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24-hour vs Spot Urinary Sodium and Potassium Measurements in Adult Hypertensive patients; A Cohort Validation Study

E R WAN BMBCh[a], J CROSS FRCP PhD[a], Reecha SOFAT FRCP PhD[b], S B WALSH FRCP PhD[a]

[a]Complex Hypertension Service, UCL Centre for Nephrology, University College London, London, UK

[b]UCL Department of Medicine, University College London, London, UK

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Correspondence to:
Stephen B Walsh,
UCL Centre for Nephrology,
Royal Free Hospital,
London NW2 3QG
Stephen.walsh@ucl.ac.uk

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ABSTRACT

BACKGROUND: Sodium intake is correlated with the development of hypertension. Guyton's principals suggest that the 24-hour urinary sodium excretion reflects sodium ingestion over the same period. 24-hour urine collections are arduous to collect, so many centres use spot urinary measurements instead. We compared spot to matched 24-hour urinary electrolyte measurements.

METHODS: We examined 419 hypertensive patients from the UCL Complex Hypertension Clinic. 77 had matched and complete 24-hour and spot urinary and serum biochemistry to examine.

We compared the spot and 24-hour urinary; sodium concentration, Na/Cr ratio, FE_{Na}, Kawasaki and Tanaka estimated sodium excretion as well as the potassium concentration, K/Cr ratio, Kawasaki and Tanaka potassium excretion.

RESULTS: Our cohort was 58% male and the median age was 41 years. The 24-hour and spot Na concentrations correlated moderately ($r=0.4633$, $p<0.0001$). The 24-hour and spot Na/creatinine ratios correlated weakly ($r=0.2625$, $p=0.0194$). The 24-hour and spot FE_{Na} results showed a weak negative correlation ($r=-0.222$, p=ns). The 24-hour sodium excretion and the Kawasaki-derived spot urine sodium excretion correlated moderately ($r=0.3118$, $p=0.0052$). All Bland-Altmann analyses showed poor agreement.

The 24-hour and spot potassium concentrations correlated very poorly ($r=0.1158$ p=ns). The 24-hour and spot urinary K/creatinine ratios correlated weakly ($r=0.47$ p=<0.0001). 24-hour and Kawasaki and Tanaka estimated potassium excretions correlated much better ($r=0.58$ $p<0.0001$).

CONCLUSIONS: Spot urinary measurements of sodium give a very poor understanding of the naturesis occurring over the same 24-hour period. The Kawasaki and Tanaka estimations of the 24-hour sodium excretion showed a much lower correlation than previously reported.

Introduction

The association of dietary sodium and hypertension in the general population was described more than a century ago[1]. Laboratory studies in mammals as diverse as rats[2] and chimpanzees[3] have demonstrated that a high salt intake elevates blood pressure.

The modern western diet is very high in sodium compared to the potassium-rich, sodium-poor diet enjoyed by our Palaeolithic ancestors[4]. In fact, modern populations who have low sodium, high potassium diets, such as the Yanomami people of Brazil[5], have negligible increases or actual decreases in blood pressure with age, unlike populations with high sodium diets.

Hypertension is prevalent in industrial societies that have high sodium diets and low in hunter-gatherer societies that do not [6]. And, as might be expected from these data, reducing salt intake in humans reduces blood pressure [5,7].

Therefore, understanding and monitoring the dietary salt intake of hypertensive patients has been a concern of physicians for decades. However, directly measuring patients' salt intake is difficult, time-consuming and error prone[8].

However, it has been understood, based on the principles espoused by Guyton[9], that a steady state of sodium balance is maintained, at all levels of sodium intake, by a balanced output [10,11].

The primary route for sodium excretion in normal circumstances is renal [12]; and the 24-hour urinary sodium excretion has therefore been used to assess sodium intake over the same period.

