BJPS

Brazilian Journal of Pharmaceutical Sciences

http://dx.doi.org/10.1590/s2175-97902017000317185

Article

Association between kidney function and Framingham risk score in an admixed population of Brazil

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Chronic kidney disease (CKD) increases cardiovascular disease (CVD) risk development. However, the mechanisms of reduced kidney function with CVD risk are unclear. This study aimed to investigate the association between kidney function and Framingham risk score (FRS) in participants with traditional cardiovascular risk factors and normal estimated glomerular filtration rate (eGFR) > 60 mL/min/1.73 m² in an admixed population of Brazil. The participants were divided into three groups according to FRS: low risk group with 0% to <10%, moderate risk group with ≥10% to 20% and high risk group with >20%. The eGFR was calculated using Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI). Data from participants were collected by questionnaire, and blood and urine samples were collected to analyze biochemical markers. A total of 214 subjects aged 53±10 years old was collected. There were 77 individuals in low risk group, 59 in moderate risk group and 78 in high-risk group. Mean $eGFR_{CKD-EPI}$ was 89.39±15.05 mL/min/1.73 m² and 90.74±16.17 mL/min/1.73 m² when race adjustment. The results indicated that there is an increasing the cardiovascular risk with a decreased of eGFR, conforming to a significant inverse correlation observed between eGFR and FRS with Spearman correlation (R^2=-0.256, p<0.001; R^2=-0.224, p=0.001, when adjusted for race). There was a statistically significant difference in $eGFR_{CKD-EPI}$ (p<0.001) and $eGFR_{CKD-EPI}$ with race adjustment (p=0.002) among risk groups. The data suggests that the reduction eGFR is associated with elevated FRS among Brazilian adults without CKD. Furthermore, the results suggest that race adjustment it's not necessary in Brazilian population.

Keywords: Chronic kidney disease. Cardiovascular diseases/risk factors. Glomerular filtration rate. Framingham risk score (FRS).

INTRODUCTION

Chronic kidney disease (CKD), defined as renal damage or glomerular filtration rate <60 mL/min/1.73 m² for at least 3 months (Andrew *et al.*, 2005), is generally considered an independent risk factor for CVD (Sarnack *et al.*, 2003; Olechnowicz-Tietz *et al.*, 2013), increasing cardiovascular morbidity and mortality (Ito *et al.*, 2015). However, kidney function mechanisms with cardiovascular risk in participants with estimated glomerular filtration rate (eGFR) >60 mL/min/1.73 m² are unclear.

Early diagnosis of CVD along with proper assessment of cardiovascular risk is crucial for further reduction of health care costs and mortality rates (Pereira, Barreto, Passos, 2009). Several cardiovascular risk prediction models have been developed to estimate risk, with the Framingham risk score (FRS) being among them. The FRS allows physicians to estimate the individual 10-year cardiovascular risk by using traditional cardiac risk factors including gender, age, systolic blood pressure, hypertension treatment, diabetes mellitus history, total cholesterol, high-density lipoprotein cholesterol (HDL-cholesterol) and cigarette smoking (D'Agostino *et al.*, 2008). In addition to traditional cardiovascular risk factors, other factors, as kidney function, are under investigation in association with CVD (Jin *et al.*, 2014; Wang *et al.*, 2014; Lu *et al.*, 2016).

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Microalbuminuria is an established biomarker that reflects glomerular damage and is closely associated with the risk of all causes and cardiovascular mortality and CVD events (Wang, Yan, Yu, 2013). However, this method requires urine samples and could show altered results due to collection errors. In clinical practice, measuring of plasma creatinine has been most-used the method to assess kidney function, however it alone is not a sensitive method to assess asymptomatic patients with chronic kidney disease (CKD) (Fontela *et al.*, 2014). Instead, eGFR is the most feasible clinical measure of kidney function (KDIGO, 2013). Some studies have demonstrated that reduced eGFR is a predictor of major cardiovascular events (Jin *et al.*, 2014; Wang *et al.*, 2014; Ito *et al.*, 2015; Lu *et al.*, 2016).

