Formula to detect high sodium excretion from spot urine in chronic kidney disease patients

Fórmula para detectar elevada excreção de sódio a partir de amostra isolada de urina de pacientes com doença renal crônica pré-dialítica

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Abstract

Introduction: Excessive sodium intake is related to adverse renal and cardiovascular outcomes in patients with chronic kidney disease (CKD) and assessment of sodium intake is complex and not evaluated very often in clinical practice. **Objective:** To develop a new formula to estimate 24h sodium excretion from urine sample (second void) of patients with CKD. **Methods:** We included 51 participants with CKD who provided 24-hour urine collection and a sample of the second urine of the day to determine the sodium excretion. A formula to estimate the 24-hour sodium excretion was developed from a multivariate regression equation coefficients. The accuracy of the formula was tested by calculating the P30 (proportion of estimates within 30% of measured sodium exection) and the ability of the formula to discriminate sodium intake higher than 3.6 g/day was evaluated by ROC curve. **Results:** Correlation test between measured and estimated sodium was significant (r = 0.57; $p < 0.001$), but P30 test identified a low accuracy (61%) of the formula. Different cutoff points were tested by *performance* tests and a ROC curve was generated with the cutoff that showed better *performance* (3.6 g/day). An area under the curve of 0.69 with a sensitivity of 0.91 and specificity of 0.53 was obtained. **Conclusion:** A simple formula with high sensitivity in detecting patients with sodium consumption higher than 3.6 g/day from isolated urine sample was developed. Studies with a higher number of participants and with different populations are necessary to test formula´s validity.

Keywords: kidney failure, chronic; sodium, dietary; urine specimen collection.

Resumo

Introdução: O consumo excessivo de sódio está relacionado a piores desfechos renais e cardiovasculares em pacientes com doença renal crônica (DRC), mas a avaliação deste consumo é complexa e mensurada com baixa frequência na prática clínica. **Objetivo:** Desenvolver uma nova fórmula para estimar a excreção de sódio de 24h a partir da concentração de sódio em amostra isolada da segunda urina do dia em pacientes com DRC pré-dialítica. **Métodos:** 51 participantes com DRC forneceram coleta de urina de 24h e uma amostra da segunda urina do dia para determinação da excreção de sódio. Uma fórmula para estimar a excreção de sódio de 24h foi desenvolvida a partir dos coeficientes da equação de regressão. A acurácia da fórmula foi testada por meio do cálculo do P30. A habilidade da fórmula em discriminar consumo de sódio superior a 3,6 g/dia foi avaliada pela curva ROC. **Resultados:** O teste de correlação entre sódio mensurado e estimado pela fórmula foi r = 0,57; $p < 0,001$, porém o resultado do P30 identificou baixa acurácia (61%). Diferentes pontos de corte foram testados por meio de testes de *performance* e uma curva ROC foi gerada com o ponto de corte de melhor *performance* (3,6 g/dia). Foi obtida uma área sob a curva de 0,69 com sensibilidade 0,91 e especificidade 0,53. **Conclusão:** Foi desenvolvida uma fórmula simples com elevada sensibilidade em detectar pacientes com consumo de sódio superior a 3,6 g/dia a partir de amostra de urina isolada. Estudos que testem a fórmula com um maior número de participantes e com outras populações são necessários.

Palavras-chave: coleta de urina; falência renal crônica; sódio na dieta.

Introduction

Chronic kidney disease (CKD) is a relevant public health issue because of its elevated prevalence and significant morbidity and mortality,[1] particularly when connected to cardiovascular disease (CVD).[2] Additionally, the progression of CKD markedly deteriorates the quality-of-life of patients and exponentially increases treatment costs.[3] Therefore, limiting progression to more advanced stages of CKD and attenuating cardiovascular risk are two of the main goals of treatment protocols offered to patients affected by this condition.[4,5]

It has been established that managing blood pressure (BP) and decreasing urinary protein play a key role in preserving renal function and controlling the complications associated with CKD.[6] Sodium intake is a modifiable risk factor associated with complications in BP management and proteinuria. In addition to the known effects of sodium on fluid overload,[7,8] evidence indicates that excessive sodium intake directly affects the vascular system by mediating factors such as inflammation, oxidative stress, endothelial dysfunction, and arterial stiffness.[9-11]

In addition to improved BP and urinary protein management, studies looking into the effects of decreasing sodium intake levels on patients with CKD[7,12] have indeed found associations between elevated sodium intake and renal function deterioration and poorer cardiovascular outcomes.[13,14]

Despite its relevance, the assessment of sodium intake levels in clinical settings is complex and rarely performed. A handful of studies in which this assessment was carried out in patients with CKD found that 60-90% of the individuals had more than 6 g of salt per day,[15-17] the maximum amount recommended by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF/KDOQI).