However, 24-hour urinary sodium measurements are difficult and cumbersome to collect and are vulnerable to incomplete collection[13]. This has led several investigators to assess whether a spot urine sample for sodium could be a reliable surrogate for the 24-hour urinary sodium concentration.

Kawasaki[14] developed a set of equations to adjust a second morning urine (SMU) specimen to an estimation of the 24-hour sodium or potassium excretion, based on SMU and 24-hour urine collections in 159 subjects. These estimated excretions were reported to be moderately to highly correlated with the 24-hour measurements in 2 validation cohorts.

Tanaka *et al* [15] also developed a set of simpler equations to estimate the 24-hour sodium or potassium excretion from spot urine specimens based on data from the INTERSALT study, and then tested them on 513 healthy volunteers. These estimated excretions were only moderately correlated with the 24-hour measured excretions, with significant differences in the mean excretion values. They concluded that the estimated excretions would be suitable for population-based studies rather than clinical practice.

Mann and Gerber[16] reported that a spot urinary sodium/creatinine ratio (collected in the afternoon of the corresponding 24-hour urine collection) correlated well with the 24-hour urinary sodium excretion, while the morning and random samples did not. Further, they found that the pm spot sample was able to predict those with a 24-hour sodium excretion of <100mg/day with a sensitivity of 100% and specificity of 82%.

The INTERSALT study [17] later reported that estimated sodium excretion from a spot urinary sodium and creatinine measurement correlated moderately well with

individual measured 24-hour sodium excretions (r 0.5-0.51) and strongly with population samples (r 0.71-0.79).

Although many of the published reports qualify that using spot urines to estimate the 24-hour sodium excretion is only reliable at the population level for research purposes, they report frequently impressive correlations with 24-hour sodium excretion measurements on an individual level.

As the evidence indicates that salt intake is (at least partly) pathogenic for hypertension, and as the diet in most industrialised countries is high in salt, clinicians dealing with hypertension have a responsibility to attempt to reduce salt intake in their patients. However, such interventions are difficult to achieve and maintain. Therefore, in order to target dietary intervention, many clinicians infer salt intake from spot urinary samples, either using the sodium concentration, or a number of derived variables.

Furthermore, the dietary potassium content also affects blood pressure; a low potassium diet is associated with increased blood pressure and a high potassium diet lowers blood pressure, significantly so in hypertensive patients[18].

We therefore decided to prospectively assess whether a number of the different described methods for estimating sodium or potassium excretion from a spot urine sample correlated and agreed with their measured 24-hour sodium excretion in incident patients to our hypertension clinic.

Methods

From September 2015 to May 2018, incident patients to the Complex Hypertension Clinic at the UCL Centre for Nephrology were eligible to participate in this prospective study.

Informed consent was obtained from all patients. All patients had a history of hypertension with ABPM mean 24-hour blood pressures of >140/90 mmHg or at least 3 clinic blood pressures 140/90 mmHg. Patients were aged between 18 and 80 years old.

Patients were all seen on their first clinic visit and had been instructed to collect a 24-hour urine sample finishing on the morning of clinic attendance. They had all also been instructed to discontinue all antihypertensives excluding oral diltiazem or doxazosin for at least 4 weeks, in case measurement of the plasma renin and aldosterone concentration was required. Spot urine samples were obtained and in all cases were the second morning urine sample of the day (SMU). Blood samples were collected the same day, immediately following the clinic visit.

The following data were obtained: age, height, weight, serum sodium, serum potassium, serum creatinine, SMU spot urinary sodium, potassium and creatinine, 24-hour urinary sodium, potassium and creatinine.

24-hour urine was collected in 4 litre screw-top canisters and patients were given written instructions on how to collect the urine. Urine was collected 24 hours prior to the first clinic visit, starting immediately after the first voided urine the morning before the clinic visit. Urine collection continued for the next 24 hours and finished with the first voided urine of the day of the clinic visit. A 24-hour urine collection was deemed to be complete if the measured urine volume was >500ml, the recorded collection

time was >20 hours and there was no more than one report of spilling or missing a void during the whole collection.

