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RESEARCH ARTICLE

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24-HOUR URINARY SODIUM EXCRETION IN CHRONIC KIDNEY DISEASE

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ABSTRACT

Objective: To correlate urinary sodium excretion in isolated sample with 24-hour urine and glomerular filtration rate in patients with chronic kidney disease. **Material and Methods:** Cross-sectional study with 185 patients. Urinary sodium excretion was evaluated in 24-hour urine and in isolated sample. The statistics used the Student or Mann Whitney t tests and Pearson or Spearman's correlation coefficients. **Results:** 58.9% were women, mean age of 59.8±12.1 years. The mean sodium excretion in 24-hour urine was 150.3±71.7 mmol/L and 108.8±51.2 mmol/L (p-value<0.001) in isolated sample were 82.5±43.6 mmol/L and 73.6±42.4 mmol/L (p-value=0.213) for men and women, respectively. They correlated with 24-hour sodium excretion, urinary sodium in isolated sample (r=0.53; p<0.001), low-density lipoprotein (r=0.32; p=0.003), high-density lipoprotein (r=-0.22; p=0.048). Low-density lipoprotein correlated with sodium in isolated urine (r=0.22; p= 0.047). **Conclusion:** Men with glomerular filtration rate <60 mL/min/1.73m² presented lower sodium excretion in 24-hour urine and isolated sample. Women with glomerular filtration rate <60 mL/min/1.73m² showed higher albuminuria, lower sodium excretion in isolated urine and lower total cholesterol and low-density lipoprotein.

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INTRODUCTION

Sodium is essential for homeostasis; its excess consumption is related to changes in blood pressure, volume overload and proteinuria, negatively influencing the emergence and development of Chronic Kidney Disease (CKD) (Riella, 2018). CKD generates high costs and high morbidity and mortality, being considered a global health problem. This article aimed to investigate whether urinary sodium excretion in isolated sample correlates with 24-hour urine and glomerular filtration rate (GFR) in CKD patients.

MATERIALS AND METHODS

This cross-sectional study was carried out with individuals met in the outpatient clinics of the Center for Prevention of Kidney Diseases (CPDR), a unit that is part of the University Hospital of the Federal University of Maranhão (HUUFMA), a reference in the state for diagnostic investigation and treatment of kidney diseases. This research is part of the project "URINARY SODIUM EXCRETION: Validation of Tanaka and Kawasaki Equations in Afrodescendants" in the city of São

Luis. The sample size was calculated considering a population of 1350 patients registered in the CPDR, an average sodium excretion of 203.1mmol/d, standard deviation of 84.9 mmol/d and a sampling error of 12 mmol/d (Santos, 2018). The minimum required number was 168 individuals, and, considering possible losses, the sample was increased by 10%, totaling 185 individuals. The analysis included individuals of both sexes, aged 18 years or older with glomerular filtration rate (GFR) $\geq 30\text{mL}/\text{min}/1.73\text{m}^2$ (corresponding to stages 1, 2, 3A and 3B of Chronic Kidney Disease). The sample did not include pregnant women, patients with autoimmune diseases, using immunosuppressive therapy, urinary infection, cancer, acquired immunodeficiency syndrome. Data were collected from October 2018 to May 2019. The selected individuals were informed of the objective of the research; those who agreed to participate signed the informed consent form. They answered a questionnaire regarding demographic, socioeconomic and lifestyle information, and were instructed about the process of laboratory examination collection and anthropometric evaluation. Laboratory dosages were processed in the laboratory, reference for patients from the University Hospital of the Federal University of Maranhão, including: fasting glucose (FG), total cholesterol (TC), low density lipoprotein (LDL-c), high density lipoprotein (HDL-c), triglycerides (TG), serum and urinary albumin, serum and urinary creatinine, serum and urinary sodium, and urine summary. Venous samples were collected after a 12-hour fast. Urinary sodium was dosed in isolated sample and 24-hour urine. For the collection of 24-hour urine, the patients were carefully instructed to pack the urine in appropriate vials, discard the first urine of the initial day of collection and, then, collect all urine produced during the 24-hour period, keeping it. Due to the possibility of collection error, 24-hour urine samples with a volume of less than 400mL or urinary creatinine $< 15\text{mL}/\text{Kg}/24\text{h}$ (men) and $< 10\text{mL}/\text{Kg}/24\text{h}$ (women) were disregarded. The isolated collection was made in the morning, at the end of the 24-hour collection in the CPDR. The reference values adopted for the lipid profile are those recommended by the National Cholesterol Education Program and for fasting blood glucose, the criteria recommended by the American Diabetics Association (Expert Panel on Detection, 2001; American Diabetes Association, 2010). For albumin, creatinine, serum and urinary sodium, the recommendations of the own method were adopted.

