Estimating 24-hour urinary sodium, potassium, and creatinine excretion in hypertensive patients: can we replace 24-hour urine collection with spot urine measurements?

Authors: Piotr Jędrusik, Bartosz Symonides, Zbigniew Gaciong

Article type: Review article

Received: May 2, 2019.

Accepted: June 14, 2019.

Published online: June 19, 2019.

ISSN: 1897-9483

This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License (CC BY-NC-SA 4.0), allowing third parties to copy and redistribute the material in any medium or format and to remix, transform, and build upon the material, provided the original work is properly cited, distributed under the same license, and used for noncommercial purposes only. For commercial use, please contact the journal office at pamw@mp.pl.
Estimating 24-hour urinary sodium, potassium, and creatinine excretion in hypertensive patients: can we replace 24-hour urine collection with spot urine measurements?

Piotr Jędrusik¹, Bartosz Symonides¹, Zbigniew Gaciong¹

¹ Department of Internal Medicine, Hypertension and Vascular Diseases, Medical University of Warsaw, Warsaw, Poland

Short title: Urinary sodium, potassium, and creatinine excretion in hypertensives

Corresponding author:

Piotr Jędrusik, MD, PhD

Department of Internal Medicine, Hypertension and Vascular Diseases

Medical University of Warsaw

Banacha 1a, 02 097 Warsaw, Poland

Phone: +48 22 599 12 07; Fax: +48 22 599 18 28

E-mail: pjedrusik@wum.edu.pl

Conflict of interest: none declared.
Abstract

Due to inconvenience of a 24-hour urinary collection, spot urine-based diagnostic approaches are increasingly popular. Spot urine sodium measurements are potential replacement for 24-hour urinary sodium excretion (24hUNa), considered a surrogate measure of dietary sodium intake. Spot urine-based approaches to estimating 24hUNa and 24-hour urinary potassium excretion (24hUK) are potentially useful in hypertensives, for example to identify increased urinary potassium excretion in patients with primary aldosteronism and high dietary sodium intake in patients with resistant hypertension. In the present review, we have summarized our research on spot urine-based estimation of 24hUNa, 24hUK, and 24-hour urinary creatinine excretion (24hUCr) to avoid the need for a 24-hour urine collection in hypertensives. We found that the PAHO formula was generally the best for predicting average 24hUNa and 24hUK in hospitalized hypertensive patients, while the Kawasaki equation was inferior for estimating 24hUNa, and the Tanaka equation was inferior for estimating 24hUK. However, all three equations were imprecise in terms of estimating individual 24hUNa or 24hUK. We also confirmed general utility of the 24hUCr-estimating equations in hypertensives but with significant differences between various equations, the best formulas being the CKD-EPI and Rule equations. Compared to the combined PAHO/CKD-EPI formula, the Tanaka and Kawasaki equations underestimated increased 24hUNa and/or 24hUK and thus the combined PAHO/CKD-EPI formula might be the best for identifying increased 24hNa and 24hUK in hypertensive patients.

Keywords: hypertension; Kawasaki formula; PAHO formula; spot urine measurement; Tanaka formula
Introduction

Due to inconvenience of a 24-hour urinary collection, attempts have been made to replace it with diagnostic approaches based on spot urine measurements. The most successful of these attempts is likely the current popularity of the albumin-to-creatinine ratio as a surrogate measure of albuminuria. At the population level, there has been much interest in using spot urine sodium measurements as a replacement for 24-hour urinary sodium excretion (24hUNa), the latter considered a surrogate measure of dietary sodium intake. Such spot urine-based approaches to estimating 24hUNa and 24-hour urinary potassium excretion (24hUK) are also potentially useful in patients with hypertension. In the present review, we have summarized our previous and current research on estimating 24hUNa, 24hUK, and 24-hour urinary creatinine excretion (24hUCr) in hypertensives with the aim to avoid the need for a 24-hour urine collection.

Rationale for measuring 24hUNa and 24hUK in hypertensives

Assessment of 24hUNa and 24hUK in patients with hypertension may be clinically useful for several important reasons. Measurements of 24hUNa are widely used to assess dietary sodium intake, as sodium restriction is recommended as an important lifestyle modification both in the population and in hypertensive patients, and 24hUNa may serve as a surrogate measure of daily oral sodium intake [1]. This approach of estimating dietary sodium intake by measuring 24hUNa may be particularly helpful in patients with uncontrolled blood pressure despite apparently adequate drug therapy, as it might provide insight on patient compliance regarding dietary sodium restriction [2].
Measuring urinary potassium excretion is most useful in patients evaluated for primary aldosteronism, a common form of secondary hypertension [3]. Although hypokalemia resulting from increased urinary potassium loss is observed in only a minority of patients with primary aldosteronism [4], it is more common in patients with an aldosterone-producing adenoma which is potentially curable by adrenalectomy. In a large study, 50% of patients with an adrenal adenoma presented with hypokalemia, compared to only 17% of patients with bilateral adrenal hyperplasia [5]. In addition, hypokalemia may produce symptoms such as muscle weakness, paresthesias, and cardiac arrhythmia. On the other hand, hypokalemia may be unrelated to aldosterone, resulting, e.g. from potassium loss due to diuretic use or gastrointestinal disorders. Thus, confirmation of an increased urinary potassium loss that accompanies hypokalemia may help establish the underlying pathophysiologic mechanism, and may also help identify those patients with primary aldosteronism who are more likely to have a disease amenable to surgical treatment.

