Prevalence of chronic kidney disease in a population in southern Brazil (Pro-Renal Study)

Prevalência da doença renal crônica em uma população do Sul do Brasil (estudo Pro-Renal)

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ABSTRACT

Introduction: Chronic kidney disease (CKD) affects 10-12% of the adult population in many countries. In Brazil, there is no reliable information about the actual prevalence of CKD. **Objective:** To determine the prevalence of CKD by estimated glomerular filtration rate (eGFR) and proteinuria/albuminuria in an urban population randomly selected in Southern Brazil. Patients and **Methods:** 5,216 individuals were randomly selected out of a pool of 10,000 individuals identified from the database of a local energy company. The screening consisted of collection of demographic data, history of *diabetes mellitus*, hypertension, kidney/cardiovascular disease in the family and obesity through the body mass index - BMI (CKD risk factors). Blood samples were collected for determination of serum creatinine and subsequent eGFR estimation by the MDRD formula and urine samples for determination of albuminuria by dipstick. Albuminuria was further evaluated by HemoCue© in a selected CKD risk group. **Results:** The population was predominantly Caucasians (93%), 64% were females and the mean age of participants was 45 years old (18-87). BMI (kg/m^2) was 27±5. Albuminuria was found in 5.25% of individuals. 88.6% of this population had no CKD (eGFR > 60 ml/min/1.73m^2 & normoalbuminuria) and 11.4% were identified as having CKD, with majority on stages 3A (7.2%) and 3B (1.1%). Hypertension, diabetes, older age and obesity was associated with a higher prevalence of CKD (p < 0.001). **Conclusions:** The prevalence of CKD in an urban population in southern Brazil mirrors other developed countries and indicates that kidney disease is an important public health problem in Brazil.

Keywords: prevalence; chronic kidney disease; creatinine; albuminuria.

RESUMO

Introdução: A doença renal crônica (DRC) afeta 10-12% da população adulta em muitos países. No Brasil, não há informações confiáveis sobre a prevalência real de DRC. **Objetivo:** Determinar a prevalência de DRC pela taxa de filtração glomerular estimada (eGFR) e albuminúria em uma população urbana selecionada aleatoriamente no sul do Brasil. Pacientes e **Métodos:** 5216 indivíduos foram selecionados aleatoriamente de um grupo de 10 mil indivíduos identificados a partir do banco de dados de uma empresa de energia local. O rastreio consistiu na coleta de dados demográficos, história de *diabetes mellitus*, hipertensão, doença renal/cardiovascular na família e obesidade pelo índice de massa corporal -IMC (fatores de risco da DRC). Foram coletadas amostras de sangue para determinação da creatinina sérica e subsequente estimativa de eGFR pela fórmula MDRD e amostras de urina para determinação da albuminúria por fita. Albuminúria foi confirmada por HemoCue© em um grupo de risco de CKD selecionado. **Resultados:** A população era predominantemente de caucasianos (93%), 64% eram do sexo feminino e a idade média dos participantes de 45 anos (18-87). O IMC (kg/m^2) foi de 27 ± 5. Albuminúria foi encontrada em 5,25 % dos indivíduos. 88,6% dessa população não apresentou CKD (eGFR > 60 ml/min/1,73 m^2 e normoalbuminúria) e 11,4% foram identificados como portadores de DRC, com maioria nos estádios 3A (7,2%) e 3B (1,1%). Hipertensão arterial, diabetes, idade avançada e obesidade foram associados a maior prevalência de DRC (p < 0,001). **Conclusões:** A prevalência de DRC em uma população urbana no sul do Brasil reflete outros países desenvolvidos e indica que a doença renal é um importante problema de saúde pública no Brasil.

Palavras-chave: prevalência; insuficiência renal crônica; creatinina; albuminúria.

Introduction

There is ample evidence in the literature that chronic kidney disease (CKD) affects 10-12% of the general population and is usually silent, leading to unawareness by individuals.[1,2]

Prevalence however of CKD in the community may vary substantially since many reported studies on impaired kidney function are based on extrapolation from serum creatinine and did not take into account urinary protein excretion.[3]

It has been advocate that early detection can prevent complications and lower health care cost through survival improvement, reduction in progression of the disease and minimization of cardiovascular morbitity.[4]

However, much debate exists on how to screen individuals and who to screen. Targeting high risk groups such as those with hypertension, known *diabetes mellitus* (DM) and cardiovascular (CV) disease history have been preferred by many over the general population since it is less costly.[5,6] Nevertheless, it has been pointed out that in practice, the automatic reporting of eGFR by laboratories whenever serum creatinine levels are measured has led to *de facto* screening of the general population.[7]

Data on the prevalence of CKD in Brazil are scarce, with serious methodology limitations and as a consequence, with variable results.

