ORIGINAL RESEARCH

Variability of 24-Hour Sodium Urinary Excretion in Young Healthy Males Based on Consecutive Urine Collections: Impact on Categorization of Salt Intake

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Objective: Several nonconsecutive 24-h urinary collections are considered the gold standard for estimating dietary salt intake. As those samples are logistically demanding, we aimed to describe the variability of 24-h sodium urinary excretion over consecutive days and report its adequacy with sodium intake.

Methods: We enrolled 16 healthy male volunteers in a prospective controlled study. All participants randomly received a low salt diet (LSD) (3 g/day of NaCl), a normal salt diet (NSD) (6 g/day of NaCl), and a high salt diet (HSD) (15 g/day of NaCl) for 7 days in a crossover design without wash-out period.

Results: On day 6, median sodium urinary excretion was 258 (216-338), 10 (8-18), and 87 (69-121) mmol/day for HSD, LSD, and NSD, respectively ($P < .001$). When considering days 4-6, sodium urinary excretion was in steady state as models with and without interaction term "diet type X sample day" were not significantly different ($P = .163$). On day 6, area under the curve (AUC) of receiver operating characteristic for urinary sodium excretion to detect HSD was 1.0 (1.0-1.0) and a cut-point of 175 mmol/day was 100% sensitive and specific to detect HSD. On day 6, receiver operating characteristic AUC to detect LSD was 0.993 (0.978-1.0) and a cut-point of 53 mmol/day was 96.4% sensitive and 100% specific to detect LSD.

Conclusion: A steady state of sodium balance, where sodium intake is proportional to its excretion, is reached within a few days under a constant diet in the real-life setting. Categorization of salt consumption into low (3 g/day), normal (6 g/day), or high (15 g/day) based on a single 24-h urine collection is nearly perfect. Based on these results, repeated nonconsecutive urine collection might prove unnecessary to estimate sodium intake in daily clinical practice provided that diet is rather constant over time.

Keywords: sodium; salt; intake; excretion; collection

Introduction

THE REGULATION OF sodium balance is a complex and integrative mechanism mainly involving the kidney under the influence of neuro-humoral factors.[1] As the kidney excretes more than 90% of ingested salt, sodium balance in humans is thought to reach a steady state after a few days on a constant diet, where sodium urinary excretion matches sodium intake.[2] Based on this principle, the determination of 24-h urinary sodium excretion is considered the reference surrogate marker of sodium intake in clinical practice. However, this "renocentric" theory of sodium balance has been challenged by recent observations. Short-term and long-term variability in sodium urinary excretion when constant sodium intake was maintained under strict conditions has been described in a small group of astronauts experimenting simulated flight to Mars.[3] Those data also raised the hypothesis that other organs could be involved in sodium homeostasis with subsequent demonstration of

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Ethics: This study was approved by the "University Hospital Ethical Committee" (2016-01779) and written informed consent was obtained. It was performed according to the declaration of Helsinki.

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Data underlying this article will be shared on reasonable request to the corresponding author.

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nonosmotic storage of sodium in skin and muscles and mobilization through lymphatics and sweat.[4,5] Altogether, those observations question the validity of a single 24-h urine collection as a surrogate marker of sodium consumption.

Salt intake is a pivotal nutritional factor that affects human health in many ways. Most prominently, high salt intake has been linked to increased mortality and cardiovascular risk in observational and interventional studies.[6-9] While single 24-h urinary collections remain the reference method to estimate individual sodium intake in routine clinical practice, this method has been criticized for its lack of precision and risk of bias in epidemiological studies.[10] Consequently, guidelines now recommend performing several nonconsecutive 24-h urinary collections when accounting for short-term and long-term variability is desirable.[11,12] However, 24-h urinary samples are logistically demanding, cumbersome for patients, and potentially prone to errors.[13]

The aim of the present study was to describe the variability of 24-h sodium urinary excretion over consecutive days and report its adequacy with sodium intake in young healthy males in a free-living environment.