Twenty-four hour urine collection versus spot urine measurements

Twenty-four hour urine collection may be difficult to perform, as it is cumbersome, labor-intensive, and requires adequate patient cooperation. The need to collect complete urine output over a 24-hour period poses a high burden on patients, especially in the outpatient settings [6]. These limitations are reflected by low response rates in large population studies [7]. In addition, the collection may be unreliable due to difficulties with obtaining a complete 24-hour sample, resulting in both under- and overcollection [1,7,8]. The rates of incomplete collection have been reported to be as high as 30% [8], and no simple methods are available to accurately identify incomplete samples.
The approach we have evaluated to eliminate the need for 24-hour urine collection is to use spot (single) urine samples as they are much easier to collect and store without a potential for under- or overcollection. Spot urine samples are routinely used for the evaluation of urinary albumin excretion [9] and have been assessed for their utility to estimate urinary sodium excretion, mostly for the purpose of estimating salt intake in populations [1,7].

Equations to estimate 24hUNa and 24hUK based on spot urine measurements

Three formulas – Kawasaki [10], Tanaka [11], and Pan American Health Organization (PAHO) [12] – have been proposed to estimate both 24hUNa and 24hUK based on spot urine measurements and used in several previous studies, mostly to estimate 24hUNa in healthy subjects from the general population [13-15]. In addition, based on previous comparisons of the Kawasaki and Tanaka formulas, the Kawasaki formula was chosen to be used for estimating 24hUNa and 24hUK in a number of large worldwide observational analyses that were performed to evaluate the relation between urinary sodium and potassium and cardiovascular events [16-18].

Other equations were also developed for sodium only but not potassium, including the INTERSALT formula [19-23]. In our studies, however, we decided to choose only those formulas that could be used for both sodium and potassium. Except for the INTERSALT equation, all other formulas were only used in single studies or developed in specific populations, such as patients with chronic kidney disease [19]. The INTERSALT equation has been more popular but in the available comparative studies, it was not superior to the equations we selected for the purpose of our studies [13,24].

The Kawasaki, Tanaka, and PAHO equations for sodium and potassium are given in Table 1.
Estimation of 24-hour urinary creatinine excretion

Any analyte evaluated in spot urine can be expressed as the analyte/creatinine ratio, as in the case of albumin, iodine, or even catecholamines [9,25,26]. However, if 24hUCr is also known, either measured or estimated, it is possible to convert the spot urine analyte/creatinine ratio into a more easily comprehensible parameter, estimated 24-hour urinary excretion of the evaluated analyte [27]. As the ultimate purpose of the spot urine-based approach is to eliminate the need for 24-hour urine collection, reasonable estimation of 24hUCr is needed, and the latter, although relatively constant, varies by a number of factors including age, gender, body weight, muscle mass, ethnicity, and others [28-33].

Although in some studies, only rough estimates of 24hUCr based on age and gender were used [15], a number of equations have been developed to estimate 24hUCr based on simple demographic and anthropometric parameters, including age, gender, race, and most commonly body weight [27-29,31,34-36]. Of other reported equations, some are not based on any anthropometric variables reflecting body size [37,38], and some others include parameters that are often not available in routine clinical practice, such as estimates of muscle mass [35,39].

The eight 24hUCr-estimating equations based on demographic and anthropometric variables (Cockcroft-Gault, Walser, Goldwasser, Rule, CKD-EPI, Gerber-Mann, Kawasaki, and Tanaka) that were included in our comparative study in hypertensives [40] are given in Table 1.

Statistical approaches to comparing measured and estimated 24-hour urinary excretion
While many older studies only evaluated the correlation between measurements in spot urine samples and 24-hour urine collections, the Bland-Altman approach we used is considered a superior method to assess the agreement between two measurement methods, particularly in relation to individual patient management [14,15]. The correlation coefficient may not be the appropriate statistical test to assess whether measurements by the two methods being compared agree with each other, as a high correlation does not necessarily indicate a good agreement between the two related measurements [41].

