Cosinor-rhythmometry for 24-h urinary sodium, potassium, creatinine excretion in the Chinese adult population

Ya-Guang Peng[1], Jing-Jing Feng[2], Ying Zhang[3], Kun Li[4], Si-Yu Cai[1], Ruo-Hua Yan[1], Xiao-Xia Peng[1]

[1]Center for Clinical Epidemiology & Evidence-based Medicine, National Center for Children's Health, Beijing Children's Hospital, Capital Medical University, Beijing 100045, China;
[2]Department of Nursing Administration and Rehabilitation Research, National Institute of Hospital Administration, Beijing 100044, China;
[3]Department of Diseases Prevention and Control, Third Hospital, Peking University, Beijing 100191, China;
[4]Center for Endocrine Metabolism and Immune Diseases, Beijing Luhe Hospital, Capital Medical University, Beijing 101149, China.

Abstract

Background: The low accuracy of equations predicting 24-h urinary sodium excretion using a single spot urine sample contributed to the misclassification of individual sodium intake levels. The application of single spot urine sample is limited by a lack of representativity of urinary sodium excretion, possibly due to the circadian rhythm in urinary excretion. This study aimed to explore the circadian rhythm, characteristics, and parameters in a healthy young adult Chinese population as a theoretical foundation for developing new approaches.

Methods: Eighty-five participants (mean age 32.4 years) completed the 24-h urine collection by successively collecting each of the single-voided specimens within 24 h. The concentrations of the urinary sodium, potassium, and creatinine for each voided specimen were measured. Cosinor analysis was applied to explore the circadian rhythm of the urinary sodium, potassium, and creatinine excretion. The excretion per hour was computed for analyzing the change over time with repeated-measures analysis of variance and a cubic spline model.

Results: The metabolism of urinary sodium, potassium, and creatinine showed different patterns of circadian rhythm, although the urinary sodium excretion showed non-significant parameters in the cosinor model. A significant circadian rhythm of urinary creatinine excretion was observed, while the circadian rhythm of sodium was less significant than that of potassium. The circadian rhythm of urinary sodium and creatinine excretion showed synchronization to some extent, which had a nocturnal peak and fell to the lowest around noon to afternoon. In contrast, the peak of potassium was observed in the morning and dropped to the lowest point in the evening. The hourly urinary excretion followed a similar circadian rhythm.

Conclusion: It is necessary to consider the circadian rhythm of urinary sodium, potassium, and creatinine excretion in adults while exploring the estimation model for 24-h urinary sodium excretion using spot urine.

Keywords: Circadian rhythm; Sodium urinary excretion; Cosinor analysis; Spot urine; 24-h urine

Introduction

Elevated blood pressure caused by high sodium intake has been a well-established risk factor for cardiovascular diseases,[1,2] as well as a primary cause of death and disability.[3-5] Recent large-scale population studies[6-9] reported a J- or U-shaped association between the estimated 24-h urinary sodium excretion and cardiovascular events. However, these findings have caused controversy. The methods to estimate 24-h urinary sodium excretion from a single spot urine sample have been questioned,[10-12] including Kawasaki formula,[13] International Study of Salt and Blood Pressure (INTERSALT) formula,[14] and Tanaka formula.[15] At present, multiple non-consecutive 24-h urine collections are widely recommended as the gold standard for assessing sodium intake.[16,17] The predictive methods based on single spot urine had poor accuracy for individual assessment, with a tendency to overestimate at low sodium intake levels and underestimate at high sodium intake levels, leading to misclassification of sodium intake.[18,19] Previous research has demonstrated that renal excretion of sodium followed a diurnal rhythm independently of the timing of sodium intake.[20] However, the above prediction formulas did not take the circadian rhythm of excretion into account and therefore were potentially biased using one single spot urine sample, specifically, second-morning urine sample for Kawasaki formula, and single random spot urine sample for INTERSALT and Tanaka formulas. The effect of the circadian rhythm on predicting 24-h urinary sodium excretion is largely unknown. By the reasonable selection

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Correspondence to: Dr. Xiao-Xia Peng, Center for Clinical Epidemiology & Evidence-based Medicine, National Center for Children's Health, China, Beijing Children's Hospital, Capital Medical University, No. 56 South Lishi Rd, Xicheng District, Beijing 100045, China
E-Mail: pengxiaoxia@bch.com.cn

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and combination of multiple spot urines accounting for the circadian rhythm, spot urines may produce a reliable estimation of 24-h urinary sodium excretion. Therefore, this study aimed to explore the circadian rhythm, characteristics, and parameters in a healthy Chinese young adult population and provide important information for improving future prediction models.