The present work is the first attempt in Brazil aimed at detecting the prevalence of CKD in a random selected population through the estimated GFR (eGFR) and urinary albumin/creatinine ratio. These two variable allow us to categorize CKD as suggested by KDIGO.[8]

Materials and methods

Population

A group of 5,216 patients from both genders and from 18-87 years of age and living in an urban area (Campo Largo) of the State of Parana, Brazil, were enrolled in the study.

All participants signed a consent form. The project has been approved by the ethics committee of the Evangelic School of Medicine of Curitiba (protocol number 2903/08).

Sample size was calculated based on a prevalence of CKD of 5.0% found previously in the Bambui Study with a 95% confidence interval in relation to the urban population of this town.[9] Population Survey Using Random (Not Cluster) Sampling software was utilized. (Statcalc Epinfo version 6). The corrected estimated sample needed was of 5,926 participants.

Giving the possibility of individual refusal to participate and loss of data, 10,000 addresses were randomly selected (computer generated) from the Energy Company (COCEL) data base from the town of Campo Largo. An invitation-letter was sent to all addresses selected.

Methodology

Inclusion criteria: individuals ≥ 18 years old who had signed the consent form.

Individuals that had accepted to participate in the study were seen at the local Hospital (São Lucas) by a trained nurse and a laboratory technician.

Each participant had to fill in a survey about demographic data, life style and known diseases such as *diabetes mellitus*, arterial hypertension, cardiovascular disease, renal lithiasis and family history of CKD. Blood pressure was determined in the sitting position three times at 5 minutes interval. Blood pressure recorded was the mean of 3 measurements and values of ≥ 140/90 mmHg were considered hypertensive.[10]

Height and weight of each participant was obtained to determine body mass index (BMI). After collecting anthropometric data, a midstream urine sample was obtained for urinalysis. Thereafter, a venous blood sample was collected for serum creatinine. Individuals were not required to be fasting. Albumin/creatinine ratio was determined only in individuals considered at risk for CKD: ≥ 60 years of age, obesity (BMI ≥ 30), hypertension, diabetes and history of cardiovascular disease and/or renal disease in the family. Individuals were considered hypertensive based on history of arterial hypertension and on use of anti-hypertensive medication or when blood pressure (BP) values were all above 140/90 mmHg on 3 measurements.

The diagnosis of *diabetes mellitus* was based on history and use of hypoglycemic agents and/or insulin. Smoking was considered when individuals smoke 10 or more cigarettes a day.[11] Alcohol consumption was registered when individuals consumed more than what is recommended: two drinks a day for men and one for women.[12]

The definition of old age was based on the UN definition of old age (≥ 60 years) and adopted in Brazil.[13]

Measurements

Urinary albumin was detected through dipsticks Combur 10 Test® (Roche, Manheim, Germany). The interpretation of maximum colour on reagent strip was as follows: less than 30 mg/dl, no change in colour; between 30 and 100 mg/dl, 1+; between 100 and 500 mg/dl, 2+ and more than 5-mg/dl, 3+.

For albuminuria per gram of creatinine, the Hemocue® Albumin 201 System (Hemocue AB, Angelholm, Sweden) was utilized. The reference standard threshold for detection of an abnormal result was defined as ACR ≥ 30 mg/g. Individuals with albuminuria (1+ or more in the reagent strip) and/or albuminuria (ACR ≥ 30 mg/g) and eGFR ≥ 60 ml/min/1.73 m^2 had a second sample of urine collected for confirmation. Creatinine was measured by the Jaffe method in the autoanalyzer Selectra Fl (Vital Scientific, Dieren, Netherlands). Reference values: 0.4-1.3 mg/dl.

Estimated glomerular filtration rate (eGFR) was estimated by the MDRD formula and classification of CKD in categories was done based on KDIGO guidelines.[8] All participants received a printed result of eGFR and proteinuria.

Statistical Analysis

Analyses were performed using the statistical package SPSS 20.0 (SPSS, Chicago, IL). A p-value ≤ 0.05 was adopted to indicate statistical significance.

Quantitative variables with normally distributed data are reported as means with standard deviation, whereas data with skewed distribution are given as medians with minimum and maximum values. Quality variables are described through frequency and percentage. Differences between groups were tested by Student's t- test for continuous data. Differences in prevalence or incidence were tested with a chi-square test. For multivariate analysis, a adjusted model of logistic regression was used, and those variables that reached a $p < 0.05$ in the univariate analysis were included. Wald test was used to evaluate the importance of each variable.