Methods

Participants and Study Design

The present study represents a post hoc analysis of data collected between 2016 and 2018 at the Geneva University Hospitals in Switzerland to investigate the impact of different levels of sodium intake on renal potassium handling.[14] Briefly, 16 healthy male volunteers recruited among medical students of the Faculty of Medicine of Geneva took part in a prospective crossover controlled study. Inclusion criteria were (1) age 18-30 years, (2) normotensive, and (3) no past medical history of cardiac, renal, or endocrine disturbance. Exclusion criteria were (1) hypertension defined as mean office blood pressure $\geq$ 140/90 mmHg on 3 consecutive measurements and (2) use of anti-inflammatory drugs, diuretics, or corticosteroids. Participants received modest financial compensation for their participation.

Experimental Procedures

All participants randomly received a low salt diet (LSD) (3 g/day of NaCl, i.e., $\approx$52 mmol/day of Na+), a normal salt diet (NSD) (6 g/day of NaCl, i.e., $\approx$103 mmol/day of Na+), and a high salt diet (HSD) (15 g/day of NaCl, i.e., $\approx$259 mmol/day of Na+) for 7 days in a crossover design without washout period between diet types. Diet sequence was allocated by blocked randomization created by a computer to prevent a sequence effect. Owing to the original protocol, 4 participants received HSD diet instead of NSD diet.[14] Consequently, those 4 participants were submitted to LSD diet once and to HSD diet twice. This was done purposefully in the original protocol to assess reproducibility and detect a potential sequence effect. All meals were composed by a dietician calibrated for constant K+ (2.7 g/day, i.e., $\approx$70 mmol/day) and Na+ (3 g/day of NaCl) intakes and supplied by the university hospital kitchen. Subjects took away their prepared meals and ate them at home. They were not allowed to eat anything else, except for some collations defined in a precise list. To obtain the NSD and HSD diets, supplemental Na+ was provided by addition of 500 mg NaCl tablets to get the precise target intake. Salt tablets were prepared by the hospital pharmacy. Volunteers were instructed to maintain a constant lifestyle during the study with prohibition of additional meals, sweet and salty drinks, alcohol, and intensive physical activity. They were instructed to drink at least 1.5 L of water daily. Finally, consecutive 24-h urine samples were collected each day during each of the 7-day periods of different diet types. Urine samples were collected in 2.5 L bottles under paraffin oil with the addition of thymol to prevent bacterial proliferation. Participants were instructed to keep their urine in the fridge overnight and bring them back every day for laboratory analysis. Adequacy of 24-h urine collection was estimated with creatininuria expected to range from 0.17 to 0.22 μmol/kg.

Statistical Analysis

Continuous and categorical variables are expressed as median (25th to 75th percentile) and number (relative frequency), respectively. No outlier was specified. Data were considered to be missing completely at random and no imputation was made. Multivariate linear regression models were used with sodium urinary excretion as the dependent variable. Diet type, sample day, and an interaction term (diet type X sample day) were considered as independent variables. Interaction was considered significant if the P value for likelihood ratio test (LRT) comparing models with and without interaction term was $< .05$. Mixed effects were implemented in regression models to account for repeated measurements with patient's identification as the clustering variable, intercept as a random effect, and other covariates as fixed effects. In postestimation analysis, marginal effects were computed based on the fitted model.

Intraindividual variability on consecutive days was defined as mean values of minimum and maximum sodium urinary excretion for each diet type. Interindividual variability on consecutive days was defined as minimum and maximum values of mean sodium urinary excretion for each diet type. Adequacy between sodium intake and sodium urinary excretion was described with receiver operating characteristic (ROC) analysis and associated area under the curve (AUC) values.

A two-sided P value $< .05$ was considered significant. Statistical analyses were conducted using STATA version 15 (Stata-Corp, 4905 Lakeway Drive, College Station, Texas, 77845).

