Validity of spot urine samples to estimate daily salt excretion in patients with CKD

Howaida El-Shinnawy, M.D, Osama Mahmoud, M.D, Hayam Aref, M.D, Walid Anwar Abdelmohsen M.D, Amr Mohab, M.D

Division of Nephrology, Ain-Shams University, Cairo, Egypt
bmz007@hotmail.com

Abstract: Objective: Alternative methods have emerged as a substitute for the gold standard 24 - hour urinary collection to estimate24 hour urinary sodium excretion. Different equations have been used to estimate Na intake using spot urine samples. This study aimed to evaluate the use of spot urine samples to estimate 24 hours excretion of sodium in patients with CKD and its correlation with the gold standard 24-hour urine collection as well as blood pressure in those patients. **Methods:** This study included 60 patients with different CKD stages admitted to the department of Internal Medicine of Ain Shams University Hospitals in the period from January 2013 till March 2014. Spot urine samples were examined on the same day that patients completed their 24-hour urine collection**.** Estimation of 24-hour urinary sodium excretion from spot urine was calculated by Tanaka's as well as Kawasaki's formulae and the results were compared to the measured urinary sodium in 24-hr urine samples. **Results:** There was a statistically significant positive correlation between the measured 24-hour urinary sodium and estimated 24-hour urinary sodium from spot urine samples using Tanaka's and Kawasaki's formulae in patients with CKD stages 2, 3 and 4 (P<0.001). This relation was stronger when using Tanaka's formula compared to Kawasaki's formula in stages 2 and 4 CKD (r=0.968 and r=0.788 compared to r=0.936 and r=0.768 respectively). In patients of CKD stage 3, Kawasaki's equation was more correlated than Tanaka's (r=0.927 compared to r=0.919), however, in stage 5, there was no significant correlation between both of them using either formula. (P =0.922 for Tanaka's equation and P =0.846 for Kawasaki's equation). There was no statistically significant relationship between SBP, DBP or MBP with measured sodium in 24 hour urine or that estimated from spot urine samples using Tanaka's equation,however, when using Kawasaki's equation, there was a statistically significant relation between estimated sodium excretion from spot urine samples and SBP (P =0.043), DBP (P =0.049) and MBP (P =0.029). **Conclusion:** Equations using spot urine samples were found to be an accurate method to estimate 24-hour urinary Na in patients with CKD. This didn't apply for patients with CKD stage 5 where both equations were invalid to estimate the 24 hour urinary Na excretion.

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Key words: CKD, urinary sodium, spot urine

1. Background:

Sodium intake is an important issue for patients with chronic kidney disease (CKD). These patients are characterized by hypertension, which is thought to be predominantly salt sensitive.[1]

Dietary sodium intake shows great promise as a modifiable risk factor for reducing the risks of cardiovascular disease and CKD progression.[2]

Although, the estimation of salt intake is essential, there are no easy methods to estimate real salt intake. The two most widely used methods to measure sodium intake are: 24-hour urine sodium excretion measurement and sodium intake estimation by dietary recall.

Alternative methods have emerged as a substitute for the gold standard 24hour urinary sodium collection. Different equations have been used to estimate Na intake using spot urine samples; of special interest are: Tanaka and Kawasaki's equations which have been used before to estimate 24 hour urine excretion of sodium and thus daily salt intake[3]. Results from the 2012 Health Survey for England reported that estimates for sodium intake obtained from using spot urine collections were similar to those of other studies using 24hour urine collections[4]**.**

Spot urinary sodium, or sodium to creatinine ratio (Na: Cr), is an objective measure of dietary sodium intake with relatively smaller participant burden than 24-hour collection. The validity of this measure to represent sodium intake is contentious, particularly in CKD where excretion of these solutes may be deranged[5]**.** There has been little research in this area; however, recent studies have been conducted to evaluate spot urine samples as a surrogate marker of sodium intake in patients with chronic kidney disease[6]**.**

The aim of the present study was thus to evaluate use of spot urine samples to estimate 24 hours excretion of sodium in patients with CKD and its

correlation with the gold standard 24hour urine collection as well as blood pressure in those patients.