The Bland-Altman approach is a method that allows both numerical and visual assessment how much the measurements using the new method (i.e., estimation using a spot urine measurement-based formula) differ from the reference method (i.e., measurement of the actual 24-hour urinary excretion). This is achieved by plotting measurement differences between the two methods against the mean of the two measurements (Bland-Altman plot). The 95% limits of agreement (LoA), i.e., the expected range of individual differences between the measurements by the two methods in 95% of cases, are estimated as the mean difference ±1.96 standard deviation of the mean difference [42,43]. The mean difference between the two measurements, also called the mean bias, is important from the population perspective, while LoA may be more important from the clinical/individual point of view. Another parameter is the slope of the regression line on the Bland-Altman plot which shows how the differences between the measurements by the two methods change over the whole measurement range. In our case, it indicated whether a given formula remained similarly precise at the lower and upper end of the 24-hour urinary excretion range.

Our studies also provided evidence corroborating the notion that the Bland-Altman approach is superior to analyses based on the correlation only. In our comparison of three formulas to estimate 24hUNa and 24hUK [44], correlations between the measured and estimated 24-hour urinary excretion were similar for all equations for both sodium (r=0.53 for
all three formulas) and potassium (r=0.69 to 0.70), and they were consistent with previous literature data [1,10,11], but analysis of the Bland-Altman plots revealed important differences between these formulas.

In some previous studies, another approach used to assess the individual precision of the evaluated formulas was to calculate the percentage of the estimated values within a certain margin of error (e.g., 15%, 30% and 50%, designated as P15, P30, and P50, respectively) compared to the measured values. We also used this approach in our comparisons of the formulas to estimate 24hUNa, 24hUK and 24hUCr. Based on previous studies [19], the 30% threshold for individual errors of urinary excretion estimation may be considered clinically most useful and might serve as a reasonably good measure of the usefulness of the given formula at an individual level. For example, P30 was commonly used to evaluate individual accuracy of equations to estimate glomerular filtration rate (GFR) [45,46].

Comparison of formulas to estimate 24hUNa and 24hUK in hypertensives

In a previous study [44], we used single morning urine samples to compare estimates of 24hUNa and 24hUK using the Kawasaki, Tanaka and PAHO equations against the actual measured 24hUNa and 24hUK in patients hospitalized in a specialist hypertensive unit and evaluated in the routine clinical practice settings. The rationale for our study was that these three formulas for estimating 24hUNa and 24hUK were rarely systematically compared to each other, and no previous study compared all three formulas in hypertensives.

The results of our study showed important differences between the three formulas. For the estimation of 24hUNa, the mean bias (measured minus estimated 24-hour urinary excretion) was significantly smaller for the Tanaka (10.5 mmol/d, 95% LoA -102 to 124 mmol/d) and PAHO equation (11.5 mmol/d, 95% LoA -142 to 165 mmol/d) compared with
the Kawasaki equation (-29.9 mmol/d, 95% LoA -151 to 91 mmol/d). The P30 values were 64%, 51% and 49%, respectively. Thus, the mean bias was lowest for the PAHO and Tanaka equations, with similar underestimation of 24hUNa by about 11 mmol/d, although 95% LoA were wider for the PAHO equation. However, the Bland-Altman plots also showed that the Tanaka equation underestimated high 24hUNa and overestimated low 24hUNa. The Kawasaki equation was clearly the least precise of the three formulas as it overestimated 24hUNa by as much as 30 mmol/l, and it was characterized by constant overestimation of 24hUNa over its whole range.

In summary, we found the both the Tanaka and PAHO equations for sodium were characterized by similarly low bias and thus might yield similar average population estimates for estimating 24hUNa. Importantly, however, the Tanaka equation became clearly less precise at the lower and upper end of the 24hUNa range compared to the PAHO equation. In contrast, the PAHO equation was somewhat more imprecise at the individual level than the Tanaka equation, but based on 95% LoA and P30 values, all three formulas did not provide particularly accurate estimates in individual subjects.

For the estimation of 24hUK, the mean bias was significantly smaller for the Kawasaki (7.3 mmol/d, 95% LoA -25 to 39 mmol/d) and PAHO equation (8.3 mmol/d, 95% LoA -28 to 44 mmol/d) compared with the Tanaka equation (-16.5 mmol/d, 95% LoA -18 to 51 mmol/d). The P30 values were 71%, 61% and 56%, respectively. Thus, the mean bias was similar for the PAHO and Kawasaki equations, and underestimation of 24hUK by these formulas was in the range of 7-8 mmol/d. However, the Bland-Altman plots showed that in contrast to the PAHO equation, the Kawasaki equation underestimated high 24hUK and overestimated low 24hUK. The Tanaka equation was clearly the least precise of the three formulas for potassium.
In summary, we found the both the Kawasaki and PAHO equations for potassium were characterized by similarly low bias and thus might yield similar average population estimates for estimating 24hUK. Importantly, however, the Kawasaki equation became clearly less precise at the lower and upper end of the 24hUK range compared to the PAHO equation. In contrast, the PAHO equation was somewhat more imprecise at the individual level than the Kawasaki equation, but again, similarly to the results for sodium, all three formulas did not provide particularly accurate estimates in individual subjects based on 95% LoA and P30 values, although their accuracy for potassium was somewhat higher that for sodium.