Results

Sample characteristics

Characteristics of the 5,216 individuals with and without CKD are presented in Table 1. In the all cohort we have observed a preponderance of females (64%) and Caucasians (93%). Prevalence of arterial hypertension was 29% and *diabetes mellitus* affected 7% of the cohort. Age varied from 18-87 years (mean 45 ± 15); BMI ranged from 14-59 Kg/m^2 (mean 27 ± 5); serum creatinine ranged from 0,65 to 5,98 (mean 0,89 ± 0,23) and eGFR range from 7 to 162 ml/min/1.73 m^2 (mean 89 ± 22).

Table 1 Characteristics of individuals with and without CKD.

Variable	CKD Patients (n = 580)	Controls* (n = 4636)	*p* Value
Age - years (± SD)	61.6(12.1)	43.8(14.2)	< 0.001
Females - n(%)	407(70.2)	2932(63.2)	0.001
Race - n(%)			
Caucasians	544(93.8)	4336(93.5)	
Blacks	23(4)	232(5)	0.093
Asians	7(1.2)	51(1.1)	
Native Americans	6(1)	17(0.37)	
Hypertension - n(%)	389(67)	1150(24)	< 0.001
Systolic BP - mmHg (± SD)	136.7(18.9)	126.9(16)	< 0.001
Diastolic BP - mmHg (± SD)	84.9(12.2)	81.1(11.7)	< 0.001
Current smoker - n(%)	189(28.7)	1309(28.2)	0.029
BMI - kg/m^2 (± SD)	29.8(5.5)	27.1(5.1)	< 0.001
Alcohol consumption - n(%)	28(4.8)	161(3.4)	0.1
Diabetes Mellitus - n(%)	129(22.2)	271(5.8)	< 0.001
Serum creatinine - mg/dl (± SD)	1.14(0.37)	0.85(0.18)	< 0.001
eGFR - ml/mim/1.73m^2 (± SD)	60.5(18.7)	93.5(20)	< 0.001
Dislipidemia - n(%)	150(25.8)	469(10.1)	< 0.001
Education Iliterate	57(9.8)	178(3.8)	
Primary school	417(71.9)	2339(50.4)	
High school	82(14.1)	1424(30.7)	<0.001
College	20(3.45)	635(13.7)	
Pos-graduate	4(0.75)	60(1.4)	

* Controls: individuals with no CKD.

Categories of CKD

As can be appreciated in Table 2, of 5,216 individuals screened, 2,553 (48.94%) had an eGFR > 90 ml/min/1.73m^2 (Category 1); 2,224 (42.64%) individuals had an eGFR between 60-89 mL/min/1.73m² (Category 2). 373 (7.20%) individuals had an eGFR between 45-59 mL/min/1.73m² (Category 3A); 59 (1.10%) had an eGFR between 30-44 mL/min/1.73m² (Category 3B); 5 (0.09%) individuals had an eGFR between 15-29 mL/min/1.73m² (Category 4) and 2 (0.03) individuals with an eGFR below 15 ml/min/1.73 m² (Category 5).

Table 2 CKD classification based on eGFR and degree of albuminuria in this population

eGFR	Albuminuria mg/g of creatinine: Normal (< 30)	moderately elevated (30 a 299)	Severely elevated (≥ 300)	Total (%)
≥ 90 (1)	2460 (47.16)	20 (0.4)	73 (1.4)	2553 (48.94)
60 a 89 (2)	2158 (41.37)	16 (0.3)	50 (0.95)	2224 (42.64)
45 a 59 (3A)	288 (5.5)	36 (0.7)	49 (0.93)	373 (7.20)
30 a 44 (3B)	36 (0.70)	13 (0.25)	10 (0.2)	59 (1.10)
15 a 29 (4)	0 (0)	0 (0.0)	5 (0.09)	5 (0.09)
< 15 (5)	0 (0)	0(0.0)	2 (0.04)	2 (0.03)
Total	4942 (94.74)	85 (1.63)	189 (3.62)	5216 (100)

Urinalysis of these 5,216 individuals revealed that 4,942 (94,74%) did not have albuminuria. However, of those without albuminuria, 324 had a eGFR < 60mL/min/1.73m².

It was also found that 5.25% of the total group had albuminuria. When taken together, eGFR < 60 ml/min/1.73m² and normoalbuminuria, 88.6% of these individuals were identified on this group. Based on this data, it was concluded that the prevalence of CKD in this population was 11.4%. When taken the confidence interval of 95%, CKD prevalence in this group was between 10.3-12%.

