8.77	57.93 ± 8.15	64.07 ± 11.6*¥	65.02 ± 12.45*¥
White	210 (36.3)	69 (37.3)	83 (35.5)	21 (35.6)	37 (36.6)
Family income, R$ [a]	1,322 (0-17,000)	1,300 (0-10,000)	1,500 (70-17,000)	1,140 (120-4,500)	1,244 (275-12,000)
SAH	414 (71.3)	90 (48.6)	189 (80.8)*	40 (66.7)*¥	95 (93.1)*¥§
DM	141 (24.3)	15 (8.1)	75 (32.1)*	7 (11.7)¥	44 (43.1)*§
Smoking	298 (51.4)	102 (55.1)	119 (50.9)	28 (47.5)	46 (45.1)
Sedentary	410 (74.0)	132 (75.0)	164 (74.2)	43 (74.1)	71 (71.7)
Creatinine, mg/dL					
Men	1.04 ± 0.33	0.96 ± 0.12	0.99 ± 0.15	1.15 ± 0.28	1.23 ± 0.71*¥
Women	0.80 ± 0.18	0.76 ± 0.12	0.76 ± 0.11	0.87 ± 0.24¥	0.91 ± 0.28*¥
BMI, kg/m^2	27.8 ± 5.2	25.7 ± 4.8	30 ± 4.7*	24 ± 5.3¥	28.7 ± 4.5*§
Uric acid, mg/dL					
Men	6.21 ± 3.22	5.43 ± 1.18	6.59 ± 2.46	7.00±6.94	6.22 ± 2.31
Women	5.19 ± 3.21	5.07 ± 4.45	5.32 ± 2.92	4.73 ± 1.42	5.35 ± 1.43
eGFRb, ml/min/1.73m^2	82.38 ± 17.94	87.40 ± 13.04	85.63 ± 13.32	72.12 ± 22.40*¥	71.86 ± 24.32*¥

Note: Unless otherwise indicated, values for categorical variables are given as number (percentage); values for continuous variables are given as mean ± standard deviation or median. Conversion factors for units: creatinine in mg/dL to µmol/L, ×88.4; uric acid in mg/dL to µmol/L ×59.48. $p < 0.05$ indicates statistical significance. SAH: Systemic arterial hypertension; DM: *Diabetes mellitus*; BMI: Body mass index; Egfr = creatinine-based estimated glomerular filtration rate. [a] Median and range. [b] Estimated glomerular filtration rate by CKD-EPI. * $p < 0.05$ *vs.* CKD-/MS-; ¥ $p < 0.05$ *vs.* CKD-/MS+; § $p < 0.05$ *vs.* CKD+/MS-

74.7%, Table 2. The frequency was statistically higher in every group when compared to CKD-/MS-. Moreover, the group CKD+/MS+ had a statistically higher frequency of CVD *versus* every other group. The risk for CVD using the CKD-/MS- as a reference is also in Table 2.

Again, a gradual increase in the magnitude of the risk for CVD was seen from the CKD-/MS+ group to the CKD+/MS+ one. The prevalence rates of CVD components in the four groups are in Table 3. As a whole, LVH and diastolic dysfunction were the most frequent abnormalities. History of myocardial infarction and stroke were statistically higher only in the CKD+/MS+ group in comparison to the CKD-/MS- one. Diastolic dysfunction was statistically more frequent in groups with CKD.

Table 2 Frequency and risk for the composite variable in the four groups

	f (%)	OR (95% CI)	*p*
CKD-/MS- (Ref.)	67 (36.6)	1.00	-
CKD-/MS+	109 (46.8)*	1.52 (1.02-2.26)	0.04
CKD+/MS-	35 (58.3)*	2.42 (1.34-4.39)	0.003
CKD+/MS+	74 (74.7)*¥§	5.13 (2.97-8.83)	< 0.001

$p < 0.05$ indicates statistical significance. CKD: Chronic kidney disease; MS: Metabolic syndrome * $p < 0.05$ *vs.* CKD-/MS-; ¥ $p < 0.05$ *vs.* CKD-/MS+; § $p < 0.05$ *vs.* CKD+/MS-

We developed a logistic regression model to analyze the association of CKD with cardiovascular disease adjusting for age, skin color, sedentary lifestyle, smoking, and MS, Table 4. CKD was maintained as an independent risk factor for CVD. Age and MS were also found to be independently associated with CVD.

Discussion

CKD and MS are well-known risk factors for CVD but few studies have compared the impact of these two conditions in this regard. We addressed such issue in 581 subjects with 45 or more years derived from a community-based health program.