Jin and contributors (2014) suggested that kidney function was also independently associated with CVD in a Chinese population without CKD (defined as eGFR <60 mL/min/1.73 m²), however their population was approximately 99% Han Yellow race, and conflicting conclusions may be obtained in different populations comprising subjects from other races. Therefore, the aim of the study was to investigate the association between kidney function and cardiovascular risk in participants with normal eGFR >60 mL/min/1.73 m² in an admixed population of Brazil.

MATERIAL AND METHODS

Study population

Originally, two-hundred and forty-eight participants were recruited for our study. However, two-hundred and fourteen male and female adults residents in the state of Rio Grande do Norte, Northeastern Brazil, were selected from the Hospital Universitário Onofre Lopes, at the Hemodynamics unit (n=138) who were undergoing cinecoronariography to investigate the presence and extent of coronary lesion and individuals from the Endocrinology unit (n=76) with metabolic syndrome criteria without endocrine disorders (except for diabetes mellitus). Exclusion criteria included diagnosis of chronic kidney disease (eGFR <60 mL/min/1.73 m²), elderly >70 years old, cardiomyopathy, heart valve disease, congenital diseases, pericarditis, coronary revascularization, liver failure, endocrine disorder (except for diabetes mellitus), chronic inflammatory diseases, malignant diseases, blood disorders, autoimmune diseases and family history of hypercholesterolemia. The study population was considered admixed due to the miscegenation of the Brazilian population, which is composed of several races. This study was approved by the hospital's Research Ethics Committee which complies with the Declaration of Helsinki under protocol number CAAE 0001.0.051.294-11 and a written informed consent was obtained from each individual.

Data collection

A questionnaire was designed to collect information on lifestyle risk factors, current medication and smoking habits (current or non-smoker). Weight and height were measured and body mass index (BMI) was calculated as the weight in kilograms divided by the square of the height in meters. Blood pressure was measured using a standardized mercury sphygmomanometer in the sitting position after at least 10 min of rest. Race was based on self-definition the Brazilian Institute of Geography and Statistics (IBGE) classification and defined into three principal race or color groups: white, brown and black subjects. Blood samples of all participants from the antecubital vein after a 12-hour overnight fast and 24-hour urine collection (76 participants) were collected. Biochemical markers, including fasting blood glucose (FBG), triglycerides (TG), total cholesterol (TC), HDL-cholesterol, serum creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and microalbuminuria were measured using colorimetric, colorimetric-enzymatic and immune-turbidimetric methods in BIO-2000 IL, a semi-automatic biochemical analyzer (Bioplus, São Paulo, Brazil). Values of LDL-cholesterol were calculated according to the Friedewald formula (Friedewald, Levy, Fredrickson, 1972).

FRS and definition of cardiovascular risk factors

The Framingham risk score equation (D'Agostino *et al.*, 2008) was used to calculate 10-year risk for developing CVD, according to cardiovascular risk factors: age, systolic blood pressure (treated or not treated), TC, HDL-cholesterol, smoking and diabetes mellitus (DM). They were divided into three groups according to FRS: low risk group with 0% to <10% risk, moderate risk group with ≥10% to <20% risk and high risk group with ≥20% risk. Hypertension was defined as using antihypertensive medication or having systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg. DM was defined as fasting serum glucose of at least 7.0 mmol/L or current use of blood glucose-lowering agents. Obesity was considered as BMI ≥30 kg/m². Dyslipidemia was defined according to V Brazilian Guidelines on Dyslipidemia and Prevention of Atherosclerosis (Xavier *et al.*, 2013) as: isolated hypercholesterolemia, LDL-c ≥ 4.13 mmol/L; isolated hypertriglyceridemia, TG ≥1.69 mmol/L; hyperlipidemia

mixed, LDL-c ≥ 4.13 mmol/L and TG ≥ 1.69 mmol/L; and low HDL-c, isolated reduction HDL-c, man < 1.03 mmol/L and woman < 1.29 mmol/L, or association with increased of LDL-c or/and TG.