The inherent inaccuracy of food intake assessment methods[18] and the inconvenience of collecting a 24-hour urine specimen[19] are the main reasons why sodium intake is seldom analyzed. Nonetheless, the WHO considers the amount of sodium excreted within a 24-hour period a gold-standard method, since renal sodium excretion reflects almost entirely an individual's sodium intake.[20]

Nocturnal, casual, and isolated urine sample testing have been proposed as simpler processes and possible substitutes for 24-hour urine specimen collection.[20] The validity of these tests in representing sodium intake levels is particularly dubious in individuals with CKD, as their sodium excretion might be altered.[21] Little research has been carried out on this matter to date, but recent studies have supported the validity of this method as a marker of sodium intake in individuals with CKD.[22-24]

We were unable to find studies performed with Brazilian patients whose purpose was to develop a formula or validate the methods in place for the estimation of 24-hour sodium excretion from urine specimens. Therefore, two formulae published by foreign authors were tested in this study: a simple formula developed from a British cohort of patients diagnosed with stage-3 CKD in the Renal Risk in Derby (RRID) study,[23] and the formula proposed by Tanaka *et al*. in 2002[24] from a group of Japanese individuals.

However, when the 24-hour sodium excretion values estimated for our patients were compared to their measured levels, either of the formulae performed to satisfaction: the P30 (portion of estimated values with differences below 30% when compared to measured values) was 27.5% for the RRID and 40% for the formula published by Tanaka *et al*.

Thus, this study aimed to develop a new formula to estimate 24-hour sodium excretion from sodium levels observed in an isolated specimen taken from the second urine of the day of a group of Brazilian patients with pre-dialysis CKD.

Methods

Participants

The participants included in this study took part in a prospective randomized controlled trial called SALTED,[25] whose main goal was to assess the impact of a dietary intervention designed to reduce sodium intake levels in patients with pre-dialysis stage CKD.

The baseline data from the SALTED trial were used in this study. The study was performed at the Nephrology Clinic of the *Santa Casa de Misericórdia* Hospital of the Catholic University of Paraná from June of 2010 to April of 2013. Patients with pre-dialysis CKD of any stage and etiology were included.

Individuals on dialysis, pregnant patients, subjects under the age of 18, and acutely decompensated patients (infection, active autoimmune disease, cardiac or liver decompensation) were excluded. The participants signed informed consent terms and the institution's Research Ethics Committee approved the study.

Data collection

In the first appointment, the patients in both groups were given a sterile container and were instructed to collect a 24-hour urine specimen (according to the established protocol) the day before their visit with the study staff. The patients were advised to fast before the visit.

On the day of the visit, each patient brought a 24-hour urine specimen and had an isolated specimen of the second urine of the day and a blood sample collected. Participants were carefully advised to collect their 24-hour urine specimens properly; the collection procedure was checked when the patients surrendered their specimens. An automated method was used to measure urine sodium levels in the 24-hour urine specimens (Architect CI-8200 - Abbott Diagnostics).

The MDRD equation was used to estimate the glomerular filtration rate.

Statistical analysis

This study employed the same formula development method used in the RRID study.[23] Correlation tests were applied to continuous variables and the *t*-test to categorical variables in order to identify potential determining factors related to 24-hour urinary sodium excretion. Pearson's or Spearman's test was applied based on variable distribution.

The variables significantly associated with 24-hour urinary sodium excretion were submitted to regression analysis; 24-hour urinary sodium excretion was the dependent variable. A formula to estimate 24-hour urinary sodium excretion was derived from the coefficients obtained from the regression equation. The P30 (portion of estimated values with differences below 30% when compared to measured values) was calculated to test the accuracy of the formula.

Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated in order to assess the ability of the formula to discriminate sodium excretion values greater than 2.4, 3.6 and 4.8 g/day (or 6, 9 and 12 g of NaCl). An ROC curve was generated to assess sensitivity and specificity and calculate the area under the curve. A Bland-Altman plot was used to analyze the concordance limits between measured and estimated urinary sodium excretion values. The data sets were analyzed with statistical package IBM SPSS version 21.

Results

Table 1 shows the demographic and biochemical variables captured for the patients included in the study. Most individuals were males aged 60+ years (66%). More than half were diagnosed with stage-3 CKD (creatinine clearance between 30 and 60 ml/min) and 88% had daily sodium excretion levels above 2.4 g/day.

Table 1 Main characteristics of the study population (N = 51)

Male (%)	55
Age (years)	64.5 ± 1.0
BMI (kg/m^2)	29.0 ± 5.3
Glomerular filtration rate (ml/min)	38.4 ± 15.4
Stage-2 CKD (%)	10
Stage-3 CKD (%)	59
Stage-4 CKD (%)	29
Stage-5 CKD (%)	2
24-hour urinary sodium (g/day)	4.2 ± 1.6
< 2.4 g/day (%)	12
2.4 to 3.6 g/day (%)	31
> 3.6 g/day (%)	57

BMI: body mass index; CKD: chronic kidney disease.