The whole prevalence of CVD of 49.6% in the present study is high but cannot be seen as a surprise. The sample was derived from a low-income population with 45 or more years who had an elevated prevalence rate of comorbidities that are strongly associated with cardiovascular disease such as diabetes (24.3%) and hypertension (71.3%). Correspondent numbers for such comorbidities in the

Table 3 Frequency and percent of composite variable components of participants in the four groups

	All	CKD-/MS-	CKD-/MS+	CKD+/MS-	CKD+/MS+
Myocardial infarction [a]	26 (4.5)	5 (2.7)	9 (3.8)	4 (6.7)	8 (7.8)*
Cerebrovascular accident [a]	24 (4.1)	2 (1.1)	10 (4.3)	3 (5.0)	9 (8.8)*
Heart failure [a]	44 (7.6)	7 (3.8)	20 (8.5)*	4 (6.7)	13 (12.7)*
LVH [b]	180 (31.3)	46 (25.0)	69 (29.6)	26 (41.7)*	40 (40.4)*
Systolic dysfunction [b]	27 (4.7)	2 (1.1)	11 (4.7)*	4 (6.7)*	10 (10.1)*
Diastolic dysfunction [b]	149 (26.1)	31 (17.0)	51 (22.2)	23 (38.3)*¥	44 (44.9)*¥

$p < 0.05$ indicates statistical significance. CKD: Chronic kidney disease; MS: Metabolic syndrome; LVH: Left ventricular hypertrophy; [a] As collected by medical history. [b] Observed by echocardiography. * $p < 0.05$ *vs.* CKD-/MS-; ¥ $p < 0.05$ *vs.* CKD-/MS+; § $p < 0.05$ *vs.* CKD+/MS-

Table 4 Multivariate logistic regression analysis to test the association of cardiovascular disease with CKD

	OR (95%CI)	*p*
CKD	2.31 (1.51 - 3.55)	< 0.001
Age	1.07 (1.05 - 1.09)	< 0.001
Male gender	0.71 (0.48 - 1.03)	0.07
White skin color	0.79 (0.54 - 1.16)	0.2
Smoking	1.09 (0.75 - 1.58)	0.7
Sedentary	0.93 (0.61 - 1.41)	0.7
MS	1.59 (1.10 - 2.30)	0.02

$p < 0.05$ indicates statistical significance. CKD: Chronic kidney disease; MS: Metabolic syndrome.

general adult population in Brazil seat around 5-7% and 20-30%, respectively.[25-27]

We also found a relatively high prevalence of CKD (27.9%) perhaps by the same reasons outlined before. In this regard, it should be stressed that age may have had an important contribution considering its relevant impact in CKD development[1]. Finally, the well-known high willingness of ill subjects to participate in studies may also have contributed to increase the prevalence of comorbidities.

The prevalence of CVD was greater in CKD patients whose majority (close to 95%) was in stage 3 or lower confirming that CVD is an early complication in the course of CKD. Consistent with previous studies,[5,28-30] the prevalence rate of CVD tended to increase with the CKD stages.

The prevalence of MS was also high in the study population.[18,31] In consonance with other studies,[31,32] abdominal circumference alteration was the most prevalent MS component in those with MS.

The CVD risk was substantially higher for participants presenting both CKD and MS. These data are similar to the ones reported in other studies[11,12,19] in spite of more participants at early stages of CKD in our sample.

In the multivariate logistic regression model, CKD was the main factor associated with CVD. Age and MS also emerged as independent factors for CVD but with less impact. The cross-sectional nature of the present study does not allow us to establish the exact interplay between CKD, MS and CVD, but some cohort studies have already suggested that the presence of CKD favors the development of CVD.[19,33]

Others studies have reported that CKD has a more powerful impact on CVD than metabolic syndrome[33,34] but the explanation for that is still a matter of controversy. Perhaps the high availability of therapeutic tools for MS had an influence in the lower effect of MS when compared with CKD. In agreement to this hypothesis, the use of drugs for hypertension and dyslipidemia was higher on the MS groups.

The marked increase in the risk of CVD when CKD and MS are concomitant deserves comments. A form of rapidly progressive arterial disease has been reported in dialysis patients for more than 30 years[35] and may initiate very early in the course of CKD. The impact of non-traditional factors predisposing to atherosclerosis such as mineral disorders, oxidative stress, anemia and inflammation may be preponderant in this regard.[36,37] The association of MS superimposes the traditional risk factors for atherosclerosis in these patients and may represent the explanation for the substantial increase in the risk for CVD found in our study.[7]

Our study presents some limitations. Patients were only seen once resulting in accomplishments of all laboratory analysis in one biological sample and measurements of blood pressure in only one visit. Apart from restrictions, these measures are thought to be useful for comparison among individuals or groups especially in epidemiological studies. Finally, some information was directly reported by the participants, which may have generated information bias.

Conclusion

Our findings confirmed CKD as an independent risk factor for CVD. MS was also confirmed as an independent risk factor for CVD, although with a lower impact than CKD. The association of MS to CKD substantially amplified the risk for CVD. Future studies may help identifying the mechanisms subjacent to the worse cardiovascular outcomes with the association of MS and CKD and help to develop new preventive public health policies in this regard.

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