Table 1. Clinical Characteristics (N = 16)

Age (years)	22 (21-23)
Ethnicity	
Caucasian	15 (93.7%)
Asian	1 (6.3%)
BMI (kg/m^2)	22.7 (22.1-25.2)
Office Systolic BP (mmHg)	128.5 (124.0-134.0)
Office Diastolic BP (mmHg)	71.5 (66.0-79.0)
eGFR (ml/min/1.73 m^2)	120 (106-123)

BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure.

Results

In total, 16 participants were included in the present study. Complete data were available for all participants in HSD and LSD phases. As specified in the methods section, data were lacking for 4 participants in NSD phase due to protocol specifications. Clinical characteristics of included participants are summarized in Table 1.

Evolution of Sodium Excretion over Time

Sodium urinary excretion over time as per diet type is depicted in Figure 1A. On day 6, median sodium urinary excretion was 10 (8-18), 87 (69-121), and 258 (216-338) mmol/day for LSD, NSD, and HSD, respectively ($P < .001$). When considering days 1-6, diet type was significantly associated with sodium urinary excretion ($P < .001$). Sodium urinary excretion was however not in steady state as models with and without interaction term "diet type X sample day" were significantly different ($P < .001$ for LRT). The marginal effect of diet type on sodium urinary excretion as per sample day is depicted in Figure 1B, representing the change over time in sodium urinary excretion attributable to HSD and LSD, respectively, as compared to NSD. When considering days 4-6, diet type was significantly associated with sodium urinary excretion ($P < .001$). Sodium urinary excretion was in steady state as models with and without interaction term "diet type X sample day" were not significantly different ($P = .163$ for LRT).

Urinary volume over time as per diet type is depicted in Figure S1A. On day 6, median urinary volume was 1975 (1600-2310), 1870 (1475-2125), and 2470 (1800-2750) for LSD, NSD, and HSD, respectively ($P = .054$). The marginal effect of diet type on urinary volume as per sample day is depicted in Figure S1B, representing the change over time in urinary volume attributable to HSD and LSD, respectively, as compared to NSD.

Table 2. AUC for ROC Analyses Representing Diagnostic Performances of Sodium Urinary Excretion (mmol/day) to Detect HSD and LSD According to Different Sample Days

	Day 4	Day 5	Day 6
HSD	0.997 (0.991-1)	1 (1-1)	1 (1-1)
LSD	0.937 (0.862-1)	0.953 (0.891-1)	0.993 (0.978-1)

HSD, high-sodium diet; LSD, low-sodium diet.

Variability of Sodium Excretion at Steady State

Regarding intraindividual variability at steady state (days 4-6), mean minimum and maximum values of sodium urinary excretion were 12 and 24 mmol/day for LSD, 49 and 100 mmol/day for NSD, and 205 and 296 mmol/day for HSD. Regarding interindividual variability at steady state (days 4-6), minimum and maximum values of mean sodium urinary excretion were 8 and 34 mmol/day for LSD, 24 and 119 mmol/day for NSD, and 178 and 366 mmol/day for HSD. Minimum and maximum values of sodium urinary excretion on days 4-6 as per diet type for each participant are depicted in Figure 2.

Adequacy Between Sodium Intake and Sodium Excretion at Steady State

On day 6, ROC AUC for urinary sodium excretion to detect LSD was 0.993 (0.978-1.0) and a cut-point of 53 mmol/day was 96.4% sensitive and 100% specific to detect LSD. On day 6, ROC AUC for urinary sodium excretion to detect HSD was 1.0 (1.0-1.0) and a cut-point of 175 mmol/day was 100% sensitive and specific to detect HSD. ROC AUC for urinary sodium excretion to detect LSD and HSD were overall lower on day 4 and 5 (Table 2). Consequently, as compared to day 6, ROC AUC obtained when combining urinary sodium excretion on days 4, 5, and 6 was lower with 0.964 (0.934-0.994) for LSD and 0.998 (0.994-1.00) for HSD. Based on those results, sodium urinary excretion cut-points of 50 mmol/day and 170 mmol/day were selected to detect LSD and HSD, respectively. Classification of individual participants as per diet type based on those cut-points using sodium urinary excretion on day 6 is depicted in Figure 3. Using those cut-points, participants on LSD and HSD were all correctly classified, whereas one subject on NSD was misclassified as being on LSD.

