ORIGINAL RESEARCH

Twenty-four-Hour Urinary Potassium Excretion, But Not Sodium Excretion, Is Associated With All-Cause Mortality in a General Population

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***Background*—**Few studies have examined the relationship between accurate monitoring of sodium or potassium consumption and mortality. We aimed to investigate the association between 24-hour urinary sodium or potassium excretion and ≈30-year mortality in a Japanese population using 24-hour urine collection.

***Methods and Results*—**We enrolled a total of 1291 participants, aged 21 to 85 years, who underwent health checkups, including a blood test and 24-hour urine collection. They were followed up for 27.5±9.9 years by December 31, 2015, and the final follow-up rate was 95.8%. Cox proportional hazards regression analysis was used to assess the association between 24-hour urinary sodium or potassium excretion and all-cause mortality. At baseline, the mean 24-hour urinary sodium and potassium excretions were 5.80±2.28 g/d and 1.85±0.82 g/d, respectively. There were 631 deaths during the follow-up. The cumulative survival rate was significantly decreased in the lowest quartile compared with the other higher groups. In the Cox proportional hazard model after adjustment for age and sex, 24-hour urinary potassium excretion, but not sodium excretion, was inversely associated with all-cause mortality. We divided the 24-hour urinary potassium excretion levels into quartiles. After adjustment for confounding factors, the hazard ratio of all-cause mortality in the highest quartile of 24-hour urinary potassium excretion versus the lowest was 0.62 (95% confidence interval, 0.48–0.79; $P<0.001$).

***Conclusions*—**The 24-hour urinary potassium excretion, but not sodium excretion, was significantly associated with all-cause mortality in the general population. **(*J Am Heart Assoc*. 2018;7:e007369. DOI: 10.1161/JAHA.117.007369.)**

Key Words: epidemiology • mortality • potassium

Potassium is an essential nutrient. It is the most abundant cation in intracellular fluid, where it plays a key role in maintaining cell function, particularly in excitable cells, such as muscles and nerves.[1,2] In general, most ingested potassium is excreted via the urine: ≈90% of potassium consumed is lost in the urine, with the other 10% excreted in the stool, and a small amount is lost in sweat.[3] Potassium is intrinsically soluble and quickly dispersed in the luminal water of the upper digestive tract.[4] The World Health Organization recommends potassium intake of at least 90 mmol/d (3.5 g/d) for adults. However, most populations around the world consume less than the recommended levels of potassium.[5,6]

It has been reported that lower potassium consumption is associated with hypertension,[7] glucose intolerance,[8,9] and stroke[10] and that higher levels of the consumption could be protective against these conditions.[11] However, the evidence on the potentially beneficial effects of increased potassium on all-cause mortality and cardiovascular diseases is not fully understood, and most of the studies have been evaluated by morning urinary spot samples. On the contrary, the 24-hour urine collection was considered to be the most reliable method to evaluate potassium intake amounts.[12,13]

Therefore, the purpose of the present study was to investigate the relationship between 24-hour urinary sodium or potassium excretion and all-cause mortality in a Japanese community-based survey using 24-hour urine collection.

Methods

Availability of Data and Material

The data, analytic methods, and study materials were not made available to other researchers for purposes of reproducing the results or replicating the procedure.

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Clinical Perspective

What Is New?

- In this relatively large and long-term prospective cohort study, we investigated the association between 24-hour urinary sodium or potassium excretion using 24-hour urine collection and mortality in a community-dwelling Japanese population.
- Our study showed that the 24-hour urinary potassium excretion, but not sodium excretion, was significantly associated with all-cause mortality in the general population.

What Are the Clinical Implications?

- Clinical usefulness of 24-hour urine collection may expand to include 24-hour urinary potassium excretion, which was associated with all-cause mortality in this Japanese population.

Study Population

The baseline study was conducted in Tanushimaru town, a typical rural farming community located in southwestern Japan, in 1980. As previously reported, the demographic background of the subjects in this area is similar to that of the general Japanese population.[14] A total of 1291 participants (535 men and 756 women), aged 21 to 85 years, underwent health checkups, which included blood tests and 24-hour urine collection. Eventually, the follow-up was 27.5±9.9 (0.3–35.7) years. The Tanushimaru survey, representing a Japanese cohort of the Seven Countries Study,[15] has been conducted since 1958, and the periodic epidemiological studies have been performed in the same area.[16,17]

Data Collection

All participants were asked about smoking and drinking habits by a questionnaire. Alcohol intake and smoking were classified as current habitual use or not. Height and weight were measured, and body mass index was calculated from measurements of height and body weight. Blood pressure was measured twice, with participants in the supine position. The second blood pressure reading was taken after 5 deep breaths, and the fifth-phase diastolic pressure was recorded and used in the analysis. Blood samples obtained from the antecubital vein were centrifuged and frozen. Using these samples, we measured fasting plasma glucose, serum lipids (total cholesterol, high-density lipoprotein cholesterol, and triglycerides), uric acid, liver enzymes (alanine aminotransferase and aspartate aminotransferase), albumin, total protein, and creatinine. Estimated glomerular filtration rate was calculated using the Modification of Diet in Renal Disease (MDRD) study equation, modified with a Japanese coefficient[18]: estimated glomerular filtration rate (mL/min per 1.73 m^2)=194×age$^{-0.287}$×serum creatinine$^{-1.094}$ (if female×0.739). We collected 24-hour urine samples by using Aliquot Cup, a simple tool for collecting 24-hour urine instead of using a large container. Causes of death were determined on the basis of a review of obituaries, medical records, death certificates, hospital charts, and interviews with primary care physicians, families of the deceased, and other witnesses. The information was coded independently, according to the rules of the Seven Countries Study[19] and the World Health Organization's *International Statistical Classification of Diseases and Related Health Problems, 10th Revision*.[20]

This study was approved by the Tanushimaru branch of the Japan Medical Association and by the local mayor, as well as by the ethics committee of Kurume University School of Medicine. All of the participants gave informed consent.