Two previous evaluations of renal function were considered to define CKD, with a minimum interval of 3 months, according to the Kidney Disease Improving Global (KDIGO 2012) (Kidney, 2013). GFR was estimated by the formula derived from the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) study, using creatinine as a reference for calculus (Levey, 2009). The results allowed obtaining the stage of the CKD. Anthropometric evaluation was performed by measuring body weight, height and waist circumference (WC). Weight was measured with the aid of a calibrated scale (FILIZOLA®, Brazil) with a maximum capacity of 150kg and subdivisions of 100g and height, with the aid of a portable stadiometer (ALTUREXATA®, Brazil), with a variation of 0.1 cm. WC was obtained at the midpoint between the last rib and the iliac crest at the time of expiration using inextensible tape (Sanny®, Brazil). Body mass index (BMI) was calculated using the ratio between body weight and height squared, using the World Health Organization (2000) classification for adults and LIPSCHITZ (1994) for the elderly (World Health Organization, 2000; Lipschitz, 1994). In the descriptive

analysis, the categorical variables were presented by frequencies and percentages and quantitative variables, by mean and standard deviation (mean \pm SD). The normality of the variables was tested by the Shapiro-Wilk test. To analyze the relationship between urinary sodium and variables of interest, Student's and Mann Whitney's t-tests and Pearson or Spearman's correlation coefficients were performed, when applicable. (STATA version 14.0, Stata Corporation, College, Sation, Texas) was used and the significance level adopted was 5%. The study approved by the Research Ethics Committee at the University Hospital of the Federal University of Maranhão, under opinion n. 2.904.987, being conducted in accordance with the principles established by the Resolution of the National Health Council of the Ministry of Health n. 466/12.

RESULTS

Of the 185 patients included, the mean age was 59.8 ± 12.1 years, 58.9% were women, 46.7% married, 55.6% received up to three minimum wages monthly and 49.5% had complete secondary education. Regarding lifestyle, 44.3% reported being smokers and 38.0% consuming alcoholic beverages (Table 1). The mean sodium excretion in 24-hour urine was 150.3 ± 71.7 mmol/L and 108.8 ± 51.2 mmol/L (p-value <0.001) and in isolated sample of 82.5 ± 43.6 mmol/L and 73.6 ± 42.4 mmol/L (p-value=0.213) for men and women, respectively. In men and women, 75.0% and 53.2% (p=0.003) had a previous diagnosis of CKD, respectively. (Data not shown in table). Upon evaluating the association between laboratory variables and GFR, males with $\text{GFR} < 60 \text{ mL}/\text{min}/1.73\text{m}^2$ expressed lower mean values in isolated sample when compared to those with $\text{GFR} \geq 60 \text{ mL}/\text{min}/1.73\text{m}^2$ (72.2 ± 34.0 mmol/L vs 110.9 ± 55.7 mmol/L; p-value=0.006). Women with $\text{GFR} < 60 \text{ mL}/\text{min}/1.73\text{m}^2$ showed higher mean urinary albumin excretion (114.1 ± 282.4 g/dL vs 19.9 ± 51.4 g/dL; p-value=0.038) and lower mean values in isolated sample (62.4 ± 33.9 mmol/L vs 86.6 ± 47.6 mmol/L; p-value=0.004), differences were also observed in relation to TC (177.0 ± 50.9 g/dL vs 199.3 ± 45.8 g/dL; p-value=0.004) and LDL-c (94.8 ± 47.1 g/dL vs 120.2 ± 39.2 g/dL; p-value <0.001) (Table 2). There was correlation between urinary sodium excretion in a 24-hour sample, urinary sodium in isolated sample (r=0.53; p <0.001), LDL-c (r=0.32; p=0.003) and HDL-c (r=-0.22; p=0.048). Only LDL-c showed correlation with sodium in isolated urine sample (r=0.22; p=0.047) (Table 3).