2. Patients and Methods:

Patients' selection:

This cross sectional study included 60 patients with different CKD stages admitted to the department of Internal Medicine of Ain Shams University Hospitals in the period from January 2013 till March 2014. The stages of CKD were defined according to the estimated glomerular filtration rate (GFR) based on recent guidelines of the National Kidney Foundation: Stage I: 90 mL / min/ 1.73 m^2; stage II: 60-89 mL / min/ 1.73 m^2; stage III: 30-59 mL / min/ 1.73 m^2; stage IV: 15-29 mL / min/ 1.73 m^2; stage V: <15 mL / min/ 1.73 m^2. The estimated GFR was obtained using the re-expressed four-variable Modification of Diet in Renal Disease study equation with standardized serum creatinine.

Patients were divided into 3 groups according to their CKD stage as follows: Group A: 20 patients stage 2 CKD; Group B: 20 patients stage 3 CKD; Group C: 20 patients stage 4, 5 CKD.

Exclusion Criteria

We excluded:

1. Patients having Congestive heart failure (associated with failure in significant sodium excretion).
2. Patients with acute or chronic liver disease.
3. Patients taking diuretics (which influence sodium reabsorption at different stages of filtration).
4. Those exhibiting inadequate urine collection (as assessed by urinary creatinine excretion: data were excluded when urinary Cr excretion <1000, >2500mg/day for male and <600, >1500 mg/day for female considering in adequate urine collection[7].

The protocol was approved by the Ain Shams Faculty of medicine ethical committee board and all participants provided verbal informed consent.

Urine specimens:

- 24-hour urine collection (All study participants were given a container for urine collection and instructed to collect a 24-hour urine sample by discarding the first voided urine upon rising in the morning and then collecting all voided urine up to and including the first void of the following morning). The 24- hour samples were used to measure:
  a) Urine volume
  b) Urinary creatinine (Cr) excretion.
  c) 24-hour urinary proteins
  d) 24-hour urinary Sodium excretion (mEq/day)
- Spot urine samples were examined on the same day that patients completed their 24-hour urine sample collection (coinciding with the second voiding urine of the day before patients have breakfast) [7].

Estimation of 24-hour urinary sodium excretion from spot urine was calculated by Tanaka's formula [8] as well as Kawasaki's formula[9]. The results were compared to the measured urinary sodium in 24-hr urine samples.

TANAKA'S FORMULA

24-h Na excretion (mEq /d) =

$$\mathbf{21.98 \{Na\ S / (Cr\ S \times 10) \times Pr.UCr24\}^{0.392}}$$

Na S: Na concentration in spot urine (mEq / L)

Cr S: Cr concentration in spot urine (mg / dL)

Pr.UCr24: Predicted 24 h urinary Cr excretion (mg / d) = −2.04 × Age (years) + 14.89 × Bodyweight (kg) +16.14 × Height (cm) − 2244.45

KAWASAKI'S FORMULA

24-h Na excretion (mEq/ d) =

$$\mathbf{16.3 \times \{(Na\ S / Cr\ S) \times 24h\text{-}UCr\}^{0.5}}$$

Males: Estimated 24h-UCr (mg/day) = 15.1× Bodyweight (kg) + 7.4 × Height (cm) − 12.4 × Age (years) − 80

Females: Estimated 24h-UCr (mg/day) = 8.6 × Bodyweight (kg) + 5.1 × Height (cm) − 4.7 × Age (years) – 75

Statistical Methods

- Data were analyzed using **Predictive Analytics Soft Ware (**PASW) version 18.
- Quantitative data were described as **Mean ± standard deviation**, and **Median (minimum-maximum)** for parametric and non-parametric data respectively.
- **Independent Student t test** was used for comparison of quantitative variables among more than independent groups.
- **One-way ANOVA** test was used to compare daily salt intake between patients belonging to different stages of CKD, statistical analysis was done to all patients at a time.
- Correlations between all the quantitative parameters were done using **Pearson's correlation coefficient.**

3. Results:

Sixty patients were included in this study (48 males and 12 females)-Table 1 shows the clinical and laboratory data of the enrolled patients-, 33patients (55%) were hypertensive, while 27(45%) were normotensive. The age of our patients ranged from 21 years to 80 years with mean 51.183±15.081, their body weight ranged from 55 Kg to 110 Kg with mean 79.250± 12.421. As regards CKD stage, 20 patients were assorted as stage 2 (33.3%), 20 patients as stage 3 (33.3%), 16 patients as stage 4 (26.7%), and only 4 patients as stage 5 (6.7%). None of the enrolled patient was assorted as CKD stage 1.