The next urine sample was the SMU spot urine at the clinic visit. An SMU was used as it was the sample used by Kawasaki; he had found that spot urine samples taken between 0800 and 1200 were best correlated with 24 sodium excretion[14]. Tanaka used a sample taken between 0800-1900[15], we collected a SMU to be able to compare directly with both Kawasaki and Tanaka.

Sodium, potassium and chloride were measured using the principle of indirect ion selective electrode (ISE), and creatinine using the Jaffe method using Roche/ Hitachi Cobas 8000 analyser and reagents (Roche Diagnostics, GmbH, D-68298 Mannheim, Germany).

For 24-hour Urine collections, volume was determined and an aliquot of the sample was analysed for the electrolyte in question.

Kawasaki proposed a formula to estimate a 24-hour sodium (and potassium) excretion from a SMU spot urine sample[14].

The formula used to calculate this was:

Estimated value of $24hrU_{Na}v$ (mmol/day) = $16.3 \times \sqrt{X_{Na}}$, where $X_{Na} = SMU_{Na} / SMU_{Cr}$ X predicted 24-hour urinary Cr excretion.

Estimated value for 24-hour U_KV (mmol/day) = $7.2 \times \sqrt{X_K}$ where $X_K = SMU_K / SMU_{Cr}$ x predicted 24-hour urinary Cr excretion.

Predicted Cr excretion (mg/day) for men = −4.72 × age (years) + 8.58 × weight (kg) + 5.09 × height (cm) − 74.5 and for women = 12.63 × age (years) + 15.12 × weight (kg) + 7.39 × height (cm) − 79.9.

Tanaka and co-workers proposed alternative formulas to estimate 24-hour sodium and potassium excretion[15].

The formula used to calculate this was:

Estimated value of 24-hour $U_{Na}V$ (mmol/day) = 21.98 x $X_{Na}^{0.392}$ where $X_{Na}=SMU_{Na}/SMU_{Cr}$ X Predicted 24-hour urinary creatinine excretion.

The estimated value of 24-hour U_KV (mmol/day) = 7.59 x $X_K^{0.431}$ where $X_K=SMU_K/SMU_{Cr}$ x Predicted 24-hour urinary creatinine excretion.

Predicted 24-hour urinary creatinine excretion (mg/day) = -2.04 x age + 14.98 x weight (kg) + 16.14 x height (cm) – 2244.45

The urinary fractional excretion of sodium (FE_{Na}) was calculated according to the formula:

FE_{Na}= ([Urinary Na] / [Serum Na]) x ([serum creatinine] / [urinary creatinine]) x100.

Statistics were analysed using GraphPad Prism V 5.0.

Results

Of 419 hypertensive eligible patients screened in the UCL Complex Hypertension Clinic over the study period, 77 had matched and complete 24-hour and spot urinary and serum biochemistry to examine. Our cohort was 58% male and the median age was 41 years (IQR: 34-53.75), median BMI was 29.33 (IQR 26.12-34.96). The morphometric and biochemical data is summarised in **Table 1**.

The 24hr urine collections appeared to be complete; the urine volume was good (median 2140mls, IQR 1552-2625mls) as was the correlation of the 24-hour creatinine excretion with body surface area (Spearman $r=0.6126$, $p=0.015$).

As our study population was European hypertensives, rather than healthy Japanese volunteers; we checked the validity of the predicted urinary creatinine excretion. The correlation between the measured creatinine excretion and the predicted Kawasaki and Tanaka creatinine excretions was good ($r=0.5825$, $p<0.0001$ and $r=0.5949$, $p<0.0001$ respectively).