Methods

Ethics

This study was conducted in accordance with the *Declaration of Helsinki* and was approved by the Ethics Committee (No.2714-34) and all participants signed informed consent.

Study populations

Data were collected from an adult population-based study on 24-h urinary sodium excretion. A total of 100 healthy participants were recruited between 2015 and 2016, including graduate students and staff from a single-center institute, aged 18 to 60 years. Participants completed a screening questionnaire before the 24-h urine collection. The exclusion criteria were as follows: (1) participants diagnosed with hypertension or diabetes by doctors; (2) currently taking diuretics or receiving diuretic treatment for any reason; (3) participants with kidney diseases or impaired renal function; (4) participants diagnosed with any heart diseases; (5) any condition that may affect dietary intakes; and (6) intravenous infusion within 3 days before or after 24-h urine collection.

Measurements

A screening questionnaire including demographic information, disease history, medication use, and physical measurements, including height, weight, and blood pressure, was required for all participants. Blood pressure was measured three times after 5-min resting in a seated position by a trained researcher using an electronic sphygmomanometer (Omron HEM-7200, Tokyo, Japan). The average of the three measurements was used. Body mass index was calculated using weight (kg) and height (m).

24-h urine collection

Participants were invited to complete a 24-h urine collection by successively collecting each of the single-voided specimens within 24 h. The training was conducted by a researcher to instruct each participant on the collection, including avoiding vigorous exercise and leakage of urine. The collection was started at the research site on the first day and was completed there the next day. Screw-capped containers (1 L) were provided onsite to collect the urine specimens. The participants were asked to empty the bladder at the start time of the study and collect each single-voided urine specimen in one container for the following complete 24-h. The start and end time of the onsite collection, marked by the first- and last-voided urine within 24 h, respectively, was recorded for each participant. Researchers recycled all containers and extracted the specimens on the next day. Any reported missing void would result in an incomplete collection and the participants were then asked to take a repeated collection. Incomplete collections were also defined when the duration time fell outside the range of 22 to 26 h, or the total volume of urine was <500 mL. The volume of each single-voided urine specimen was measured with a scaled cylinder, and a 3-mL aliquot was extracted as the spot urine sample. The total volume of 24-h urine was measured after mixing all the spot urines in a 5-L container, and a 4-mL aliquot was extracted as the 24-h urine sample. Urine samples were stored at −80°C in the refrigerator until centralized testing.

Laboratory examination

Urinary sodium and potassium were measured with an electronic analyzer (MEDICA EasyLyte PLUS, Bensenville, IL, USA) using the ion-selective electrode method; urinary creatinine was measured with an automatic biochemical analyzer (Hitachi 7080, Tokyo, Japan) by the enzymatic method in a qualified laboratory. The laboratory was calibrated with standard samples before performing the analyses. All samples were tested at the same time. Quality control was conducted using 20% of all samples as blinded samples.

Urinary excretion data processing

Urine excretion data included the volume of each spot urine specimen, urination order number, urination time, and the concentration of sodium, potassium, and creatinine. The urination time was categorized into eight timings of the urine specimen that covered 24 h [Table 1]. Only the second-morning urine, identified by the sequence number and time of urination, included only one spot urine sample, while other timings might include a few spot urines during the given time. While comparing the parameters of urinary excretion by timing, the mean value method was applied if there were multiple spot urines during the timed period considering the collinearity. Participants might not urinate during some timed period. Therefore, missingness could happen for some timing. The interval was calculated as the time difference between two consecutive voids, to further compute the excretion per unit hour (mg/h) with the following formula:

$$\text{Excretion per hour (mg/h)} = \frac{\text{Concentration (mmol/L)} \times \text{Volume (L)} \times \text{Molecular equivalent (mg/mmol)}}{\text{Interval (h)}}$$

Table 1: Urination durations definition for spot urines.

Urination time duration	Spot urine name
0:00–6:00	Overnight urine (OU)
6:01–8:00	Second morning urine (SMU)
8:01–11:00	Before noon urine (BNU)
11:01–13:00	Noon urine (NU)
13:01–16:00	Afternoon urine (ANU)
16:01–18:00	Before dinner urine (BDU)
18:01–20:00	After dinner urine (ADU)
20:01–23:59	Before bed urine (BBU)

The accumulative excretion per hour at each timing was computed by summation if there were multiple spot urines at the given timing.