The overall conclusion from our study was that we found the PAHO formula to be generally the best for predicting the average 24hUNa and 24hUK in hospitalized hypertensive patients. In addition, we found that the Kawasaki equation was clearly inferior for estimating 24hUNa, and the Tanaka equation was clearly inferior for estimating 24hUK. However, neither of the evaluated equations was very precise in terms of estimating individual 24hUNa or 24hUK, and thus even with the best formulas, their individual precision and accuracy may be inadequate for the purpose of individual clinical decision-making.

Our findings indicating that the individual precision and accuracy of the evaluated equations were suboptimal are generally consistent with the results of previous studies, although most of these studies evaluated these formulas only for sodium and usually in generally healthy subjects in the general population [13,47]. In a number of reviews that evaluated estimating 24hUNa based on spot urine measurements, it has been concluded that this approach may provide adequate mean estimates at the population level but it is inadequate to evaluate individual 24hUNa [1,7]. For example, Ji et al. [1] reviewed 20 studies with 1,380,130 participants comparing 24-hour urine collections and spot or timed urine samples for estimating population salt intake, including eight studies that used a single spot urine. Based on these studies, spot urine sodium could not be established as a reliable marker
of individual sodium intake/24-hour urinary excretion. In contrast, many studies have shown
that the mean sodium intake in a population estimated using spot urine sampling and
equations to estimate 24hUNa approximates the actual mean 24hUNa in that population. A
review of 19 studies with 6803 participants that reported estimates of the mean population salt
intake based upon 24-hour urine collections and spot urine samples concluded that estimates
made using spot urine samples are likely to be suitable for estimating population salt intake
[48]. Similar conclusions were also drawn in studies that used P30 or P40 as the measure of
individual accuracy of the evaluated formulas [19,24,49].

Regarding the relative value of the compared equations, the available data also come
mostly from studies performed in the general population. In a number of previous studies,
estimates of 24hUNa using the Kawasaki and Tanaka equations were found to be inadequate
in non-Asian populations [15,20,48]. In one of these studies, performed in New Zealand in
healthy subjects aged 18-65 years [15], the PAHO equation was better than the Kawasaki and
Tanaka equations for estimating 24hUNa. The usefulness of the PAHO equation for
estimating 24hUNa and 24hUK was confirmed in studies performed in various ethnic groups
and geographical regions of the world including Israel and Africa [50,51]. The above results
are generally consistent with our findings but those of some other studies are not. For
instance, in the only study that directly compared the Tanaka and Kawasaki equations for both
potassium and sodium in a large international sample of 1083 individuals aged 35-70 years
from the general population in 11 countries, reported by Mente et al. [34], the Kawasaki
formula performed better than the Tanaka formula for both potassium and sodium. In that
study, the Kawasaki equation overestimated 24hUNa by on average 13.6 mmol/d, and the
Tanaka equation underestimated it by on average 23.8 mmol/d. Both formulas underestimated
24hUK: the mean bias was 11.8 mmol/d for the Kawasaki equation and 20.7 mmol/d for the
Tanaka equation. Importantly, however, both the Kawasaki and Tanaka equations in that
study included 24hUCr estimated using formulas derived in Asian populations, and the optimal formula for estimating 24hUCr may be different in non-Asian compared to Asian populations, as shown in our study [40] (see below). Of note, the PAHO formula was not evaluated in the study by Mente et al. However, in a recent study, the Tanaka formula for sodium was found to be more precise than the Kawasaki formula [24].

Only few previous studies assessed the usefulness of these formulas for sodium and potassium in hypertensive patients. For example, the Kawasaki formula for sodium was better than the Tanaka formula with morning urine samples in untreated hypertensives who had normal renal function [52]. In addition, most earlier studies evaluated correlations only but did not use the Bland-Altman approach [53,54]. As noted above, no previous study compared all three equations for estimating 24hUNa and 24hUK based on spot urine measurements in patients with hypertension. In addition, prior to our studies, the Bland-Altman approach has not been used to evaluate the diagnostic precision of estimating 24hUK based on spot urine potassium measurements in hypertensives.

Comparison of formulas to estimate 24hUCr in hypertensives

Any spot urine-based formulas to estimate 24hUNa and 24hUK require input about 24hUCr. As noted above, the ultimate purpose of the spot urine-based approach is to render 24-hour urine collection unnecessary, and thus estimation of 24hUCr is needed. A number of equations are available to estimate 24hUCr, preferably using easily available demographic and anthropometric parameters. However, the relative performance of various equations to estimate 24hUCr has not been well studied, and published comparisons against measured 24hUCr [36] include only some of these formulas. In particular, prior to our study, various 24hUCr-estimating formulas have never been compared in patients with hypertension. Thus,
we aimed to compare various 24hUCr-estimating equations in hospitalized hypertensives undergoing routine inpatient clinical evaluation which provided an opportunity to obtain 24-hour urine collections for the reference measurement of 24hUCr. Our study therefore provided the first assessment of bias, precision, and accuracy of a number of available 24hUCr-estimating equations in this population.