In order to estimate prevalence of risk factors for CKD in this population, univariate and multivariate analysis were made and the following variables were taken into account: age, gender, arterial hypertension (AH), *diabetes mellitus* (DM) and body mass index (BMI). CKD was the dependable variable. Results are shown in Table 3. Age ≥ 60 had the highest OR (5.25) of association with CKD followed by the presence of hypertension (2.91), BMI ≥ 30 Kg/m² (1.81) and diabetes (1.78).

Table 3 Multivariate analysis of variables associated with CKD.

CKD	OR (CI 95%)	*p* value **
Age ≥ 60 (years)	5.25 (4.18 - 6.6)	< 0.001
Women	1.67 (1.32 - 2.12)	< 0.001
HTN	2.91 (2.27 - 3.74)	< 0.001
DM	1.78 (1.35 - 2.34)	< 0.001
BMI (kg/m²) 25 a 29,9	1.38 (1.02 - 1.86)	0.233
≥ 30	1.81 (1.34 - 2.45)	0.004

** Logistic regression model and Wald test, $p < 0.05$. Dependent variable: CKD; CKD - Chronic kidney disease; HTN - Arterial hypertension; DM - *Diabetes Mellitus;* BMI - Body mass index; OR- odds ratio; CI- confidence interval.

Table 4 Relationship of eGFR, age and albuminúria

eGFR (Categories)	Age: 18 - 29 (years)	30 - 59 (years)	≥ 60 (years)	Total patients (Albuminuria)#
≥ 90 (1)	756 (15)*	1648 (66)	149(12)	2553 (3.6 %)
60 a 89 (2)	129 (7)	1528 (20)	567 (39)	2224 (2.9%)
45 a 59 (3A)		139 (34)	234 (51)	373 (22.7%)
30 a 44 (3B)		7 (5)	52 (18)	59 (38.9%)
15 a 29 (4)		2 (2)	3 (3)	5 (100.0%)
< 15 (5)		1 (1)	1 (1)	2 (100.0%)
Total	885	3325	1006	5216

*Numbers in brackets represent absolute number of patients with albuminuria in each age group and CKD category, except the column of albuminuria # where the % of patients with albuminuria in each eGFR category is given.

CKD

Risk factors and CKD

Age.CKD was more prevalent in older patients (Table 1). Among 5,216 individuals, 4,210 (80.7%) were < 60 years old and those had a prevalence of CKD of 5.7%. In 1,006 individuals ≥ 60 years of age, 340 (33.8%) had CKD (p > 0,001). Of those, 234 individuals (68.8%) were in category 3A and 52 (15.3%) in category 3B (Table 4).

eGFR, age and albuminuria. As expected, albuminuria was more prevalent in those individuals with eGFR less than 60 ml/min. and in those older than 60 years of age (Table 4). In the age group (18-29), albuminuiria was present in 22 individuals (2.4%); in the age group (30-59) it was present in 128 (3.6%) and in those 60 years and older, 124 (12.0%). In those 60 years of age and older in CKD 3A, albuminuria was present in 21.7% and 34.6% in category 3B.

CKD and gender

CKD was more prevalent in women than men in this cohort. In the sample of 5,216 individuals, 580 had CKD and of those, 407 were women (70.2%) ($p < 0.001$) (Table 1).

Hypertension and CKD

Of those 580 patients with CKD, hypertension was detected in 389 (67%), whereas in those individuals with no CKD, hypertension was present in only 24% (Table 1).

Diabetes and CKD

In the CKD group (n = 580), 129 (22.2%) were diabetics whereas in the group without CKD (n = 4,636) diabetes was present in 271 (5.8%) individuals ($p < 0.001$) (Table 1).

Bmi and ckd

A BMI of 29.8 ± 5.5 was observed in the CKD group, while the control group had a BMI of 27.1 ± 5.1 ($p < 0.001$) (Table 1).

Discussion

This is the first evidence about the prevalence of CKD in Brazil that takes into account eGFR and albuminuria based on the KDIGO categorization.[8] The CKD prevalence of 11.4% in this randomly selected population from southern Brazil is not different of what has been found in other countries.[14]

None of the previous studies on CKD prevalence in Brazil took into account an estimated GFR and albuminuria. In 2002 Passos *et al.*[9] reported the prevalence of elevated serum creatinine in a small sample of 818 individuals in southeast Brazil. Besides the small sample, renal function was arbitrarily set based on serum creatinine levels for men (1.3 mg/dL) and 1.1 mg/dL for women. The authors only found elevated serum creatinine in the older group (5.0%).