Statistical analysis

Cosinor analysis was used to explore and determine the parameters, the Midline Estimating Statistic of Rhythm (MESOR), acrophase, and amplitude of the circadian urinary excretion data were analyzed with the Cosinor package in R software (version 3.6.3, https://www.r-project.org/). The model of cosinor analysis[21] was:

$$Y(x) = \text{MESOR} + \text{Amplitude} \times \cos\left(\frac{2\pi x}{\text{Period}} + \text{Acrophase}\right) + \varepsilon$$

where the MESOR (M) is a rhythm-adjusted mean, the amplitude (A) is a measure of half the extent of predictable variation within a cycle, the acrophase (ϕ) is a measure of the time of overall high values recurring in each cycle, the period (τ) is the duration of one cycle, set at 24-h, and epsilon (ε) is the error term. The cosinor analysis demonstrates a pattern of urinary excretion in a consecutive timeline. Therefore, it did not require the imputation for the missing spot. For the analyses on the urinary excretion change per unit hour and the repeated-measures analysis of variance (ANOVA), the missing spot would be imputed with the values of the closest spot urine sample because no missing value in all timing groups was allowed.

Mean ± standard deviation was used to describe normally distributed data, while the median and interquartile range (IQR) was used for skewed data. Considering the physical and physiological characteristics between males and females, sex differences in urinary excretion were compared and tested using *t*-test or Wilcoxon signed-rank test determined by the distribution of the variable. Similarly, the sex-stratified cosinor analysis was conducted. The cubic spline function was used to fit the curve of individual urinary excretion changes and the distribution trends over time. Repeated-measures ANOVA was conducted to compare the parameters of urinary excretion by timing after the missing value imputation. Mauchly test was conducted for the condition of sphericity. The Greenhouse-Geisser correction was used when the spherical hypothesis was not met. Sensitivity analysis was used to determine the robustness of the statistics to eliminate the influence of excluded individuals with incomplete urine collection. Statistical significance was defined as $P < 0.05$.

Results

Characteristics of the study participants

A total of 100 participants were enrolled in this study. After excluding 15 participants due to incomplete urine collection, low urine volume, or high urinary creatinine level, 85 (30 males and 55 females) were included in the analysis. No other differences in characteristics except the void times were found between the excluded and included participants [Supplement Table 1, http://links.lww.com/CM9/A428]. In all 85 participants, the creatinine excretion (mg) from 24-h urine collection was higher in males than that in females [Table 2], the same as the concentration of sodium excretion (mmol/L). Female participants had 8.3 voids per day on average, more frequently than male participants ($P < 0.05$). The mean volume of 24-h urine of females was much greater than that of males ($P < 0.05$).

Circadian rhythm of urinary excretion

Table 3 presents the parameters of cosinor analysis models for 24-h urinary excretion, including the total mass and

Table 2: Characteristics of study participants grouped by sex.

Parameters	Male	Female	*t/Z* value	*P* value
Cases	30	55	–	–
Age (year)	29.1 ± 10.3	34.2 ± 12.4	2.036	0.046
Height (cm)	174 .4 ± 5.3	160.6 ± 5.2	–11.619	<0.001
Weight (kg)	72.3 ± 11.3	57.5 ± 9.4	–6.383	<0.001
BMI (kg/m^2)	23.7 ± 3.4	22.3 ± 3.4	–1.862	0.066
SBP (mmHg)	118.3 ± 11.9	113.3 ± 12.6	–1.707	0.092
DBP (mmHg)	70.4 ± 7.7	69.4 ± 8.9	–0.482	0.631
Pulse (/min)	72.6 ± 10.9	75.7 ± 11.9	1.133	0.261
Void Frequency (per day)	7.2 ± 1.6	8.3 ± 1.8	2.848	0.006
24-h urine				
Sodium Concentration (mmol/L)	117.4 (72.6)	101.4 (50.9)	–1.766	0.077
Potassium Concentration (mmol/L)	26.1 (24.7)	25.2 (15.7)	–0.244	0.807
Creatinine Concentration (μmol/L)	8667 (5964.7)	3880 (2627)	–5.334	<0.001
Volume (mL)	1522 (675)	2062 (961.5)	–2.520	0.012
Sodium Excretion (mg/day)	3863.7 (3113.8)	4074.7 (2589.2)	–0.515	0.607
Potassium Excretion (mg/day)	1446.3 (1300.6)	1803 (975.6)	–1.453	0.146
Creatinine Excretion (mg/day)	1473.5 (741.6)	861.2 (392.6)	–5.793	<0.001

Normality data were presented as mean with standard deviation (SD). Skewed data were presented as median with interquartile ranges (IQR). BMI: Body mass index; DBP: Diastolic blood pressure; SBP: Systolic blood pressure.