In our study, we confirmed a general utility of the equations to estimate 24hUCr in hypertensives but we also found significant differences between various compared equations. The best formulas in our study population were the CKD-EPI equation (mean bias 0.002 g/d, P30 86%, 95% LoA -0.52 to + 0.53 g/d) and the Rule equation (mean bias 0.022 g/d, P30 89%, 95% LoA -0.51 to + 0.55 g/d), while some other formulas including the Gerber-Mann, Tanaka and Kawasaki equations were clearly inferior. Of note, the Bland-Altman plots showed that the two best formulas, i.e. the CKD-EPI and Rule equations, tended to underestimate high 24hUCr. Two of the older equations (Cockcroft-Gault and Walser) were worse in terms of the mean bias, 95% LoA, and P30 but did not underestimate high 24hUCr.

Another interesting novel finding of our study is an inferior precision of the 24hUCr-estimating component of the Kawasaki equation compared to a number of other equations. This observation may be of particular importance due to the fact that the Kawasaki formula was previously chosen for spot urine-based estimation of 24hUNa and 24hUK in a number of large worldwide observational analyses that evaluated the relation between urinary sodium and potassium excretion and cardiovascular events [16-18].

In summary, we concluded that at the individual level, precision of estimating 24hUCr in hypertensives was not ideal even when using the best equations due to underestimation with higher excretion values but it was generally similar to the precision of established clinical tools such as GFR-estimating equations [36,45] which are considered sufficiently precise for individual clinical decision-making.
Our results can be compared with previously published studies that compared some of these equations, mostly in patients with chronic kidney disease. For example, five equations were compared by Ix et al. [36] who developed the CKD-EPI formula. In that study, the mean bias for the CKD-EPI equation was -0.01 g/d, and P30 was 79%, while for the other four evaluated equations (Cockcroft-Gault, Walser, Goldwasser, and Rule), the mean bias ranged from -0.028 g/d to 0.063 g/d, and P30 values ranged from 76% to 81%. All these results are generally similar to our estimates. Of note, we were unable to identify any previous comparative studies that would include both the Gerber-Mann equation and the Asian formulas (Kawasaki and Tanaka).

Estimates based on spot urine measurements only

In the previous study [44], actual measured 24hUCr was used in our comparative assessment of the three formulas for sodium and potassium, similarly to the approach used in other studies [14,15]. However, 24hUCr must also be derived indirectly to truly eliminate the need for a 24-hour urine collection, and identification of the best formula for creatinine was the purpose of our subsequent study [40]. In these studies, we found that the PAHO formula was overall the best for sodium and potassium (taking into account the mean bias, presence or absence of under-/overestimation at the extreme ends of the urinary excretion range, and parameters describing individual precision of the formulas), and the CKD-EPI equation was one of the two best formulas for creatinine. Therefore, the next step was to combine the best 24hNa- and 24hUK-estimating formula and a superior 24hUCr-estimating formula to allow “spot urine only” approach to estimating 24hNa and 24hUK in hypertensive patients. The resulting combination of the PAHO and CKD-EPI equations was compared against the
existing reference for spot urine-based estimates, i.e. the Tanaka and Kawasaki equations for sodium and potassium.

This analysis included 293 patients from the previous dataset (170 women and 123 men, mean [SD] age 54 [16] years) who underwent clinical evaluation and diagnostic tests for hypertension in our tertiary care unit, and for whom results of sodium, potassium, and creatinine measurements in spot urine and 24-hour urine collection and necessary demographic and anthropometric data were available. Details regarding the study protocol and patient characteristics are available in the previously published papers [40,55]. A non-interventional nature of the study was formally conformed by the local ethics committee at our institution.

Similarly to the approach used in our previous study on equations for creatinine, to reduce bias related to potential 24-hour urine under- or overcollection, affecting the accuracy of reference measurements in 24-hour urine collection, for the main analysis we only included patients in whom the measured 24hUCr expressed in mg/kg/d was within the expected/reference range, serving as a measure of completeness of individual 24-hour urine collections. However, various reference ranges for the measured 24hUCr were reported in the literature [56,57], and to include the largest number of patients, we used the most liberal inclusion criteria, based on the reference ranges reported by the Mayo Clinic (men: 13-29 mg/kg/d, women: 9-26 mg/kg/d) [56]. As a sensitivity analysis, we repeated our analysis in the overall study population.