Using Pearson correlation coefficient, we found a statistically significant positive correlation between the measured 24-hour urinary sodium and estimated 24-hour urinary sodium from spot urine samples using Tanaka's and Kawasaki's formulae in patients with CKD stages 2, 3 and 4 (P<0.001). This relation was

stronger when using Tanaka's formula compared to Kawasaki's formula in stages 2 and 4 CKD (r=0.968 and r=0.788 compared to r=0.936 and r=0.768 respectively). While in patients of CKD stage 3, Kawasaki's equation was more correlated than Tanaka's (r=0.927 compared to r=0.919), however, in stage 5 CKD, there was no significant correlation between both of them using either formula. (*P*=0.922 for Tanaka's equation and *P*=0.846 for Kawasaki's equation) (Table 3, figures 1-8).

In our study, there was no statistically significant relationship between SBP, DBP or MBP with measured sodium in 24 hour urine or that estimated from spot urine samples using Tanaka's equation (*P*=0.144 and *P*=0.076, *P* =0.075 and *P* =0.074, *P* =0.073 and *P* =0.052 for SBP, DBP and MBP respectively). However, when using Kawasaki's equation, there was a statistically significant relation between estimated sodium excretion from spot urine samples and SBP (*P* =0.043), DBP (*P* =0.049) and MBP (*P* =0.029). It also shows that the relationship was stronger with MBP (r=-0.282) when compared to SBP or DBP (r=-0.262 and r=-0.256 respectively) (Table 4).

Table 1: Clinical and Laboratory data of the enrolled patients

	Range	Mean ± SD
Age (years)	21.00 - 80.00	51.183 ± 15.081
Body Weight (kg)	55.00 - 110.00	79.250 ± 12.421
Height (cm)	150.00 - 185.00	170.233 ± 6.126
BMI (kg/m2)	18.590 - 39.440	27.353 ± 4.130
Serum Creatinine (mg/dl)	1.100 - 9.500	2.778 ± 1.675
Serum Sodium (mmol/L)	126.000 - 145.000	137.850 ± 4.281
Serum Potassium (mmol/L)	3.100 - 6.000	4.353 ± 0.668
Serum Uric acid (mg/dl)	4.100 - 9.800	7.718 ± 1.274
Serum Calcium (mg/dl)	6.800 - 10.500	9.048 ± 0.823
Serum Phosphorous(mg/dl)	3.500 - 6.700	4.915 ± 0.782
Hemoglobin (gm/dl)	7.700 - 15.300	10.395 ± 1.798
24-hr urinary protein (gm/24hrs)	0.110 – 6.780	2.026 ± 1.712
Measured 24-hr Urinary Creatinine Excretion(mg/24hrs)	770.000 - 2376.000	1497.391 ± 394.990

Table 2: Values of measured 24-hr Urinary Sodium versus those estimated by spot urine samples using Tanaka and Kawasaki equations

	Range	Mean ±SD
Measured 24-hr Urinary Sodium	23.000 - 315.100	124.291 ± 57.908
Estimated 24-hr Urinary Sodium (Tanaka)	32.620 - 236.260	136.080 ± 53.177
Estimated 24-hr Urinary Sodium (Kawasaki)	19.160 - 231.210	116.463 ± 55.129

Table3: Correlation between measured 24-hour urinary sodium and estimated 24-hour urinary sodium from spot urine samples in each stage of CKD

	Estimated 24-hr Urinary Sodium from spot urine sample	Measured 24-hr Urinary Sodium	
All CKD Stages		r	P value
	Tanaka	0.904	<0.001
	Kawasaki	0.888	<0.001
CKD stage 2	Tanaka	0.968	<0.001
	Kawasaki	0.936	<0.001
CKD stage 3	Tanaka	0.919	<0.001
	Kawasaki	0.928	<0.001
CKD stage 4	Tanaka	0.788	<0.001
	Kawasaki	0.768	0.001
CKD stage 5	Tanaka	0.078	0.922
	Kawasaki	0.154	0.846

Table4: Correlation between SBP, DBP, MBP and sodium excretion measured in 24 hour urine and estimated from spot urine using Tanaka and Kawasaki's equations

	Measured 24 hour sodium excretion		Estimated 24 hour sodium excretion (Tanaka)		Estimated 24 hour sodium excretion (Kawasaki)	
	r	*P* value	r	*P* value	r	*P* value
Systolic BP	-0.191	0.144	-0.231	0.076	-0.262	0.043
Diastolic BP	- 0.232	0.075	-0.232	0.074	-0.256	0.049
Mean arterial BP	-0.233	0.073	-0.253	0.052	-0.282	0.029