Significant correlations were found between 24-hour urinary sodium excretion and weight (r = 0.31; $p < 0.05$) and sodium in the urine specimen (r = 0.40; $p < 0.01$); sodium excretion was significantly higher in males when compared to females (4.8 ± 1.7 *vs.* 3.7 ± 1.2 g/day; $p < 0.05$).

The three variables mentioned above were included in the regression analysis and all were considered as independent determining factors for 24-hour urinary sodium excretion values. A formula was derived from the coefficients of the regression equation to estimate 24-hour urinary sodium excretion based on the three variables:

Females:
Estimated 24-hour urinary sodium excretion (g/day) = 0.15 + (weight in kg x 0.03) + (sodium in the urine specimen in g/L x 0.63)

Males:
Estimated 24-hour urinary sodium excretion (g/day) = 0.96 + (weight in kg x 0.03) + (sodium in the urine specimen in g/L x 0.63)

The difference between measured and excreted sodium was -0.01 g/day (Figure 1). The correlation between measured and estimated sodium excretion was moderate (r = 0.57; $p < 0.001$), but the P30 test revealed that the accuracy of the formula was low (61%). Therefore, sensitivity, specificity, PPV, and NPV were calculated for the chosen cutoff points (2.4, 3.6 and 4 g/day) in order to assess the ability of the formula to identify individuals with sodium intake above recommended levels, as shown in Table 2.

Figure 1. Bland-Altman plot eliciting the differences between estimated and measured sodium excretion.

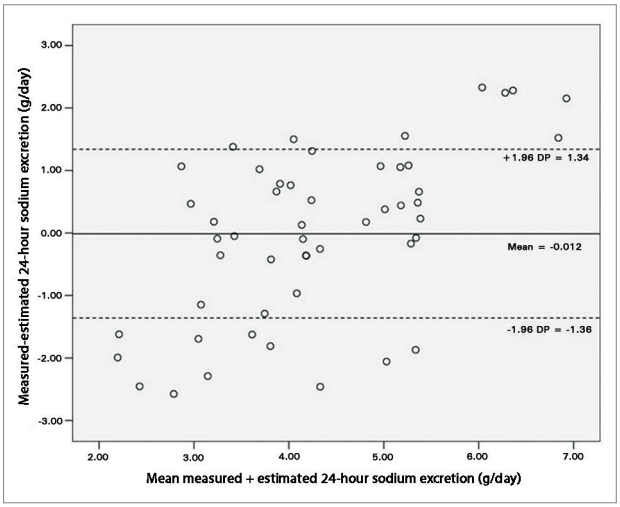


Table 2 Tests to assess the *performance* of the formula at detecting excessive sodium intake for different cutoff points

Sodium (g/day)	Sensitivity	Specificity	PPV	NPV
2.4	97	0	88	88
3.6	91	47	77	73
4.8	70	58	65	63

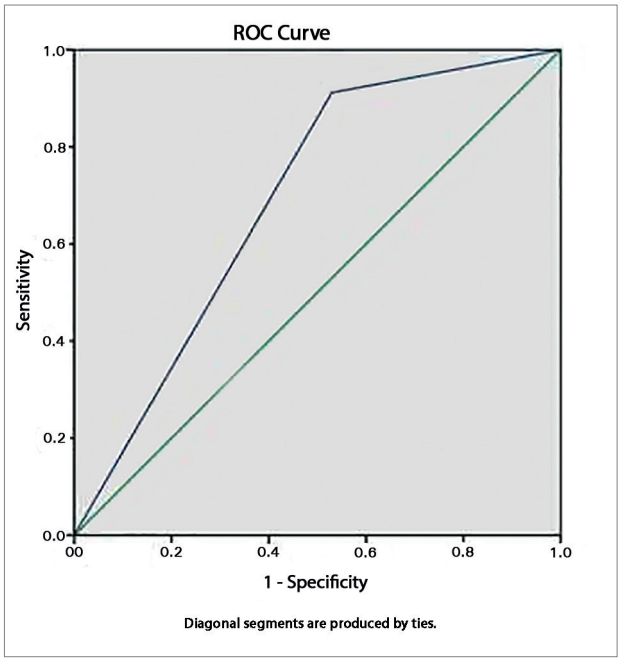
PPV: positive predictive value; NPV: negative predictive value.

An ROC curve was generated ROC and the cutoff point with better *performance* was identified (3.6 g/day) with an area under the curve of 0.69, sensitivity of 0.91, and specificity of 0.53 (Figure 2).