Discussion

In this study, we analyzed the variability of sodium urinary excretion in young healthy males based on consecutive 24-h urine collections on 3 different diet types. We found that sodium balance was reached at 4 days of constant salt intake, at which point intravariability and intervariability in sodium urinary excretion was relatively low. Once steady state was achieved, a single 24-h urinary collection allowed precise categorization of low, normal, or high sodium intake.

Rigorously collected 24-h urine collection is considered to allow accurate estimation of daily sodium intake at the individual level. However, in the highly controlled environment of a simulated flight to mars, Lerchl et al showed that a steady state between sodium intake and excretion was achieved only after several weeks in 10 healthy male

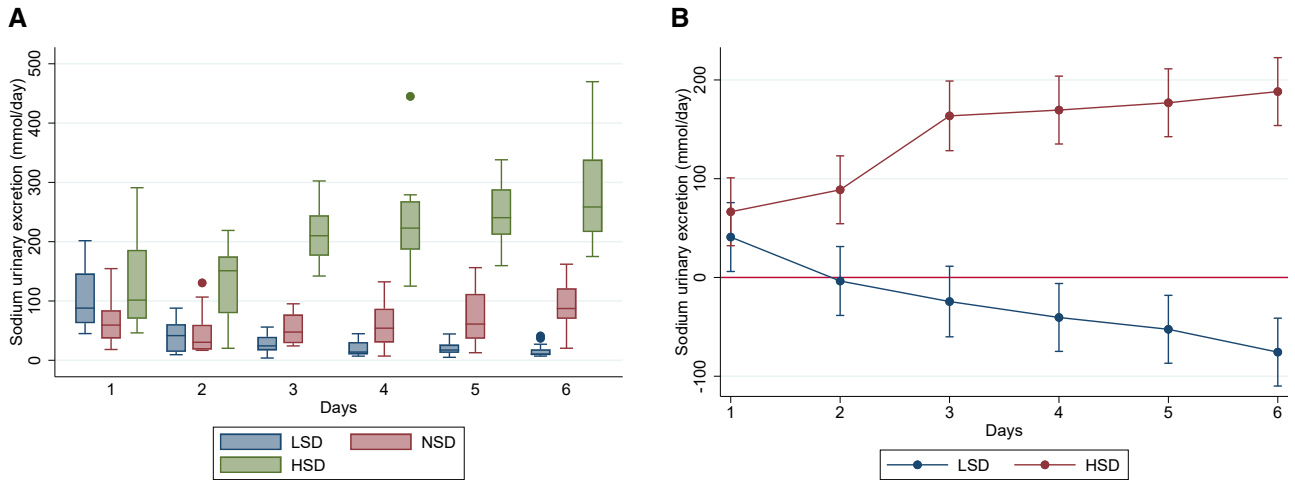

Figure 1. Sodium urinary excretion (mmol/day) according to study days. (A) Overall effect of diet type. (B) Marginal effect of HSD and LSD as compared to NSD. Abbreviations: HSD, high sodium diet; LSD, low sodium diet; NSD, normal sodium diet.

volunteers.[11] This finding could potentially be explained by the rhythmical variability in the secretion of aldosterone and the associated fluctuations in sodium accumulation and release.[3] Luft et al previously described similar variability in sodium urinary excretion in 43 individuals living under daily-life conditions.[15] Moreover, interindividual variation in tissue storage of sodium could explain a certain mismatch between salt intake and estimated sodium excretion.[16,17] Overall, those studies concluded that several nonconsecutive 24-h urine collections were necessary to improve accuracy of sodium intake estimation.[11,15] It has even been suggested that up to 10 repeated 24-h urine collections were required to accurately estimate sodium intake.[12,18]

However, repeated 24-h urine collections are notably difficult to obtain in a daily clinical setting where categorization of sodium intake at the individual level is desired. Daily sodium intake can be approximated by the Kawasaki formula based on a single-spot urine measurement.[19] Nevertheless, such formulas have been reported to perform relatively poorly in estimating 24-h sodium urinary excretion at the individual level in various populations.[20-23] Moreover, Kawasaki's formula integrates variables such as age, gender, height, and weight that are potentially associated to adverse prognosis, thus potentially confounding the actual clinical association between sodium intake and cardiovascular outcomes.[24] Consequently, while estimation of sodium intake based on a single 24-h urine collection could be inaccurate, the use of formulas on single-spot urine could be even less informative.