Estimated glomerular filtration rate

Several equations have been proposed to estimate GFR based on serum creatinine and the most employed and analyzed equations are Modification of Diet in Renal Disease (MDRD) (Levey *et al.*, 1999) and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) (Levey *et al.*, 2009). When compared to MDRD equation, the CKD-EPI equation has shown greater accuracy, with better performance and risk prediction, using the same variables, especially when eGFR >60 mL/min/1.73 m² (Levey *et al.*, 2009; Matsushita e*t al.*, 2012), including healthy Brazilian adults (Soares *et al.*, 2010).

The eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation as follows:

$$eGFR = 141 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018 \text{ [if female]} \times 1.159 \text{ [if black when race adjustment]}$$

where S_{cr} is serum creatinine in mg/dL, κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of S_{cr}/κ or 1, and max indicates the maximum of S_{cr}/κ or 1(Levey *et al.*, 2009).

Statistical analyses

Statistical analysis was performed using SPSS® 20.0 software (SPSS, Chicago, IL, USA). Normal distribution was evaluated using the Kolmogorov-Smirnov test. Continuous variables are presented as mean and standard deviation and were compared using ANOVA followed by Tukey post-hoc test. Continuous variables with skewed distributions were analyzed using the Kruskal-Wallis test followed by the Mann-Whitney's test. Categorical variables were presented as number and percentage and were compared by chi-square test or Fisher test. Pearson and Spearman correlations were performed between all continuous variables. The level of statistical significance was accepted as $p < 0.05$.

RESULTS

Originally, two hundred forty-eight participants were recruited for our study, however, thirty-four participants with eGFR < 60 mL/min/1.73 m² were excluded. Thus, a total of 214 subjects aged 24-70 (53±10) years old remained. They were divided into three groups according to their FRS: low risk group – 77 individuals (36.0%), moderate risk group – 59 individuals (27.6%), high-risk group – 78 individuals (36.4%). No microalbuminuria was observed in 24-hour urine collection analyzed, confirming the preserved kidney function of these participants. Table I outlines the demographic and clinical data for all participants stratified by FRS. The majority of participants were white (51.4%). Compared with the low risk group, individuals with high cardiovascular risk were much older, had higher levels of fasting blood glucose and blood pressure and lower levels of HDL-cholesterol, as would be expected, since these variables were used for calculating FRS. Cardiovascular risk was much higher in men than in women.

Mean $eGFR_{CKD-EPI}$ was 89.39±15.05 mL/min/1.73 m² with a range of 60.05mL/min/1.73 m² to 133.97 mL/min/1.73 m², and mean $eGFR_{CKD-EPI}$ was 90.74±16.17 mL/min/1.73 m² with a range of 60.05mL/min/1.73 m² to 149.18 mL/min/1.73 m² when adjusted by the black race. A significant inverse correlation between eGFR and FRS was observed with Spearman correlation ($p<0.001$, $r^2=-0.256$; $p=0.001$, $r^2=-0.224$, when race adjustment), indicating that with increased cardiovascular risk, there is a decreased of eGFR. There were statistically significant differences in $eGFR_{CKD-EPI}$ ($p<0.001$) and $eGFR_{CKD-EPI}$ with race adjustment ($p=0.002$) among risk groups. Both equations are highly correlated ($p<0.001$, $r^2=0.976$).

The prevalence of traditional cardiovascular risk factors is displayed in Table II. Compared with individuals of low risk group, those of high risk group had higher prevalence of diabetes mellitus ($p<0.001$), hypertension ($p<0.001$) and dyslipidemia ($p=0.004$). In addition, the high risk group had a higher proportion of smokers.

Table III shows the distributions of race and kidney variables. It can be seen that no significant difference was found in serum creatinine between black, brown and white people, showing that in the Brazilian population it's not necessary race adjustment. In addition, it is worth mentioning that only the moderate risk group presented a significant difference between $eGFR_{CKD-EPI}$ (without adjustment race) and race.