Table 3: Parameters of cosinor model for 24-h urinary excretion circadian analysis.

	MESOR			Amplitude			Acrophase		
Parameters	Mean	SE	*P*	Mean	SE	*P*	Mean	SE	*P*
Na (mg)									
Female	568.8	18.0	<0.001	31.1	25.7	0.225	0.3	0.7	0.713
Male	648.9	28.4	<0.001	35.2	43.2	0.415	0.5	1.0	0.585
Total	595.0	15.3	<0.001	33.9	22.4	0.131	0.4	0.6	0.496
K (mg)									
Female	249.4	9.3	<0.001	36.5	11.3	0.001	–0.9	0.4	0.021
Male	264.8	13.6	<0.001	40.7	18.0	0.024	–1.4	0.5	0.005
Total	254.6	7.7	<0.001	37.0	9.5	<0.001	–1.0	0.3	<0.001
Cre (mg)									
Female	124.9	4.0	<0.001	56.2	5.8	<0.001	1.2	0.1	<0.001
Male	241.4	10.2	<0.001	70.9	15.2	<0.001	1.2	0.2	<0.001
Total	163.1	4.8	<0.001	63.3	7.1	<0.001	1.2	0.1	<0.001
Na (mmol/L)									
Female	118.2	3.5	<0.001	17.8	5.2	<0.001	1.0	0.2	<0.001
Male	131.4	4.6	<0.001	6.9	6.8	0.306	0.3	0.9	0.742
Total	122.4	2.8	<0.001	14.2	4.2	<0.001	0.9	0.2	<0.001
K (mmol/L)									
Female	33.1	1.3	<0.001	9.7	1.7	<0.001	–1.4	0.2	<0.001
Male	32.5	1.5	<0.001	4.1	2.0	0.038	–1.3	0.5	0.015
Total	32.9	1.0	<0.001	7.8	1.3	<0.001	–1.4	0.2	<0.001
Cre (mmol/L)									
Female	6.3	0.2	<0.001	3.4	0.3	<0.001	1.2	0.1	<0.001
Male	10.5	0.4	<0.001	2.7	0.6	<0.001	1.2	0.2	<0.001
Total	7.6	0.2	<0.001	3.2	0.3	<0.001	1.2	0.1	<0.001
Volume (mL)									
Female	250.0	6.9	<0.001	26.3	9.9	0.008	1.4	0.3	<0.001
Male	247.2	10.8	<0.001	6.4	16.5	0.700	1.0	2.1	0.631
Total	249.2	5.8	<0.001	19.8	8.5	0.019	1.3	0.4	0.005

MESOR: Midline estimating statistic of rhythm.

concentration of sodium, potassium, and creatinine, as well as the volume by gender. The circadian rhythm of the urine volume was significant in females but not in males, although the cosinor model plot illustrated a fluctuating pattern. Through the cosinor analysis, a significant circadian rhythm of urinary creatinine excretion was observed, while the circadian rhythm of sodium was less significant than that of potassium.

Sodium

The MESOR both in mass and concentration of urinary sodium excretion indicated a higher mean level in males than that in females. The amplitude and acrophase of urinary sodium excretion (mg), which was tested for the circadian rhythm, was not significant for both sexes. In contrast, the parameters of the concentration of sodium urinary excretion showed a circadian rhythm. According to the cosinor analysis model plots [Figure 1A and Supplement Figure 1A, http://links.lww.com/CM9/A427], urinary excretion presented a circadian rhythm regardless of sex. Specifically, it surged from the evening, gradually increased, peaked at night, decreased after morning until reached the lowest level at noon or afternoon. Slight variations in the phase were observed between males and females.

Potassium

It was worth mentioning that the amplitude of concentration of urinary potassium excretion in females was three times as much as males, although showed a little difference in the MESOR of urinary potassium excretion between males and females. The urinary potassium metabolism peaked in the early morning and continued to decline during the day until it reached the lowest level in the evening [Figure 1B and Supplement Figure 1B, http://links.lww.com/CM9/A427].