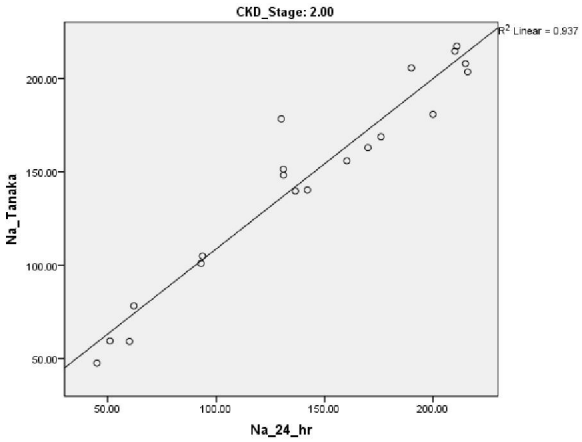


FIGURE 1

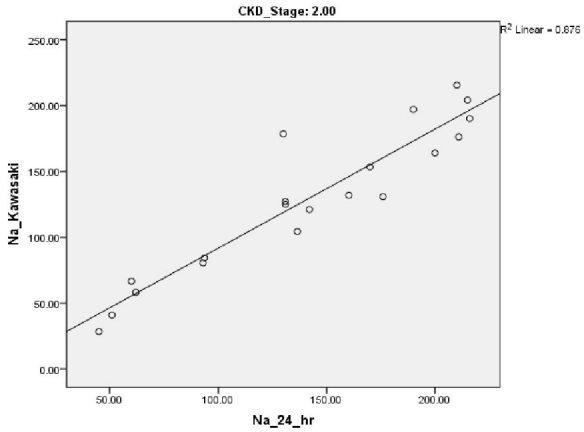
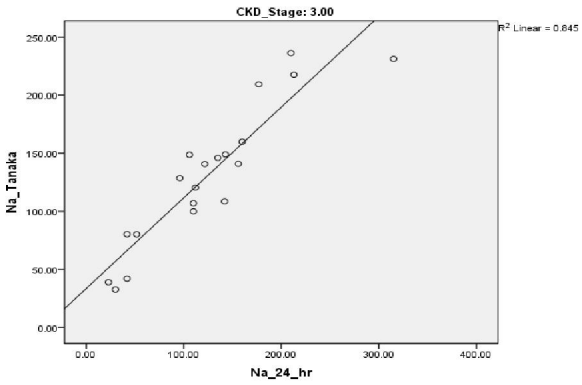


FIGURE 2



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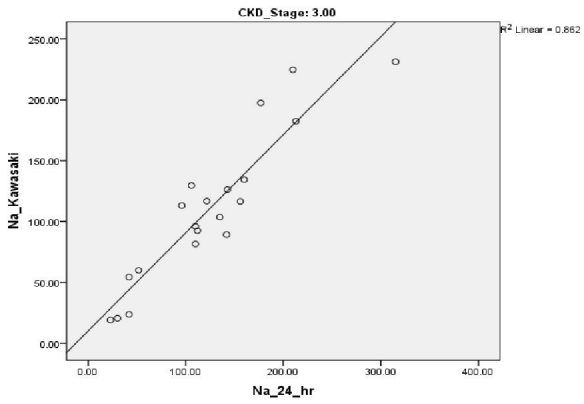
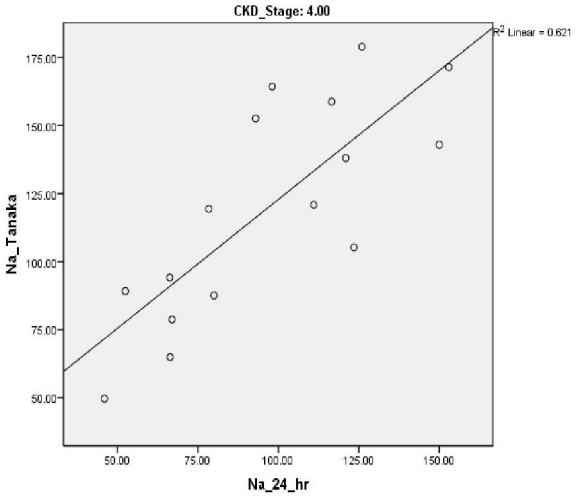