DISCUSSION

Although the association between kidney function mechanisms and CVD risk incident still not fully understood, there are explanations why the level of kidney function may be an independent risk factor

TABLE I - Demographic and clinic data of the different groups of patients, classified according to FRS

Variables	Total (n=214)	Low risk group (n=77)	Moderate risk group (n=59)	High risk group (n=78)	*p-value*
Age, years	53±10	45±9	56±8*	59±7*§	<0.001
Sex male, n, %	105 (49.0)	28 (36.4)	21(35.6)	56 (71.8)	<0.001
BMI, kg/m²	28.6±5.4	27.9±5.7	28.9±5.8	29.0±4.7	0.364
Self-definition race					0.722
Black	19 (8.9)	5 (6.5)	5 (8.5)	9 (11.5)	
Brown	85 (39.7)	29 (37.7)	23 (39.0)	33 (42.3)	
White	110 (51.4)	43 (55.8)	31 (52.5)	36 (46.2)	
Fasting blood glucose, mmol/L	6.10±2.86	5.40±2.31	6.42±2.83*	6.55±3.25*	<0.001
Total cholesterol, mmol/L	4.98±1.40	5.06±1.45	4.94±1.33	4.92±1.41	0.774
HDL-cholesterol, mmol/L	1.05±0.32	1.23±0.32	1.01±0.28*	0.90±0.27*	<0.001
LDL-cholesterol, mmol/L	3.06±1.21	3.07±1.30	3.06±1.16	3.05±1.17	0.981
Triglycerides, mmol/L	1.89±1.15	1.66±0.89	1.91±0.74†	2.10±1.55†	0.036
ALT, µKat/L	0.58±0.90	0.63±1.44	0.61±0.32	0.51±0.33	0.067
AST, µKat/L	0.51±0.28	0.49±0.29	0.55±0.24	0.52±0.29	0.070
Creatinine, mmol/L	75.02±15.81	72.56±15.67	74.02±16.16†	78.20±15.35†‡	0.022
$eGFR_{CKD-EPI}$, mL/min/1.73 m²	90.49±14.90	95.85±15.19	88.86±15.13†	86.43±13.19*	<0.001
$eGFR_{CKD-EPI}$ (race adjustment), mL/min/1.73 m²	91.81±16.18	96.80±15.70	90.30±17.89†	88.02±14.08*	0.002
Diastolic pressure, mmHg	84±15	80±10	84±10†	89±19*§	<0.001
Systolic pressure, mmHg	137±25	125±15	131±18†	154±28*‡	<0.001

(*) compared with low risk group, p<0.001; (†) compared with low risk group, p<0.05; (‡) compared with moderate risk group, p<0.001; (§) compared with moderate risk group, p<0.05;BMI - Body Mass Index; HDL-cholesterol - High density lipoprotein; LDL-cholesterol - Low density lipoprotein; AST - aspartate aminotransferase; ALT - Alanine transaminase. Data are presented as mean ± standard deviation for parametric samples and percentage for non-parametric samples. Categorical variables were compared by Chi-square test. Parametric analysis was performed by one-way ANOVA followed by Tukey post hoc test. Non-parametric samples were performed by Kruskal-Wallis test followed by Mann Whitney test. P-values< 0.05 were considered statistically significant.

TABLE II - Prevalence of traditional cardiovascular risk factors among the groups (FRS)

Variables	Total (n=214)	Low risk group (n=77)	Moderate risk group (n=59)	High risk group (n=78)	*p-value*
Obesity, n, %	76 (35.5)	23 (29.9)	25 (42.4)	28 (35.9)	0.236
Sedentary lifestyle, n, %	107 (50.0)	29 (37.7)	34 (57.6)	44 (56.4)	0.032
Smoking, n, %	30 (14.0)	3 (3.9)	9 (15.3)	18 (23.1)	0.003
Dyslipidemia, n, %	194 (90.6)	63 (81.8)	56 (94.9)	75 (96.2)	0.004
Diabetes mellitus, n, %	60 (28.0)	9 (11.7)	16 (27.1)	35 (44.8)	<0.001
Hypertension, n, %	152 (71.0)	28 (36.4)	50 (84.7)	74 (94.9)	<0.001
Antihypertensive, n, %	148 (69.2)	28 (36.4)	48 (81.4)	72 (92.3)	<0.001