Lessa[15] reported in 2004 the prevalence of higher serum creatinine levels in a population of 1,439 individuals in northeast of Brazil. However, a serious limitation of the study was the cut-off for abnormal serum creatinine of 1.3 mg/dL for either gender.

Our group previously reported in 2009 the results of a general chronic kidney disease awareness program applied to an urban population in a large Brazilian city. A total of 8,883 individuals were screened and the prevalence of proteinuria was of 6%.[16]

In another Brazilian study, 38, 721 individuals were evaluated in the State of São Paulo for the prevalence of CKD based on a urine dipstick test for detection of proteinuria. Proteinuria was detected in 7.3% of these individuals.[17]

De Moura *et al.*[18] reported in Brazil a 1.4% prevalence of self-reported chronic kidney disease among 60,202 individuals aged ≥ 18 years.

It remains to be seen if this prevalence reported here in our study is similar in northern Brazil where there is less Caucasians and a higher preponderance of afro-descendants (AD). There is evidence that afro--descendants have a four fold higher risk for CKD than Caucasians,[19-23] despite the fact that both groups have a similar CKD prevalence in the earlier stages of CKD.[23] although a more rapid decline of kidney function in the early stages of the disease.[24]

It was thought in the past that this difference was ascribed to social economic status and health care access but recent data point out the association of genetic variants and nephropathy in AD.[19,21,24,25] It has been shown that AD have two genetic variants of the gene responsible to codify apolipoprotein L1 (gene APOL1).[19] and these APOL1 gene variants are responsible for most cases of focal global glomerulosclerosis, HIV-associated nephropathy, hypertensive nephrosclerosis and lupus nephritis in this population. There is evidence that AD have 4 fold greater incidence of CKD than Caucasians[19,20] and have a more rapid decline of kidney function in the early stages of the disease.[24]

The finding of decreased GFR with aging as reported here raises some interesting points and labeling those individuals as having CKD, has given rise to a heated debate in the literature. It has been pointed out that reduction of GFR seen as part of "healthy" kidney aging in the absence of signs of kidney damage, usually identified by high albumin excretion, leads to over-diagnosis of CKD in many elderly subjects.[26,27]

Moreover, CKD Category G3A/A1 in the elderly is not associated with any significant reduction in remaining life expectancy.[28] Glassock *et al.*[29] pointed out that the presence of abnormal albuminuria, not a requirement for diagnosis of CKD G3A/A1, is much more important as a risk predictor in the elderly and in the young. Based on these facts, Glassock *et al.*[29] have proposed an age-sensitive approach to diagnosing CKD based on GFR alone, using a threshold of < 45 ml/min/1.73m^2 rather than < 60 ml/min/1.73m^2 in those over 65 years of age.

With regard to gender and CKD prevalence, our finding of higher CKD prevalence in women is supported by many reports in the literature, although our sample of individuals is biased since 64% were women. Nonetheless, the most recent USRDS data reveals a CKD prevalence between the years 2007-2012 of 15.1% for women and 12.1% for men.[30]

However, there are several opposing articles regarding this issue[31] (the role of gender in chronic kidney disease). It appears to be some geographic variability in the effect of gender on the prevalence of CKD. Interesting is the fact that the incidence of ESRD seems to be higher in men than women. The fact that most studies, including ours, use an estimated GFR equation based on patient's gender, among other variables, introduces a bias on the results.[31]

The association of higher prevalence of CKD in patients with hypertension, diabetes and or obesity found in our study corroborates the reported increase in CKD prevalence as a result of the ongoing epidemics of these entities, all recognized as important risk factors for CKD.[32,33]

Our study has several limitations. Serum creatinine was determined only once and the diagnosis of CKD requires a sustained GFR value for at least 3 months. The population of the study reflects a predominant Caucasian group not representative of the Brazilian population. According to the most recent ethnic data (2010), in Brazil 47.51% are Caucasians, 43.42% are "brown" or multiethnic background (Caucasians, afrodescendants and indigenous people) and 7.52% are "blacks" (afrodescendants).[34] Furthermore, one may argue that individuals that accepted to participate were those with known kidney disease and therefore raising the prevalence of CKD in this cohort.

In conclusion, the present study reveals for the first time a prevalence of CKD of 11.4% in southern Brazil in a predominantly Caucasian population randomly selected and based on estimated GFR and albuminuria. It remains to be seen if this data are reproduced in other regions of Brazil with a more prevalent afro-descendant population.

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