Creatinine

The urinary creatinine excretion level in males was higher than that in females. The circadian rhythm of urinary creatinine excretion was consistent between males and females, with a relatively steady difference. The excretion level reached a peak in the morning, decreased in the day to the bottom level at about 17:00 to 18:00, and gradually increased at night [Figure 1C and Supplement Figure 1C, http://links.lww.com/CM9/A427].

Change of urine excretion over durations

To explore the levels of urinary excretion turbulence over time, repeated-measures ANOVA was performed. The

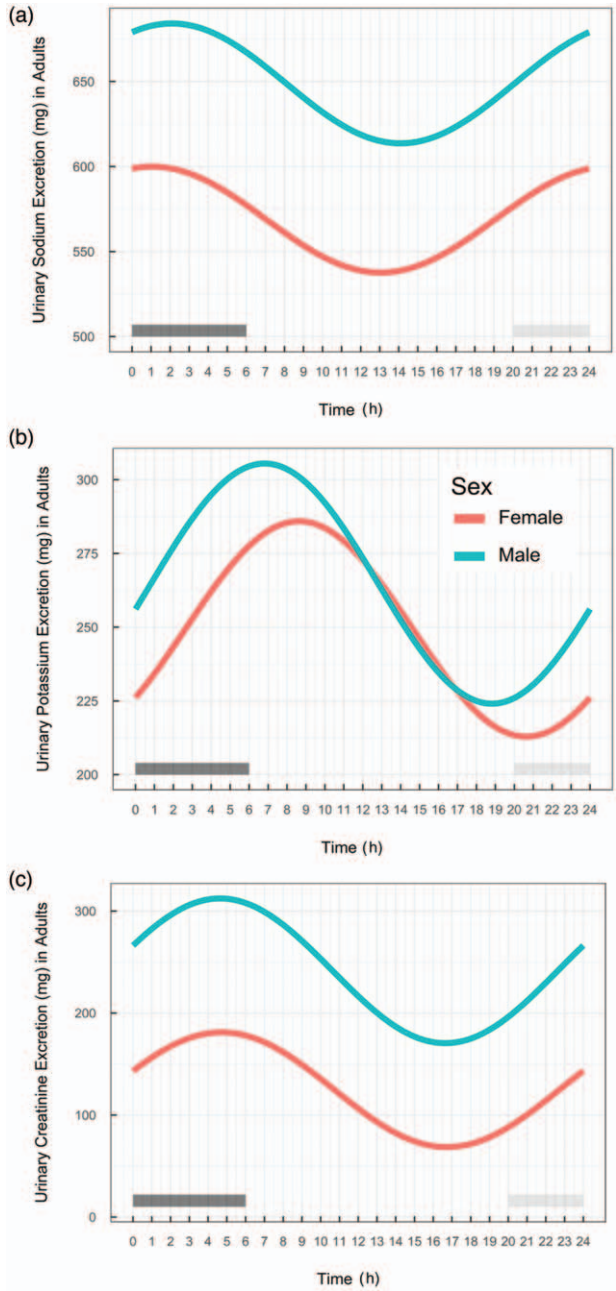

Figure 1: Cosinor model of urinary excretion sodium, potassium, and creatinine excretion (mg) for 85 participants stratified by sex. A cosinor model fitted to urinary sodium (A), potassium (B), and creatinine (C) excretion (mg) of 33 men (green line) and 52 women (red line). Light gray bars upper *x*-axis represent the duration from 20:00 to 24:00 and the dark bar shows the nocturnal period from 0:00 to 6:00.