DISCUSSION

Increased levels of sodium excretion increases the risk of progression of CKD (He, 2016). Urinary sodium excretion was higher among males, both in the 24-hour urine evaluation and in isolated sample, regardless of GFR values. Concerning sodium in isolated sample, urinary excretion was higher for men when compared to women (82.5 ± 43.6 mmol/day vs 73.6 ± 42.0 mmol/day). Data from 827 individuals from the National Health and Nutrition Examination Survey (NHANES) aged 20 to 69 years demonstrated, in the analyses by gender, mean sodium excretion of 420 mg (95% CI, 3959-4452) in men and 303 mg (95% CI, 2844-3234) in women (Cogswell, 2018). The higher sodium intake in men is probably related to higher energy intake, i.e., higher sodium intake per calorie (Angell, 2014). Of the participants, the majority smoked or drank at some point in their lives (44.3% and 38%), respectively. Smoking, added to other risk factors, such as diabetes and hypertension, further raises the possibility of kidney damage.

Table 1. Demographic, socioeconomic and lifestyle characterization, by gender, of CKD patients met by the Center for Prevention of Kidney Diseases in São Luís - MA, Brazil 2019

Variables	Total	Male	Female	<i>p-value</i>
	n (%)	n (%)	n (%)	
Age				0.190
<40 years	13 (7.0)	3 (3.2)	10 (9.2)	
≥40 and <60 years	63 (34.0)	23 (30.3)	40 (36.7)	
≥60 years	109 (58.9)	50 (65.8)	59 (54.1)	
Mean ± sd	59.8±12.1	60.8±10.8	59.1±12.0	
Income (minimum wages)				0.037
≤1	68 (36.8)	20 (26.3)	48 (44.0)	
>1 - ≤3	103(55.6)	48 (63.2)	55 (50.5)	
≥3	14 (7.6)	8 (10.5)	6 (5.5)	
Education				0.643
No education	10 (5.5)	3 (4.0)	7 (6.6)	
Primary education	66 (36.3)	30 (39.5)	36 (33.9)	
Secondary education	90 (49.5)	38 (50.0)	52 (49.1)	
Higher education	16 (8.7)	5 (6.5)	11 (10.4)	
Smoking				0.714
Yes	81 (44.3)	33 (44.0)	48 (44.4)	
No	12 (6.6)	6 (8.0)	6 (5.6)	
Ex-smoker	90 (49.1)	36 (48.0)	54 (50.0)	
Alcohol consumption				0.018
Yes	70(38.0)	19 (25.0)	51 (47.2)	
No	31(16.9)	17 (22.4)	14 (13.0)	
Ex-consumer	83(45.1)	40(52.6)	43 (39.8)	
Marital Situation				<0.001
Unmarried	46 (25.0)	9 (11.8)	37(34.3)	
Married	86 (46.7)	50 (65.8)	36 (33.3)	
Others	52(28.3)	17(22.4)	35 (32.4)	

Table 2. Distribution of laboratory and anthropometric variables, by gender and Glomerular Filtration Rate, of CKD patients met by the Center for Prevention of Kidney Diseases in São Luís - MA, Brazil, 2019