Although our cohort had very little renal impairment (median serum creatinine 84, IQR 70-102 µmol/L), reduced GFR might bias results by altering either the spot or 24hr sodium excretion. This was not supported by our data, which showed very poor correlation between the serum creatinine and the spot Na/K ratio ($r=0.08292$, $p=0.3354$) and between serum creatinine and the measured 24hr urinary sodium excretion ($r= -0.02637$ $p=0.7677$).

The 24-hour and spot urinary sodium concentrations were moderately correlated (Spearman $r=0.4633$, $p<0.0001$); Bland-Altmann (BA) analysis showed poor agreement between tests but little bias (3.378, SD 46.5 mmol/L). The 24-hour and spot urinary Na/creatinine ratios were weakly correlated (Spearman $r=0.2625$,

p=0.0194); BA analysis showed poor agreement and moderate bias (3.371, SD 8.668). The 24-hour and spot fractional excretion of sodium results showed a weak negative correlation (Spearman r=-0.222, p=ns); BA analysis showed poor agreement but little bias (0.1956, SD 0.6502%) (see **Figure 1**). The 24-hour sodium excretion and the Kawasaki derived spot urine sodium excretion were moderately correlated (Spearman r=0.3118, p=0.0052) and BA analysis demonstrated very little agreement or bias (0.2071, SD 83.99 mmol/24hr). The Tanaka estimation of the sodium excretion and the measured 24-hour sodium excretion were likewise moderately correlated (Spearman r=0.3118, p=0.0052) with poor agreement and significant positive bias (33.6 SD73.56) (see **Figure 2**).

As the correlations and agreement between spot urinary sodium excretion estimations and measured sodium excretion were so poor, we reasoned that spot urinary sodium measurements would still be helpful if they could differentiate between a binary output state of the urinary sodium excretion, ‘high’ and ‘low’ output. We chose a 24-hour urine sodium excretion of 100mg/day or less (equivalent to a salt intake of 6g/day or less) as being ‘low’ and more than this value as being ‘high’. As we wished to analyse 5 different ways of assessing the 24-hour sodium excretion, and as were unable to determine useful cut off values for the different methods, we generated receiver operator curves (ROCs) for each measurement.

To differentiate between ‘low’ and ‘high’ 24-hour sodium excretion, the ROC for the spot urine sodium concentration had a low area under the curve (AUC 0.5727) indicating poor discriminatory ability, which also did not significantly refute the null hypothesis of being non-discriminatory (p=0.339). This was also true for the FE_{Na} (AUC 0.5452, p=0.5635), the spot Na/Cr ratio (AUC 0.5619, p=0.4268), the

Kawasaki estimated Na excretion (AUC 0.6339, p=0.08583) and the Tanaka estimated Na excretion (AUC 0.6237, p=0.1119), (see **Figure 3**).

The 24-hour and spot urinary potassium concentrations were very poorly correlated (r=0.1158 p=ns), with poor agreement revealed by BA analysis with significant bias (-27.21 SD 38.58 mmol/L). The 24-hour and spot urinary K/creatinine ratios were weakly correlated (r=0.47 p=<0.0001). BA analysis showed fair agreement and bias (-0.1203 SD 2.927).

The 24-hour and Kawasaki estimated potassium excretion were much better correlated (r=0.58 p<0.0001) with better agreement on BA analysis but some bias (19.01 SD 28.02 mmol/day). Unsurprisingly, the Tanaka estimation also had moderate correlation (r=0.58 p<0.0001) with somewhat better agreement, but significant bias (32.49 SD 26.98) (see **Figure 4**).