The results of these analyses are shown in Table 2 and Figure 1. In the main analysis for sodium, the combined PAHO/CKD-EPI formula fared somewhat worse than the Tanaka formula in terms of the mean bias (5.5 vs. 14.4 mmol/d), 95% LoA and P30 values (45% vs. 60%), while the Kawasaki formula had the highest mean bias (-34.7 mmol/d), with similar 95% LoA and P30 values as the combined PAHO/CKD-EPI formula. However, the Tanaka
formula clearly underestimated high 24hUNa, unlike the Kawasaki and combined PAHO/CKD-EPI formulas.

In the main analysis for potassium, the combined PAHO/CKD-EPI formula was characterized by similar mean bias compared to the Kawasaki formula (7.8 vs. 6.4 mmol/d) but had somewhat wider 95% LoA and lower P30 value (53% vs. 64%). The Tanaka formula had the highest mean bias (15.1 mmol/d), with similar 95% LoA and P30 values as the combined PAHO/CKD-EPI formula. However, both Kawasaki and Tanaka formulas clearly underestimated high 24hUK, unlike the combined PAHO/CKD-EPI formula. Overall differences between formulas for both sodium and potassium were significant by the Friedman rank sum test (P < 0.001).

P30 values were rather low even for the best formulas for both sodium and potassium, and this, together with wide 95% LoA, indicates that the individual precision of both the combined PAHO/CKD-EPI formula and the comparator formulas is clearly suboptimal for the purpose of individual clinical decision-making. However, the accuracy of both the combined PAHO/CKD-EPI and the Kawasaki formulas for potassium was somewhat higher than for sodium. All the above results were generally similar when these analyses were performed in the overall study population (all patients, Table 2).

In summary, we were unable to show a clear superiority of the combined PAHO/CKD-EPI formula over the Tanaka formula for sodium, and the Kawasaki formula for potassium in hypertensive patients. However, these Asian population-derived formulas underestimated 24hUNa and/or 24hUK when it was increased in our hypertensive population. Thus, for the two purposes identified as the main rationale for measuring 24hUNa and 24hUK in hypertensives, i.e., identification of increased urinary potassium loss in patients with primary aldosteronism, and identification of high dietary sodium intake in patients with resistant hypertension, the combined PAHO/CKD-EPI formula might be actually the best.
Regarding generalizability of our findings, this issue was discussed in more detail in our previous papers [40,44]. In brief, we studied patients admitted to a specialist hypertension unit, and our study was performed in typical in-hospital clinical settings using standard laboratory methods in patients undergoing routine clinical and diagnostic evaluation, without any special oversight over the quality of urine collection. Thus, our findings are likely to represent the accuracy of estimating 24hUNa and 24hUK that may be expected in routine inpatient clinical practice and not in the research settings. In addition, based on the patient characteristics, our findings are likely generalizable to a Caucasian hypertensive population that is seen by hypertension specialists or admitted to specialized hypertension units due to such problems as difficult-to-control hypertension or suspected secondary hypertension. However, due to the fact that all our patients were Caucasians, our results are not necessarily valid for populations of other racial/ethnic characteristics.

Factors responsible for imprecision of the spot urine-based formulas to estimate 24-hour urinary excretion

A perfect agreement between the measured 24-hour urinary excretion of an analyte and any estimates of 24-hour urinary excretion based on spot urine measurements cannot be expected for several reasons, regardless of which formula is used. These include inherent imprecision of the equations, inherent variation in spot urine levels of the analyte and its 24-hour urinary excretion, and errors in urine collection for the determination of actual 24-hour urinary excretion. For example, spot urine measurement-based estimates of 24hUNa or 24hUK cannot be expected to match the actual 24-hour urinary excretion with a very high degree of precision as spot urine measurements reflect urinary excretion over a shorter time period of only a few hours, and urinary sodium and potassium excretion is not constant throughout 24 hours. It
may fluctuate depending on a number of factors such as dietary intake, patient activity and posture, kidney and urinary system function, and neurohormonal influences [1,58].

Urinary creatinine excretion is considered relatively stable when serum creatinine level is at steady state and in these conditions, 24hUCr depends mainly on endogenous creatinine generation. The latter is largely a function of muscle mass [35] and varies by such factors as age, gender, body weight, and race [28-31]. The equations to estimate 24hUCr are based on demographic and anthropometric variables because they are readily available in clinical practice and correlate with muscle mass which is the primary source of creatinine generation but this correlation is imperfect (although, as shown in this review, formulas for creatinine are generally more precise than formulas for sodium and potassium). In addition, 24hUCr may also show some variation in relation to other factors that are not accounted for in the formulas, such as day-to-day variation in protein intake, physical activity, and emotional stress [32,33].