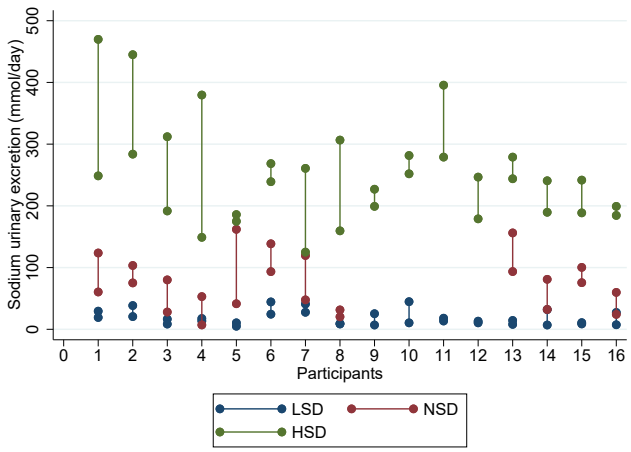

Figure 2. Minimum and maximum values of sodium urinary excretion (mmol/day) on days 4-6 according to diet type for each participant. Abbreviations: HSD, high sodium diet; LSD, low sodium diet; NSD, normal sodium diet.

In daily clinical practice, accurate estimation of sodium intake may not be of uttermost importance to guide management, provided of course that 24-h urine collection is complete and adequate. In most cases, the prescribing physician is rather interested in categorizing the patient's sodium intake into low, normal, or high. Therefore, the following categories of salt intake have been formalized by Campbell et al in 2015: recommended $<$ 5.0 g/day, high $>$ 5.0 g/day, very high $>$ 10 g/day, and extremely high $>$ 15 g/day.[25] In a Swiss nationwide survey conducted in 2010-2011, the estimated mean dietary salt intake using a 24-h urine collection was 10.0 g/day in healthy men aged 15-29 years.[26] Consequently, in the present study, categories of salt intake were adapted and simplified with 3 g/day, 6 g/day, and 15 g/day defining low, normal, and high sodium intake categories, respectively. When submitted to such intakes, healthy volunteers rapidly adapted their 24-h sodium urinary excretion to reach a clinically apparent steady state at day 4. Once in sodium balance, over days 4-6, intraindividual and interindividual variability in sodium excretion were both relatively low, especially under LSD and NSD diets. Specifically, overall sodium excretion

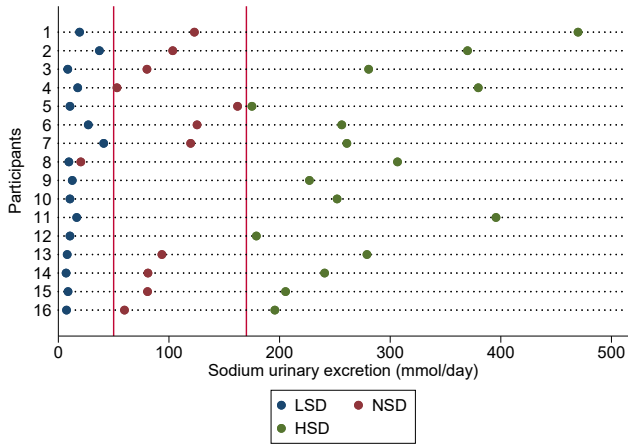

Figure 3. Classification of individual participants on day 6 according to diet type based on 50 and 170 mmol/day sodium urinary excretion cut-points.