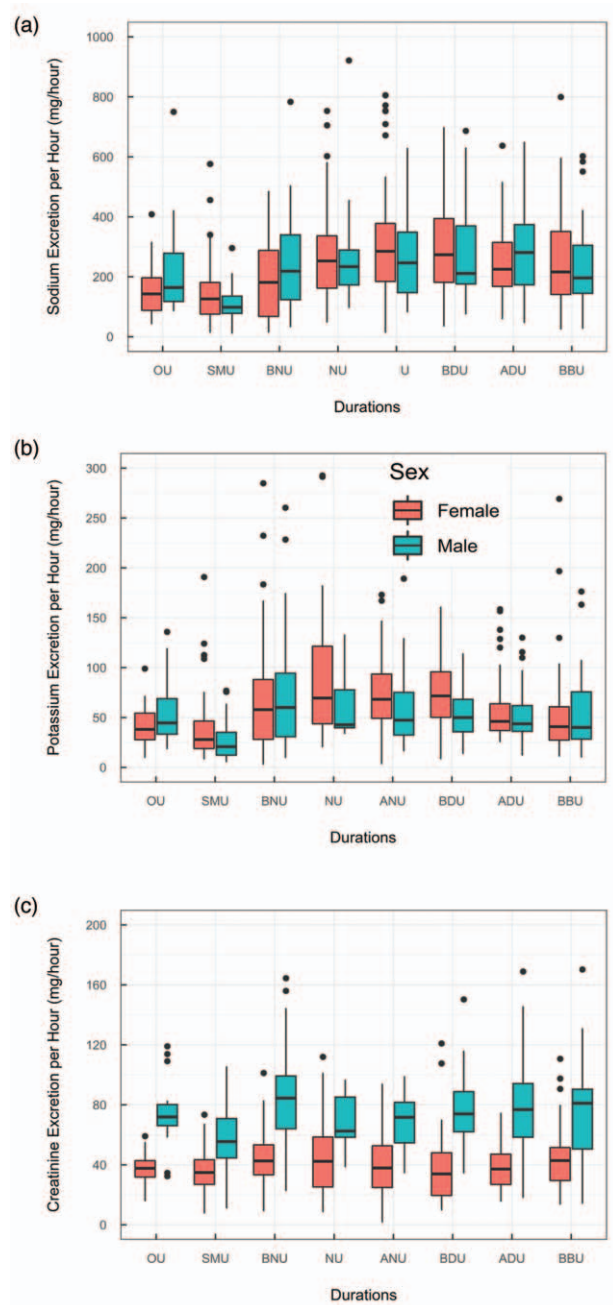

Figure 2: The tendency of urinary excretion sodium, potassium, and creatinine excretion per hour (mg/h) in eight durations for 85 participants stratified by sex. Box plots were depicted to urinary sodium (A), potassium (B), and creatinine (C) excretion per hour (mg/h) of 33 men (green box) and 52 women (red box). ADU: After dinner urine; ANU: Afternoon urine; BBU: Before bed urine; BDU: Before dinner urine; BNU: Before noon urine; NU: Noon urine; OU: Overnight urine; SMU: Second-morning urine.

timing of urine was included as a within-participant factor, sex as a between-participant factor, urinary excretion levels, and concentrations as dependent variables. The effects of timing on urinary excretion were significant for potassium ($P = 0.009$) and creatinine ($P < 0.001$) using repeated-measures ANOVA, but not for sodium excretion ($P = 0.105$). There was a sex difference of urinary creatinine excretion in the ANOVA model [Figure 2A–2C], where the level in males was consistently higher than that in females ($P < 0.001$). No significant difference in sodium or potassium excretion between males and females was found in the model. The patterns of sodium, potassium, and creatinine urinary excretion per unit hour, depicted with IQRs over 24 h for males and females separately, were similar to the circadian rhythms showed in the cosinor analysis [Supplement Figure 2, http://links.lww.com/CM9/A427].

Sensitivity analysis

The exclusion of 15 participants failed to bias the circadian rhythm and the characteristics of urinary excretion including

sodium, potassium, and creatinine in this study [Supplement Figures 3–5, http://links.lww.com/CM9/A427].

Discussion

Circadian rhythm is a common phenomenon that occurs as a cycle over 24 h, synchronized to the day and night cycle.[22] Peripheral molecular clocks are involved in the regulation of circadian blood pressure, as well as sodium and potassium homeostasis by kidneys.[23,24] Early researches have reported that the excretion of sodium, potassium, and water by renal metabolism followed a strong circadian pattern in both humans and non-human primates, independently of the time of day when food and water were ingested.[20,25] This study verified this circadian rhythm of urinary excretion in healthy adults, which might help improve the prediction formulas for 24-h urinary sodium excretion using single spot urine samples.