Variable	Male			Female		
	GFR≥60 X±sd	GFR<60 X±sd	<i>p-value</i>	GFR ≥60 X±sd	GFR <60 X±sd	<i>p-value</i>
Serum Na	140.0±2.5	139.4±12.6	0.266	137.2±19.2	140.0±19.2	0.479
24h Na	137.2±19.2	140.0±3.9	0.242	127.4±66.0	124.7±5.8	0.566
Isolated Na	110.9±55.7	72.7±34.0	0.006	86.6±47.6	62.4±33.9	0.004
Urinary Alb.	31.1±45.5	258.4±742.7	0.659	19.9±51.4	114.1±282.4	0.038
CRP	0.2±0.3	0.4±0.8	0.369	0.2±0.2	0.3±0.5	0.683
FG	113.3±47.5	108.8±31.7	0.419	107.8±41.1	111.6±34.9	0.164
TC	172.5±21.3	161.9±41.4	0.052	199.3±45.8	177.0±50.9	0.004
HDL-c	42.9±17.4	39.7±10.4	0.755	51.9±16.9	51.4±17.6	0.865
LDL-c	100.4±25.7	91.1±36.0	0.163	120.2±39.2	94.8±47.1	<0.001
TG	166.9±124.8	155.8±63.6	0.557	140.6±70.7	153.7±69.6	0.289
BMI	30.0±5.5	28.0±3.9	0.079	29.5±4.8	28.0±4.8	0.099
WC	102.7±13.9	99.9±11.2	0.384	94.6±9.7	92.7±12.2	0.372

GFR - glomerular filtration rate (mL/min/1.73m²), Serum Na - Serum Sodium, 24h Na - sodium in a 24-hour urine sample, Isolated Na - Sodium in isolated urine sample, Urinary Alb. - Urinary albumin, CRP - C-reactive protein, FG - Fasting glycaemia, TC - Total cholesterol, HDL-c - High Density Lipoprotein, LDL-c - Low density lipoprotein, TG-Triglycerides, BMI - Body Mass Index, WC - Waist Circumference.

Table 3. Correlation of laboratory and anthropometric variables with sodium excretion in 24-hour urine and in isolated sample, in CKD patients met by the Center for Prevention of Kidney Diseases in São Luís - MA, Brazil 2019.

Variables	24h Na		Isolated Na	
	r	<i>p-value</i>	r	<i>p-value</i>
Isolated Na	0.53	<0.001*		
Urinary Albumin	-0.08	0.448	-0.18	0.098
CRP	-0.16	0.155	-0.04	0.970
FG	0.14	0.204	0.10	0.391
TC	0.17	0.133	0.11	0.299
HDLc	-0.22	0.048*	-0.18	0.096
LDL-c	0.32	0.003*	0.22	0.047*
TG	0.04	0.724	0.07	0.507
BMI	0.19	0.081	0.10	0.388
WC	0.26	0.018*	0.07	0.535

24h Na - sodium in a 24-hour urine sample, Isolated Na - sodium in isolated sample, Serum Na - serum sodium, HDL-c - High Density Lipoprotein, LDL-c - Low Density Lipoprotein, BMI- body mass index and WC- waist circumference. PCR - C-reactive protein, FG - fasting glycaemia, TC - total cholesterol.

A cohort that evaluated alcohol consumption in CKD based on the comparison of subgroups of non-alcoholics, occasional alcoholics and frequent alcoholics, identified that there was no change in GFR and concluded that alcohol consumption in moderate amounts has a cardioprotective effect (Wu, 2018). The prevalence of CKD was higher in males. The progression of CKD is arguably faster in men than in women. Gender dimorphism in the course of kidney disease is replicated by hormonal manipulation, suggesting that the actions of sex hormones, not structural differences between the sexes, are responsible for gender-related differences in the progression of kidney disease. Sex hormones greatly influence, by mediating progressive kidney injury, including cell proliferation, synthesis and degradation of the mesangial matrix, generation of reactive oxygen species and expression of pro-inflammatory cytokines, hormones and vasoactive agents (Neugarten, 2020). A trial involving 3,939 adults with CKD demonstrated, in the model adjusted for age, race/ethnicity and renal function, that women had a 17% lower risk of progression and death compared to men. The mean non-adjusted GFR was 21.09 mL/min per 1.73 m² per year in women and 21.43 mL/min per 1.73 m² in men (Ricardo, 2019).