Discussion

Despite its relevance, the assessment of sodium intake levels in clinical practice is hindered by the inconveniences of the 24-hour urine specimen collection process. The main contribution offered by this study was the development of a simple and highly sensitive formula to detect individuals with

Figure 2. ROC curve showing sensitivity and specificity of measured *vs.* estimated sodium excretion at a cutoff point of 3.6 g/day.



elevated sodium intake levels based on a specimen of the second urine of the day.

As mentioned previously, the formula published by Tanaka *et al.*[24] and the equation developed to estimate sodium intake by British patients with CKD were tested in our patient population and neither performed adequately.

The formula published by Tanaka *et al.*[24] was developed in 2002 from urine specimens collected at any time from 591 Japanese patients enrolled in the INTERSALT study; the equation includes variables such as urinary sodium and creatinine levels, age, weight, and height.

This formula was tested by Ogura *et al.*[15] in 96 Japanese patients with various stages of CKD (mean glomerular filtration rate: 53 ± 27 mL/min) based on urine specimens collected at any time.

The authors found a moderate correlation of 0.52 between measured and estimated sodium levels ($p < 0.01$) and better *performance* at detecting patients with sodium intake levels greater than 170 mmol/day, or 4 g/day (area under the curve 0.83). Differences pertaining to ethnicity, renal function, and collection method might explain the poor *performance* the Tanaka formula had in our population.

Considering the formula proposed in the RRID study, although both studies enrolled individuals with CKD, the time at which urine specimens were

collected differed (first *vs*. second urine of the day) and a number of other factors may have influenced the formula's poor *performance* with our patient population. To name a few, the Brazilian study included patients diagnosed with CKD of other stages and, more importantly, sodium intake was significantly higher than that of the British study population (4.2 ± 1.6 *vs*. 2.8 ± 1.4 g/day).

The formula published in the RRID study was developed to estimate the sodium intake levels of more than 1,700 patients who were not offered 24-hour urine specimen collection. Similarly to our study, the accuracy of their formula was low (P30 = 60%), but the sensitivity to detect individuals with sodium intake above the recommended level of 2.4 g/day was equally high (85%).

Thus, in the subsequent analyses, sodium intake was granted the status of categorical variable, which meant patients were divided into groups of individuals with adequate (up to 2.4 g/day) or excessive (> 2.4 g/day) sodium intake levels.[23] The determining factors connected to excessive sodium intake were identified,[17] as well as the relationships with risk factors for renal disease progression and cardiovascular disease[26] and the effects of decreasing sodium intake to adequate levels after one year of follow-up.[27]

The observed results (and the relationships with blood pressure and urinary protein) were similar to the ones of better controlled studies,[7,12] in which 24-hour urinary sodium was also used as part of the method, thus reinforcing the reliability of this assessment method.

In our study, only 12% of the patients presented sodium intake below recommended levels (2.4 g/day), while in the RRID study 42% of the individuals complied with the recommendations. This fact may have precluded the use of the same cutoff point, since specificity was 0%, i.e., the formula was unable to detect patients with sodium intake levels below 2.4 g/day.

Therefore, as most participants had sodium intake levels well above the recommendation, using a higher cutoff point for sodium intake may be more useful from the clinical standpoint. In fact, the sodium intake levels observed in the participants of the study were similar to the levels seen in the Brazilian population in general.

According to the Family Income Poll (*Pesquisa de Orçamentos Familiares* - POF) of 2008-2009, the availability of sodium per household adjusted for an intake of 2,000 kcal was 4.7 g/person/day, or 11.7 g of salt daily.[28] Unlike wealthy nations, most of the sodium available in Brazilian households comes from cooking salt and salt-based condiments (74.4%).[28]

The differences related to the time of urine specimen collection were tested in a cross-sectional study enrolling patients with pre-dialysis stage CKD, in which three urine samples were collected at different times (morning, afternoon, and evening); the best correlation with 24-hour urinary sodium was obtained when the mean sodium level as calculated for the samples taken at different times ($r = 0.48$; $p < 0.001$) *versus* when the isolated samples were analyzed separately.[22]

The limitations of this study include the relatively small population enrolled in the study, the use of one single urine specimen collected the day after the collection of the 24-hour urine specimen, and the lack of validation of the formula for other populations.

Additionally, we were unable to assess the adequacy of the 24-hour urine specimen collection based on the urine creatinine/weight ratio, as we ran into technical problems when trying to measure this variable. However, the verification performed, the urine volumes and sodium excretion levels consistent with those of the Brazilian population support the idea that specimen collection was performed adequately by the participants.

Conclusion

In conclusion, a simple formula was developed to identify individuals with sodium intake levels above 3.6 g/day (9g of cooking salt). More studies are required to assess the *performance* of this method in other populations.

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