Discussion

Our results showed a much lower correlation of the estimated 24-hour sodium excretion with the measured 24-hour sodium excretion by either the Kawasaki or the Tanaka method than the studies by either author. Both studies used healthy volunteers, not hypertensive patients. Kawasaki used data from 159 patients to develop his formulae. The validation cohorts showed moderate correlation (r 0.531 n=91) over a 24-hour collection period and strong correlation (r 0.821 n=15) over a 72-hour collection period. Tanaka used a larger sample size and found a similar correlation over a 24 collection (r 0.54 n=336). Larger sample sizes will generate better correlation coefficients, all else being equal. This may explain in part why the correlation of estimated and measured urinary sodium excretion that we saw was lower, but does not explain the discrepancy with Kawasaki's group 2 (see **Supplementary Figure 1**). Our results show a markedly poor agreement between individual estimated and measured sodium excretion. While poor agreement was noted by Tanaka, who suggested that the method only be adopted for population studies, Kawasaki found that agreement (based on differences of mean measurements, not individual ones) was good enough to recommend the method for estimation in individuals[14].

In fact, other studies have shown that the estimated sodium excretion from a spot urine sample has a lower correlation and agreement with the measured individual 24-hour sodium excretion than with population-based measurements[5,15].

Population based studies, be they population surveys[19], epidemiological studies[5] or population health programs[20], measure mean daily sodium excretions using pooled samples. It is reasonable to suppose that such measurements reflect the average

salt intake of their respective populations, and so that estimated sodium excretion rates estimated from spot urine samples would correlate well with these values. Our data neither supports nor refutes this hypothesis. Why, then, do individual estimated sodium excretions correlate less well (and very poorly in our study) with measured 24-hour sodium excretion rates?

This may not be surprising, given the known intra-individual variability in 24-hour sodium excretion. Luft *et al*[21] showed that 24-hour urinary sodium measurements had a moderate correlation with measured sodium intake on a given day, but that over a 10 day period with fluctuating sodium intakes (as occurs in normal daily life), 9 24-hour urine collections were optimal to reflect sodium intake, and that morning spot urine samples correlated very poorly with intake over this period.

However, variability in sodium intake does not appear to explain the variability in individual 24-hour sodium excretion measurements. Lerchl and co-workers[22] examined volunteer cosmonauts in a simulated Russian Mars space voyage. This simulation effectively had the volunteers in a human metabolic cage, on a tightly regulated diet, with all of their waste products collected and analysed. At all levels of sodium intake, the intake of sodium in a 24-hour period did not correlate with the 24-hour sodium excretion. In fact, there appeared to be a circaseptal rhythm to sodium excretion while on a tightly fixed salt intake.

This has profound implications for the use of the urinary sodium excretion to infer the intake of sodium in the diet. Logically it follows that any estimation of this 24-hour excretion from a spot urine sample will be even less accurate.

This problem need not only affect individual clinical decisions. A recent large epidemiological study concluded that a salt intake of 3-6g day resulted in lower risk

of death and cardiovascular events than either a higher or lower intake[23]. Individual intake was estimated from estimated 24-hour urinary sodium excretions based on a morning spot urine sodium concentration using the Kawasaki formula. This study has been widely cited in the popular press as evidence that a low salt diet may be harmful[24], yet the potential for error in estimating salt intake on an accurate 24-hour sodium excretion is in the order of 3g/day[22].

The average daily dietary salt intake in the UK is 8.1g/day. This has been decreased from an estimated 9.5g/day in 2003[20]. In the US mean salt intake has been estimated at 10.4g/day for men, and 7.3g/day for women[25]. In hypertensive patients the mean salt intake is higher. Given the low likelihood of incident hypertensive patients having a low salt intake, and the inaccuracy of either a spot or 24-hour urinary sodium in estimating sodium intake, it seems likely that non-targeted approaches to reducing salt intake in hypertensive patients would be less labour intensive and thus more productive. The apparent futility of estimating the sodium intake from the urinary excretion of sodium has led some to suggest that measuring the long term effect of lowering dietary salt can only feasibly be carried out in a 'closed environment', such as a population of prisoners incarcerated for a long period[26].