Summary and conclusions

Obtaining a spot urine sample is clearly more convenient compared to 24-hour urine collection, and thus spot urine measurements, despite their potentially lower accuracy, are preferred in large population studies [16-18]. However, individual precision of these formulas has been consistently shown to be suboptimal. Despite this, some clinical utility at the individual level is still foreseeable. For example, we have previously showed that the PAHO formula may be useful for identification of increased urinary potassium excretion, as indicated by the AUC of 0.84 for identifying 24hUK of 40 mmol/d or higher in our study in hypertensives [55].
Our attempts to identify a single and simple formula that would be superior to the Tanaka and Kawasaki equations for sodium and potassium brought mixed results. In our analysis presented in the current review, we were unable to show a clear superiority of the combined PAHO/CKD-EPI formula in hypertensive patients, especially over the Tanaka formula for sodium and the Kawasaki formula for potassium. However, we found that the Tanaka formulas for sodium and potassium and the Kawasaki formula for potassium underestimated high 24hUNa and 24hUK, respectively. Several previous studies also demonstrated a systematic bias at extremes of urinary sodium excretion when comparing spot urine-based estimates and 24-hour urine measurements [19,34]. Of note, whether the bias of a formula is stable across the range of urinary excretion of the evaluated analyte (i.e., whether a formula under- or overestimates at extreme ends of this range) may be very important even at the population level. This varying bias of the Kawasaki formula over the range of urinary sodium excretion was suggested as one possible explanation of the observed discrepancies between studies based on 24-hour urine collection, showing a linear association between higher sodium excretion and cardiovascular events, and studies using spot urine specimens which consistently demonstrated J-shaped or U-shaped relationships with cardiovascular disease and mortality [59].

Thus, the present analysis showed that for the two purposes identified in this review as the main rationale for measuring 24hUNa and 24hUK in hypertensives, i.e., identification of increased urinary potassium excretion in patients with primary aldosteronism, and identification of high dietary sodium intake in patients with resistant hypertension, the combined PAHO/CKD-EPI formula for both sodium and potassium might still prove the best approach for spot urine-based estimates, perhaps superior to the respective Kawasaki equations for sodium and potassium that were previously used in large international population studies with hard cardiovascular endpoints.
References


Table 1. Equations for estimating 24-hour urinary sodium, potassium, and creatinine excretion.

<table>
<thead>
<tr>
<th>Formula</th>
<th>Equation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Estimated 24-hour urinary sodium excretion, mmol/24 hr</strong></td>
<td></td>
</tr>
<tr>
<td>Kawasaki [10]</td>
<td>$16.3 \times \frac{\text{spot urine Na (mmol/L)}}{\text{spot urine Cr (mmol/L)}} \times \text{estimated 24-hour urinary Cr (mg)}^{0.5}$</td>
</tr>
<tr>
<td>Tanaka [11]</td>
<td>$21.98 \times \left{\frac{\text{spot urine Na (mmol/L)}}{\text{spot urine Cr (mg/dL) \times 10}} \times \left[ \text{estimated 24-hour urinary Cr (mg)} \right] \right}^{0.392}$</td>
</tr>
<tr>
<td>PAHO [12]</td>
<td>$(\text{measured spot urine Na} / \text{measured spot urine Cr}) \times \text{estimated 24-hour urinary Cr}$</td>
</tr>
<tr>
<td><strong>Estimated 24-hour urinary potassium excretion, mmol/24 hr</strong></td>
<td></td>
</tr>
<tr>
<td>Kawasaki [10]</td>
<td>$7.2 \times \frac{\text{spot urine Na (mmol/L)}}{\text{spot urine Cr (mmol/L)}} \times \text{estimated 24-hour urinary Cr (mg)}^{0.5}$</td>
</tr>
<tr>
<td>Tanaka [11]</td>
<td>$7.59 \times \left{\frac{\text{spot urine K (mmol/L)}}{\text{spot urine Cr (mg/dL) \times 10}} \times \left[ \text{estimated 24-hour urinary Cr (mg)} \right] \right}^{0.431}$</td>
</tr>
<tr>
<td>PAHO [12]</td>
<td>$(\text{measured spot urine K} / \text{measured spot urine Cr}) \times \text{estimated 24-hour urinary Cr}$</td>
</tr>
<tr>
<td><strong>Estimated 24-hour urinary creatinine excretion, mg/24 hr</strong></td>
<td></td>
</tr>
<tr>
<td>CKD-EPI [36]</td>
<td>$879.89 + 12.51 \times \text{weight (kg)} – 6.19 \times \text{age} + (34.51 \text{ if black}) – (379.42 \text{ if female})$</td>
</tr>
<tr>
<td>Cockcroft-Gault [28]</td>
<td>$[28 – (0.2 \times \text{age})] \times \text{weight (kg)} \times 0.85 \text{ if female}$</td>
</tr>
<tr>
<td>Walser [29]</td>
<td>Men: $(28.2 – 0.172 \times \text{age}) \times \text{weight (kg)}$</td>
</tr>
<tr>
<td></td>
<td>Women: $(21.9 – 0.115 \times \text{age}) \times \text{weight (kg)}$</td>
</tr>
<tr>
<td>Goldwasser [31]</td>
<td>$(23.6 – (\text{age}/8.3))(+ 1.9 \text{ if black}) \times \text{weight (kg)}$</td>
</tr>
<tr>
<td>Rule [35]</td>
<td>( {\exp[7.26 - 0.26 \text{ (if female)} - (0.011 \times (\text{age} - 55) \text{ if age &gt; 55 years})]} \times \text{BSA}/1.73 \text{ (m}^2)</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Gerber and Mann [27]</td>
<td>(699 - 421.9 \text{ if female} + (16.83 \times \text{weight}) \text{ (kg)} - 25.82 \text{ (if white)} - 2.67 \times \text{age})</td>
</tr>
</tbody>
</table>
| Kawasaki [34] | Men: \(-4.72 \times \text{age} + 8.58 \times \text{weight} \text{ (kg)} + 5.09 \times \text{height} \text{ (cm)} - 74.5\)  
Women: \(-12.63 \times \text{age} + 15.12 \times \text{weight} \text{ (kg)} + 7.39 \times \text{height} \text{ (cm)} - 79.9\) |
| Tanaka [34] | \(-2.04 \times \text{age} + 14.89 \times \text{weight} \text{ (kg)} + 16.14 \times \text{height} \text{ (cm)} - 2244.45\) |