Men with GFR < 60 mL/min/1.73m² exhibited lower mean values of sodium excretion in isolated sample when compared to individuals with GFR ≥ 60 mL/min/1.73m² (p-value=0.006). Reference analyses in the human population showed that patients with primary hypertension had significantly fewer nephrons than control individuals; however, when questioning this observation, whether hypertension is a cause or consequence of nephron deficiency is unknown and the precise role of this deficiency in the progressive decline of GFR remains an unanswered question (Fong, 2014). Women with GFR < 60 mL/min/1.73m² had higher mean urinary albumin with statistically significant difference (p-value 0.0038). KDIGO (2012) highlights albuminuria as a risk marker for diagnosis and adverse outcomes, as it makes up urinary proteins in most kidney diseases (Kidney, 2013). Researchers also point out that 1/4 of the people in stage 3 of CKD have micro or macroalbuminuria (Riella, 2018). In relation to sodium in isolated sample, the mean excretion was lower in women. Data from the longitudinal study of adult health Brazil (ELSA Brazil) show a significant difference by gender in relation to sodium intake, attributing this difference to women's greater concern with health and, because of this, they probably have a better quality eating, consume a greater amount of fruits and vegetables when compared to men (Deeks, 2009; De Assumpção, 2017; Malta, 2015).

They also had lower TC and LDL-c values. The mean age of women of this study was 59.1±12.05 years, beyond the reproductive phase and, consequently, with decreased hormone production. These changes are related to decreased levels of estrogen and progesterone, which leads to muscle and bone mass loss in women, who tend to accumulate fat reserves, generating weight and abdominal circumference elevation, added to increased total cholesterol and LDL-c levels and reduced HDL-c (Conte, 2017). Moreover, physiological and biochemical changes related to chronic kidney disease, regardless of its stage, may cause changes in the lipid profile of patients. Dyslipidemia is also able to damage kidney cells and favor the progression of CKD (Peres, 2015). Among the variables that correlated with 24-hour urinary sodium, sodium in isolated urine sample was positively correlated (0.53<0.001). The 24-hour urinary sodium excretion is

considered the gold standard to evaluate excretion, as it reflects the amount of sodium ingested during the day, however, presents inconveniences related to the collection and depends on the person's understanding (Mill, 2015). Thus, a comfortable alternative to this situation is the collection in isolated sample. Data from a population with characteristics similar to this evaluated the relationship between urinary sodium excretion and associated factors, stressing that the isolated urine sample can generate biased data, because urine alone is the elimination occurred in a given temporal cutoff, which ends up disregarding possible circadian variations in sodium elimination. Nevertheless, this would be an alternative to minimize the errors arising from the 24-hour collection, especially in population-based surveys (Santos, 2018). HDL-c was negatively correlated with a risk factor for greater sodium excretion in a 24-hour sample, while LDL-c was positively correlated. However, LDL-c also correlated with sodium excretion in isolated sample. Both total cholesterol and LDL-c, when very high, can induce or cause stenosis in blood vessels, limiting blood flow through atheroma plaques, thus increasing the risk of infarction or cerebrovascular accident (22). Furthermore, the increased HDL-c and the decreased LDL-c can protect against cardiovascular risk (Barbosa, 2015). An important limitation of the study is the sample size, which is statistically representative of the population studied, which limits inferences of precision, but does not compromise the validity of our findings. A strong point is the use of a method considered gold standard to evaluate sodium intake.

Conclusion

The results showed that men with GFR < 60 mL/min/1.73m² presented lower mean sodium excretion in both 24-hour urine and in isolated sample. Women with GFR < 60 mL/min/1.73m² had higher albuminuria value and lower sodium excretion values in isolated urine samples as well as lower mean TC and LDL-c. It is noteworthy that, although the mean values of excretion corresponded to a consumption of 3.5 g for men and 2.6 g for women, within the established for the general population, this population already has renal dysfunction. Therefore, it is important to emphasize that the measurement of sodium excretion, either in 24-hour urine, as is recommended, for being the gold standard, or the collection of urine alone, can be incorporated into clinical practice as a preventive measure to slow the progression of CKD.

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