The absolute potassium concentration in the spot urine sample was poorly correlated, but the K/Cr ratio, and the Kawasaki and Tanaka estimations, had much better (albeit moderate) correlation with the measured 24-hour urinary potassium excretion. This implies that the rate of potassium secretion is relatively preserved, as the correlation is improved by taking the urinary creatinine (i.e. the urinary concentration) into account, and improved further (in the Kawasaki and Tanaka formulae) by further accounting for the predicted 24-hour potassium excretion.

However, does a 24-hour urinary potassium excretion tell us about oral potassium intake in the preceding 24-hour period? According to a follow on study to the Mars Mission work, Birukov and co-workers reported that the agreement between 24-hour urinary potassium excretion has as little agreement with the 24-hour potassium intake as the sodium excretion does; moreover it appears to follow the same circaseptal rhythm and this appears to be mediated by aldosterone secretion[27].

In short, the widespread use of spot urinary samples to estimate the 24-hour sodium excretion in individual patients, from our data as well as others, is very likely to be misleading. It cannot even determine whether the patient has a 'high' or 'low' sodium excretion in the same 24-hour period. Our data suggest that the spot urinary potassium and its derived variables are a more reliable, but still imperfect, guide to the 24-hour urinary potassium excretion. Recent data has demonstrated that the 24-hour excretion of these electrolytes has poor agreement with the oral intake of the same electrolytes in the preceding 24 hours.

Disclosure

No conflicts of interest declared

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Table and Figure Legends

Table 1: Morphometric and biochemical data. None of these data were distributed normally. Therefore median values with interquartile ranges are given.

Figure 1: Shows XY plots with regression curves and Spearman correlation coefficients on the left side, with Bland-Altmann plots showing bias (red interrupted line) and 95% confidence limits (black interrupted lines). A represents 24-hour vs. spot urinary sodium concentration. B represents 24-hour vs. spot urinary Na/Cr ratio. C represents the 24-hour vs. the spot urinary fractional excretion of sodium (FE_{Na}).

Figure 2: Shows XY plots with regression curves and Spearman correlation coefficients on the left side, with Bland-Altmann plots showing bias (red interrupted line) and 95% confidence limits (black interrupted lines). A represents the 24-hour measured vs. the Kawasaki estimated 24-hour sodium excretion. B represents the 24-hour measured vs the Tanaka estimated 24-hour sodium excretion.

Figure 3: Shows receiver operator curves (ROC) for the five variables to distinguish between a binary 'high' (>3g/day) and 'low' (<3g/day) 24-hour sodium excretion. 'Area' defines the area under the curve (AUC) and the p value represents the significance value to refute the null hypothesis of being non-discriminatory. A represents the discriminatory value of the spot urinary sodium concentration. B represents the discriminatory value of the spot urinary FE_{Na}. C represents the discriminatory value of the spot Na/Cr ratio. D represents the discriminatory value of the Kawasaki estimated sodium excretion. E represents the discriminatory value of the Tanaka estimated sodium excretion.

Figure 4: Shows XY plots with regression curves and Spearman correlation coefficients on the left side, with Bland-Altmann plots showing bias (red interrupted

line) and 95% confidence limits (black interrupted lines). A represents 24-hour vs. spot urinary potassium concentration. B represents 24-hour vs. spot urinary K/Cr ratio. C represents the 24-hour measured vs. the Kawasaki estimated 24-hour potassium excretion. B represents the 24-hour measured vs the Tanaka estimated 24-hour potassium excretion.

Supplementary Figure Legend

Supplementary Figure 1: This is a graphic illustration of the differences in correlation coefficient and sample size between our study (Wan) and the Tanaka and Kawasaki studies. White bars represent the correlation coefficient (r value) while the black bars represent the sample size. ‘Wan (K)’ and ‘Wan (T)’ represent our results using the Kawasaki and Tanaka estimations respectively. Kawasaki’s validation cohorts over a 24-hour collection period and over a 72 hour collection period are represented by the paired columns ‘Kawasaki 1’ and ‘Kawasaki 2’ respectively.