fluctuated from 12 to 24 mmol/day and from 49 to 100 mmol/day under LSD and NSD, respectively. As expected, variability under HSD was substantially higher both intraindividually and interindividually. Consequently, under the conditions of the present study, cut-off points at 50 mmol/day and 170 mmol/day of sodium excretion were able to almost perfectly categorize participants into low, normal, or high salt eaters when urine was collected at steady state. Low and high salt intake categories showed no overlap. As for NSD category, however, one participant was wrongly classified as a low salt eater. Misclassification in this category is rather unexpected and nonadherence to study protocol cannot be excluded. Importantly, once in sodium balance, diagnostic performances to classify individual salt intake were not improved when 24-h urine collections were consecutively repeated on a daily basis over days 4-6. Thus, overall results suggest that a single 24-h urine collection is sufficient to accurately categorize patients into clinically meaningful categories of sodium intake, provided that diet is rather constant over the prior few days.

Interestingly, urine volume was not significantly associated with diet type in our study. Moreover, the influence of sodium intake on urine volume over time was nonsystematized and patients under LSD had higher urine volumes than those under NSD at time of maximum separation of sodium urinary excretion (day 6). The classical concept is that high sodium intake would trigger thirst and consequently an increase in fluid intake with excessive sodium eliminated through augmentation of urine volume. In support of this view, urine volume was more in participants with a salt intake $>$ 5 g/day in the Swiss Survey on Salt as compared to those with $<$ 5 g/day.[27] Conversely, subjects with a high urinary volume had increased sodium urinary excretion.[28] However, Bankir et al reported that urine volume was not necessarily higher when sodium intake increases even drastically, thereby challenging the traditional concept of proportional handling of sodium and water by the kidney.[29] Data from the Mars project tend to confirm this hypothesis as 24-h urine volume did not differ when subjects were on different sodium diets despite dose-dependent differences in sodium urinary excretion.[30] Reasons for this apparent discrepancy are not clear but differences between acute changes in sodium intake in short-term studies and the long-term adaptation to a high sodium intake in epidemiological surveys might contribute to those findings.

Of course our study has some limitations. First, only Caucasian normotensive healthy male were included, which limits generalizability of our results to other populations and gender. Second, a short-term protocol was used and our findings do not account for long-term fluctuations and potential rhythmicity in sodium intake and excretion. Third, there was no washout period between various diets. Although this could induce a carryover effect, it also allowed precise characterization of time-dependent stabilization in sodium urinary excretion. A major strength of our study is the rigorous protocol with consecutively repeated 24-h urinary collections on 3 different clear-cut sodium regimen with constant potassium and other nutrients. Variations in sodium urinary excretion and urine volume could thus be differentiated from potential effects of other urinary solutes in a free-living environment, contrasting with prior studies using nonstandardized diets or highly controlled settings.

Practical Application

Findings of the present study suggest that a steady state of sodium balance, where sodium intake is proportional to its excretion, is reached within a few days under a constant diet in the real-life setting. Once sodium balance is achieved, intravariability and intervariability of sodium urinary excretion is limited, with lowest variability under low salt conditions. Categorization of salt consumption into low (3 g/day), normal (6 g/day), or high (15 g/day) based on a single 24-h urine collection is nearly perfect. Based on these results, repeated nonconsecutive urine collection might prove unnecessary to estimate sodium intake in daily clinical practice, provided that diet is rather constant over time. More stringent but less convenient approach to estimation of salt intakes might be restricted to specific settings or research protocol.

CRediT authorship contribution statement

David A. Jaques: Formal analysis, Writing – original draft. **Belén Ponte:** Formal analysis, Writing – review & editing. **Valérie Olivier:** Writing – review & editing. **Sophie de Seigneux:** Writing – review & editing. **Eric Feraille:** Conceptualization, Methodology. **Michel Burnier:** Formal analysis, Writing – review & editing. **Antoinette**

Pechère-Bertschi: Conceptualization, Methodology, Writing – review & editing.

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Supplementary Data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1053/j.jrn.2022.12.010.

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