Using single spot urine to estimate 24-h urinary sodium excretion has advantages over 24-h urine collection, including great convenience and improved feasibility of individual sodium intake evaluation. About 90% of the sodium intake is eventually excreted in the urine *in vivo*. It was reported that the correlation coefficient between sodium intake and urinary sodium excretion was >0.75.[18] Single spot urine might be poorly representative of urinary sodium excretion because it did not reflect metabolic circadian rhythm, leading to biased individual assessment. Some recent clinical studies have demonstrated the drawbacks of the prediction formulas using single spot urine.[12,26-28] As the results showed, for instance, the urinary sodium excretion level of the second-morning urine, commonly in the period from 7:00 to 9:00, which was used in the Kawasaki formula, seemed close to the bottom for males, while near the MESOR for females. Single spot urine failed to produce a valid estimation for 24-h urinary excretion, particularly random spot urine samples, which were applied in INTERSALT and Tanaka formulas. The parameters in the cosinor analysis [Table 3] and the distributions from boxplots [Supplement Figure 1, http://links.lww.com/CM9/A427] both showed a turbulent variation of the urinary sodium excretion, indicating that a single spot urine sample might not be sufficient for 24-h urinary excretion estimation. Therefore, it might be promising to select and combine multiple spot urine samples to account for the circadian rhythm, to improve the prediction models for 24-h urinary sodium excretion. However, the selected multiple spot urines, for instance, two or more timed spot urine samples to include the peak, lowest, and MESOR levels. Further studies on statistical modeling are needed, which is also one of the key technical points to better the accuracy of the prediction formula in the future study.

Our study showed a difference in parameters of circadian rhythm between male and female participants, although the rhythm was less significant in males. One experiment research for rats reported a clear dissociation between circadian blood pressure and control of sodium excretion that is sex-dependent.[29] The differences in the void frequency and the volume of the 24-h urine might be a major explanation for the difference in the cosinor phase between male and female. The smaller sample size of male might also affect the power of the cosinor analysis.

It should be noted that urinary creatinine metabolism, as previously reported,[22] has a relatively stable circadian rhythm. The metabolism of creatinine is finally excreted from urine *in vivo* in healthy individuals through the kidney. Urinary creatinine level is not the primary indicator of renal function, but it still could be a calibration variable applied to the prediction model for urinary sodium excretion. It might be the reason that urinary creatinine was included as an independent variable in the Kawasaki and Tanaka formulas. Thus, this relatively stable correction method should be introduced as well for further improvement of the equations.

The circadian rhythm of urinary sodium excretion, as shown in the present study, should not be ignored while using the spot urine to predict the 24-h urinary sodium excretion, especially using random single spot urine samples. One adult population study used the sodium mean level from three spot urines in the prediction model. Even though it did not account for the circadian rhythm, the correlation coefficient between the estimated value and the measured value reached over 0.8.[30] According to the circadian rhythm, considering the parameters as spot urine selection indicator, such as MESOR, amplitude, acrophase, and including the timing of the spot urine and the parameters of circadian rhythm in the predictive equations, such as MESOR, amplitude, and acrophase, may improve the validity.

The present study adopted a modified 24-h urine collection method where each single-voided urine sample was separately collected for 24 h, facilitating a detailed analysis of the urinary sodium, potassium, and creatinine excretion in healthy adults. The results illustrated a circadian rhythm of 24-h urinary excretion. However, several limitations should be noted. First, the participants enrolled in this study were young adults from a research institute, therefore, may not be representative of the general population due to some unique characteristics, such as daily schedule, meals, accommodation, and nature of work, which might affect the circadian rhythm of 24-h urinary excretion. However, they had a better understanding and compliance with the study protocol, ensuring good data quality which was indispensable for the circadian rhythm analysis. The circadian rhythm for the community population, the elders should be further investigated before the findings can be generalized. Second, the relation between blood pressure and urinary sodium metabolism was not analyzed because ambulatory blood pressure monitoring was not performed due to weak feasibility. Finally, multiple consecutive 24-h urine collections, which were considered as the gold standard for sodium intake evaluation, were not available in the present study. Therefore, it was not possible to assess whether a hyperdiurnal rhythm existed in the urinary excretion.

We conclude that the metabolism of urinary sodium, potassium, and creatinine excretion in adults exhibites circadian rhythm over 24 h but is not taken into account

in the existing equations predicting 24-h urinary sodium excretion. These findings highlight the need for considering the circadian rhythm in estimation models of 24-h urinary sodium excretion using multiple spot urines. Further study is needed to develop a new algorithm and modeling statistics considering the urinary excretion circadian rhythm to improve the accuracy of individual estimation and promote public health strategies on sodium reduction.

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Conflicts of interest

None.

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