Categorical variables were compared by Chi-square test. P-values< 0.05 were considered statistically significant.

for increased cardiovascular risk. First, many of the traditional and nontraditional CVD risk factors that could affect endothelial function, such as older age, smoking, hypertension and dyslipidemia, can be found in association with CKD (Culleton e*t al.*, 1999). Second, reduced kidney function itself may be a risk factor for progression of

TABLE III - Distributions of races and kidney function among the groups (FRS)

Variables	Black	Brown	White	*p-value*
Total				
Creatinine, mmol/L	73.05±18.60	73.84±14.09	76.27±16.59	0.478
$eGFR_{CKD-EPI}$, mL/min/1.73 m²	96.03±16.00	91.50±15.91	88.75±13.68	0.104
$eGFR_{CKD-EPI}$ (adjustment race), mL/min/1.73 m²	110.89±18.46 *‡	91.50±15.91	88.75±13.68	<0.001
Low risk group				
Creatinine, mmol/L	77.79±17.00	70.72±16.54	73.19±15.11	0.731
$eGFR_{CKD-EPI}$, mL/min/1.73 m²	94.92±15.94	99.22±16.92	93.68±13.77	0.316
$eGFR_{CKD-EPI}$ (adjustment race), mL/min/1.73 m²	109.60±18.39	99.22±16.92	93.68±13.77	0.056
Moderate risk group				
Creatinine, mmol/L	60.11±17.00	74.18±14.54	76.14±16.57	0.128
$eGFR_{CKD-EPI}$, mL/min/1.73 m²	110.42±13.85 *‡	87.86±14.60	86.12±13.22	0.002
$eGFR_{CKD-EPI}$ (adjustment race), mL/min/1.73 m²	127.50±15.98 †§	87.86±14.60	86.12±13.22	<0.001
High risk group				
Creatinine, mmol/L	77.60±18.64	76.35±11.01	80.05±17.92	0.521
$eGFR_{CKD-EPI}$, mL/min/1.73 m²	88.65±12.70	87.26±13.60	85.13±12.48	0.686
$eGFR_{CKD-EPI}$ (adjustment race), mL/min/1.73 m²	102.38±14.65 †§	87.26±13.60	85.13±12.48	0.003

(*) compared with white group, p≤0.001; (†) compared with white group, p<0.05; (‡) compared with brown group, p≤0.001; (§) compared with brown group, p<0.05; Data are presented as mean ± standard deviation. Parametric analysis was performed by one-way ANOVA followed by Tukey post hoc test. Non-parametric samples were performed by Kruskal-Wallis test followed by Mann Whitney test. P-values< 0.05 were considered statistically significant.

ventricular remodeling and cardiac dysfunction, because it may alter sodium and fluid transport and, therefore, alter cardiac function (Jin *et al.*, 2014). Elevated asymmetric dimethyl arginine, reduced nitric oxide bioavailability and endothelial dysfunction from renal disease, which are associated with atherosclerosis, are recognized as kidney-damaging factors and contribute to increasing CVD risk (Kielstein *et al.*, 2002; Schiffrin, Lipman, Mann, 2007). Some studies have affirmed that CKD is an independent risk factor for developing CVD, therefore, subjects with CKD have higher cardiovascular risk (Chang, Kramer, 2011; Rule *et al.*, 2013; Chia, Lim, Ching, 2015). Thus, it's suggested that with the decrease eGFR, these biological effects should be occurring minimally, however enough to increase cardiovascular risk.