Abbreviations: BSA, body surface area; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; Cr, creatinine; K, potassium; Na, sodium; PAHO, Pan American Health Organization.
Table 2. Performance of the combined PAHO/CKD-EPI formula versus the Tanaka and Kawasaki formulas for estimating 24-hour urinary sodium and potassium excretion.

<table>
<thead>
<tr>
<th>Formula</th>
<th>Mean bias(^a), mmol/d</th>
<th>95% limits of agreement</th>
<th>P15</th>
<th>P30</th>
<th>P50</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Main analysis – Mayo Clinic inclusion criteria(^b) (n=248)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24-hour urinary sodium excretion</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAHO/CKD-EPI</td>
<td>14.4</td>
<td>-149 to 178</td>
<td>29</td>
<td>45</td>
<td>69</td>
</tr>
<tr>
<td>Tanaka</td>
<td>5.5</td>
<td>-124 to 135</td>
<td>32</td>
<td>60</td>
<td>81</td>
</tr>
<tr>
<td>Kawasaki</td>
<td>-34.7</td>
<td>-179 to 110</td>
<td>27</td>
<td>46</td>
<td>69</td>
</tr>
<tr>
<td>24-hour urinary potassium excretion</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAHO/CKD-EPI</td>
<td>7.8</td>
<td>-34 to 50</td>
<td>29</td>
<td>53</td>
<td>82</td>
</tr>
<tr>
<td>Tanaka</td>
<td>15.1</td>
<td>-24 to 54</td>
<td>26</td>
<td>57</td>
<td>85</td>
</tr>
<tr>
<td>Kawasaki</td>
<td>6.4</td>
<td>-31 to 43</td>
<td>39</td>
<td>64</td>
<td>90</td>
</tr>
<tr>
<td><strong>All patients (n=293)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24-hour urinary sodium excretion</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAHO/CKD-EPI</td>
<td>1.9</td>
<td>-180 to 180</td>
<td>26</td>
<td>40</td>
<td>62</td>
</tr>
<tr>
<td>Tanaka</td>
<td>-3.6</td>
<td>-141 to 134</td>
<td>29</td>
<td>54</td>
<td>75</td>
</tr>
<tr>
<td>Kawasaki</td>
<td>-44.7</td>
<td>-200 to 111</td>
<td>25</td>
<td>42</td>
<td>63</td>
</tr>
<tr>
<td>24-hour urinary potassium excretion</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAHO/CKD-EPI</td>
<td>2.8</td>
<td>-49 to 54</td>
<td>27</td>
<td>50</td>
<td>76</td>
</tr>
<tr>
<td>Tanaka</td>
<td>12.1</td>
<td>-30 to 54</td>
<td>24</td>
<td>55</td>
<td>81</td>
</tr>
<tr>
<td>Kawasaki</td>
<td>3.1</td>
<td>-38 to 44</td>
<td>36</td>
<td>60</td>
<td>84</td>
</tr>
</tbody>
</table>

\(^a\) Measured minus estimated 24-hour urinary sodium/potassium excretion.

\(^b\) Measured 24-hour urinary creatinine excretion 13-29 mg/kg/d in men, 9-26 mg/kg/d in women [56].
Abbreviations: CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; P15, P30, P50, percentage of estimated values within ±15%, 30%, 50% of the actual measured values; PAHO, Pan American Health Organization.
Figure 1. The Bland-Altman (B_A) plots showing the difference between measured and estimated 24-hour urinary sodium (Na; left) and potassium (K; right) excretion plotted against the mean 24-hour urinary sodium and potassium excretion by the two methods (mmol/d) in the main analysis (n=248). Upper panel: the Tanaka formula, middle panel: the Kawasaki formula; lower panel: the combined PAHO/CKD-EPI formula.