FIGURE 4

4. Discussion

As nearly all sodium ingested is excreted in the urine, repeated 24-hour urine measurements are considered by the World Health Organisation to be gold standard to estimate 24 hour urinary sodium excretion[10]. However, as sodium intake can vary significantly from day to day, accuracy of 24-hour urinary excretion to reflect sodium intake over a given time is directly related to the number of collections gathered[11]. When examining the potential effect of day to day variation in sodium intake on outcomes in research trials, Lui *et al.* estimated that the correlation between sodium and an outcome variable (e.g., blood pressure) could be weakened by half if a single measurement of 24-hour urinary sodium excretion was used[12]. This study estimated that even with four measurements of 24-hour urinary sodium excretion, potential correlations could be diminished by 25% (compared with 10 days)[12].However, increased number of samples involve higher participant burden, increasing the likelihood of error related to improper collection[10]. For this reason, it is recommended to supplement 24-hour urinary sodium measurements with other methods to maximise accuracy of estimated dietary sodium intake[10].



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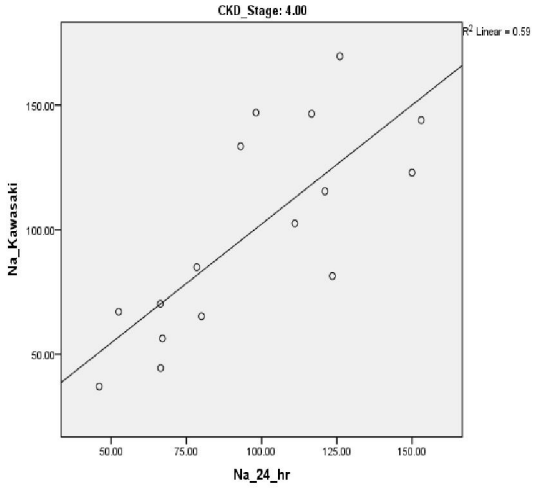

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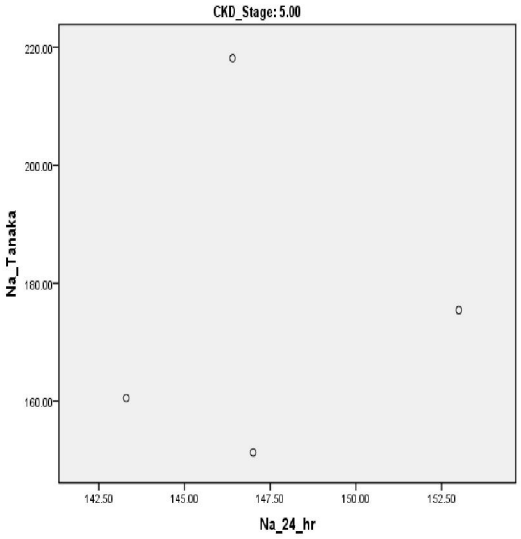

FIGURE 7

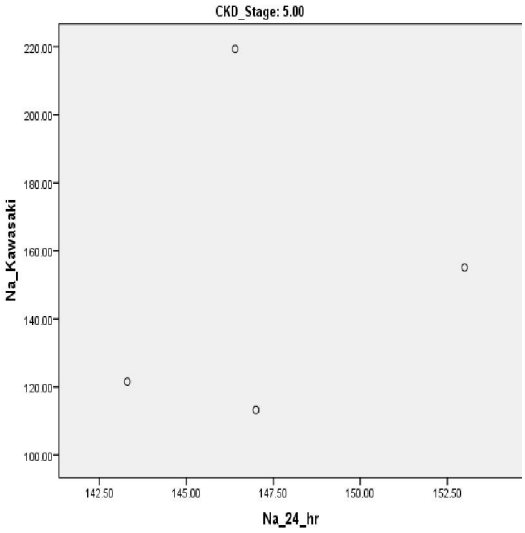

FIGURE 8

In this study, we tried to find out the validity of spot urine samples in estimating the 24 hour urinary sodium excretion (and thus daily sodium intake). The first morning void, or an overnight collection, was not assessed in this study because of the known considerable differences between nocturnal and diurnal rates of sodium excretion[13-16]. In most normotensive individuals, nocturnal sodium excretion, and hence the sodium content of the first morning void, are lower than diurnal values, whereas in many hypertensive individuals, they are considerably higher, particularly among those with a non-dipping salt-sensitive form of hypertension[13].In this study, the AM samples, i.e, the second morning void, obtained at the start of the 24-hour collection. Although an individual's 24-hour creatinine excretion is traditionally regarded as being constant, it does vary by as much as 10% to 20%, largely attributable to the level of protein intake and intense exercise on a given day[17-20]. Since urine creatinine concentration increases during the first few hours after a high protein meal, in this study, the sample was collected prior to breakfast to avoid effects of a high-protein meal.