This study demonstrated an inverse association between eGFR and cardiovascular risk in subjects without CKD, since individuals with higher cardiovascular risk had reduced eGFR, compared to other risk groups. This result is similar to recent studies which reported that subjects without renal dysfunction had a significantly higher cardiovascular risk (Jin *et al.*, 2014; Wang *et al.*, 2014; Ito *et al.*, 2015; Lu *et al.*, 2016). In a cohort study, an inverse correlation (R^2 = -0.291, p<0.01) was found in Japanese patients with obesity and type 2 diabetes without severe renal dysfunction (Ito *et al.*, 2015). In a Chinese population, a longitudinal study confirmed a significant inverse association between eGFR and FRS (R^2 = -0.669 in 2008, R^2 = -0.698 in 2011, p_{all}<0.01) (Jin *et al.*, 2014). Moreover, a significantly higher FRS was observed among Chinese age 40 years or old with mildly decreased eGFR (60-89 mL/min/1.73 m²) (Lu *et al.*, 2016). However, there are conflicting findings from community-based studies on the association between mildly reduced eGFR and CVD, showing that eGFR is not independently associated with cardiovascular outcome in the general population (Smink *et al.*, 2012). The conflicting results can be explained by differences in study populations and the use of different formulas for the eGFR calculation, such as the MDRD equation. The results from our study provide additional support for the hypothesis that eGFR could be an independent risk factor for CVD.

However, it is difficult confirm the association between decreased renal function and increased cardiovascular risk in the current study, once the participants were generally accompanied by several comorbidities, considered as cardiovascular risk factors (Olechnowicz-Tietz *et al.*, 2013). Hypertension and

diabetes can affect renal filtration power and may enhance urinary albumin leakage, and together are major risk factors for the development of endothelial dysfunction and progression of atherosclerosis (Schiffrin, Lipman, Mann, 2007). In addition, in individuals with diabetes, the CKD-EPI equation presents poor performance with pronounced underestimation, especially for high-normal eGFR, because it seems to be associated with specific characteristics of patients with diabetes, such as hyperglycemia, glomerular hyperfiltration and obesity (Silveiro *et al.*, 2011).

Furthermore, age is the major confounding factor contributing to increased FRS and decreased eGFR. In the CKD-EPI equation, age is used as a central component to integrate muscle mass decrease with age, since the GFR begins to decrease between 30 and 40 years old and accelerate after 65-70 years old (Glassock, Rule, 2012). The average decline in GFR has been estimated at 1 mL/min/year (Bitzer, Wiggins, 2016). In addition, age is one of major risk factors for CVD in healthy populations (Jin *et al.*, 2014).

Our results showed that there is no difference when there is race adjustment. Barcellos *et al.* (2015) suggest that the inclusion of race adjustment in the eGFR is not necessary in the Brazilian population, because it did not contribute to more accurate results (Zanocco *et al.*, 2012). Survival studies evidence that the populations of different regions of Brazil are ancestrally more similar than previously realized, and the results showed that the predominant ancestry was European (white color) with a proportion around 60.1% in the Northeast Brazilian (Pena *et al.*, 2011; Zanocco *et al.*, 2012). Therefore, the intense biological miscegenation could attenuate the possible difference in the mean serum creatinine levels among races (Barcellos *et al.*, 2015). It's important to realize that race is equivalent of color in Brazil (in Portuguese, cor) and is based on a complex subjective phenotypic evaluation that includes skin pigmentation, hair pigmentation and type, eye melanization and facial features (Pena *et al.*, 2011).

To the best of our knowledge, this is the first study to report the association between eGFR and Framingham risk score in Brazilian population without CKD. However, our study has several limitations that merit comment. First, our population was small and had few black participants which limits the generalizability of this study. Second, the eGFR alone is relatively insensitive to clinically relevant gradients of risk (Freire-Aradas e*t al.*, 2014). In addition, our definition of eGFR was limited to a single measurement of serum creatinine on one occasion, not measured during period ≥ 3 months (Andrew e*t al.*, 2005). Finally, we did not have information on proteinuria and albuminuria, which may be independent risk factors for CVD outcomes (Wang *et al.*, 2014).

Although a single marker, our results indicate that the eGFR can identify CVD risk at an early stage. Also, the results confirm that it's not necessary to use race adjustment in the Brazilian population. More investigations should be made in other populations.

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Received for publication on 30th March 2017
Accepted for publication on 07th June 2017