Our results showed a strong positive correlation between the results of 24 hour urinary sodium excretion and those estimated from spot urine samples using both Tanaka and Kawasaki's equations (P<0.001). This applies to patients of CKD stages 2, 3 and 4 with the relation being stronger in stages 2 and 3. However, for stage 5 CKD, there was no statistically significant relation between the two methods using either equation.

Our results agreed in part with the study of Imai et al., who compared both measured 24-hour urine excretion and that estimated from the first morning urine using both equations for 136 patients with CKD and concluded that using Tanaka's equation for estimating Na excretion was accurate for CKD population and that it can be applied to estimate Na excretion in clinical practice[21].

Similarly, this result was partly in agreement with the results declared by Ogura et al., in his study on 96 CKD patients in which he compared the measured 24-hour urinary sodium with that estimated from spot urine samples using Tanaka's equation. The study demonstrated that estimated sodium excretion significantly correlated with measured sodium excretion (R = 0.52, $P < 0.01$). However, in contrast to our study where the results were less strongly correlated in patients with e-GFR= 15-29 mL / min/ 1.73 m2 (stage 4 CKD) and non-correlating at all with e-GFR <15 mL / min/ 1.73 m2 (stage 5 CKD), they found that the correlation was more apparent in patients with e-GFR <30 mL/min[22].

However, our results disagreed with those reported by Okada *et al.,* on their study on 182 CKD patients who collected 24-hour urine, first morning spot urine, and casual daytime spot urine on the same day. They stated that the estimation of urinary sodium excretion using spot urine is currently inadequate to apply to the clinical assessment of salt intake in CKD patients. They suggested that this may be attributed to the fact that urinary creatinine excretion values calculated by these equations tended to be overestimated compared with measured urinary creatinine excretion[23].

Comparing both Tanaka and Kawasaki's equations as an accurate method to estimate 24-hour urinary sodium excretion, our study showed that Tanaka's equation had stronger correlation with measured 24 hour urinary sodium and thus is a more accurate method for estimation of sodium excretion than Kawasaki's equation in stages 2 and 4 CKD (r=0.968 and r=0.788 compared to r=0.936 and r=0.768 respectively). However, in stage 3, Kawasaki's equation was more accurate than Tanaka's equation (r=0.928 compared to 0.919 respectively).

These results were supported in part by Imai et al., in his previously mentioned study in which they stated that Tanaka's equation consistently provided more accurate values of estimated Na excretion compared with Kawasaki's equation[21].

As regards the relationship between urinary sodium excretion and blood pressure, our study showed no statistically significant relationship between degree of hypertension (as reflected by systolic, diastolic and mean blood pressure readings) and values of measured 24 hour urinary sodium excretion (P=0.144, P=0.075 and P=0.073 for SBP, DBP and MBP respectively) or that estimated from the spot urine sample by using Tanaka's equations. (P=0.076, P =0.074 and P =0.052 for SBP, DBP and MBP respectively). On the contrary, in our study, the estimated 24-hour urinary Na by the Kawasaki equation was found to have a significant statistical relationship with the degree of hypertension as reflected by SBP (P =0.043), DBP (P =0.049) and MBP (P =0.029). This agrees in part with the results found by Campagnoli *et al.,* where 72 students were studied as regards the relationship between their 24-hour sodium excretion and their SBP and DBP. They stated that no significant relationships were found between SBP and natriuria (P =0.6 r=0.003) or between DBP and natriuria (P =0.7 r=0.002.) [24]

There were some limitations in the present study. The number of patients recruited was relatively small. Moreover, there were no stage 1 CKD patients. Further studies with larger numbers of patients allocated equally by e-GFR may be needed. We relied on a single 24-h urine collection for each participant, this may not be adequate for accurate measurement as salt intake differs largely from day to day.

The method of Tanaka et al, is population specific; requires internal calibration with age, weight, and creatinine; overestimates low intakes and underestimates high intakes[25,26], which was not practically considered in this study. Additional studies are merited to further evaluate the role of the spot urine samples (random, morning and night samples) in assessing sodium intake at different stages of CKD.

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