Statistical Analysis

Results are presented as mean±SD. Because of skewed distributions, natural logarithmic transformations were performed for triglycerides. This variable was represented in the original scale after analysis using the logarithmic (natural) transformed values. Mean 24-hour urinary potassium excretion was classified into quartiles, as follows: 0.09 to 1.28, 1.29 to 1.75, 1.76 to 2.30, and 2.31 to 7.51 g/d. Analysis of variance was used to compare the means of variables, stratified by quartile of 24-hour urinary potassium excretions. The χ^2 test was used to test differences between groups in categorical variables. Survival curves of death from all causes for each 24-hour urinary potassium excretion were estimated by the Kaplan-Meier method and compared using the log-rank test. We also added the number at risk and significant time points. To obtain hazard ratios (HRs) for all-cause mortality, we performed Cox proportional hazards regression analysis after adjusting for confounding factors by quartiles of 24-hour urinary potassium excretion. Statistical significance was defined as $P<0.05$. All statistical analyses were performed using the SAS system (Release 9.4; SAS Institute, Cary, NC).

Results

Study Participants and Outcomes

A total of 1291 subjects were followed up for 27.5±9.9 years by December 31, 2015. There were 631 deaths: 153 (27.5%) from cancer, 142 (25.5%) from cardiovascular diseases, 89 (15.9%) from infection, and 173 (31.1%) from other causes. A total of 55 subjects (4.2%) were unavailable for follow-up; 25 of these subjects moved, and the details were unknown in the others. The final follow-up rate was 95.8% in this study.

Baseline Characteristics

Characteristics of participants at baseline stratified by 24-hour potassium excretion (g/d) quartiles were shown in Table 1. The 24-hour urinary potassium excretion was significantly and positively associated with weight, body mass index, albumin, urine, and 24-hour urinary sodium excretion and inversely associated with age, pulse pressure, and the ratio of sodium/potassium excretion.

Kaplan-Meier Curve

The Figure shows the cumulative survival curves for all-cause death stratified by 24-hour urinary potassium excretion quartile in univariate analysis. The HRs by 24-hour urinary potassium excretion quartiles were 0.64 (95% confidence interval [CI], 0.51–0.80) for quartile 2, 0.68 (95% CI, 0.54–0.85) for quartile 3, and 0.54 (95% CI, 0.43–0.68) for quartile 4. The cumulative survival rate was significantly decreased in the lowest quartile (quartile 1) compared with the other higher groups (quartile 2–quartile 4).

Cox Proportional Hazards Regression Analysis of All-Cause Death

In the Cox proportional hazards regression analysis of all-cause death after adjustment for age and sex, systolic and diastolic blood pressures, pulse pressure, fasting plasma glucose, aspartate aminotransferase, and alanine

Table 1. Characteristics of Participants at Baseline Stratified by 24-Hour Potassium Excretion Quartiles

Variables	Quartile 1 (0.09–1.28 g/d)	Quartile 2 (1.29–1.75 g/d)	Quartile 3 (1.76–2.30 g/d)	Quartile 4 (2.31–7.51 g/d)	*P* Value for Trend
Total n	321	319	325	324	. . .
Urinary potassium excretion, g/24 h	0.95±0.26	1.53±0.13	2.01±0.16	2.91±0.72	<0.001
Age, y	53.0±14.7	50.7±14.7	51.1±13.5	49.0±13.8	0.004
Male sex, n (%)	151 (47.0)	123 (38.6)	130 (40.0)	131 (40.4)	0.13
Weight, kg	52.7±9.0	53.7±9.2	54.8±9.2	57.3±9.4	<0.001
Body mass index, kg/m^2	21.9±2.9	22.2±2.9	22.5±2.9	23.2±3.2	<0.001
Systolic BP, mm Hg	129.4±20.8	126.5±21.5	127.1±19.6	126.6±19.4	0.22
Diastolic BP, mm Hg	74.7±11.7	73.5±11.9	74.8±11.7	74.5±12.2	0.45
Pulse pressure, mm Hg	55.7±15.5	49.4±12.4	53.9±13.2	53.1±15.7	<0.001
Smoking (yes), %	33.0	26.7	25.9	24.8	0.085
Alcohol (yes), %	33.3	28.5	29.6	30.3	0.59
Total protein, g/dL	7.3±0.5	7.3±0.5	7.3±0.5	7.3±0.5	0.57
Albumin, g/dL	4.6±0.4	4.7±0.4	4.7±0.4	4.8±0.4	<0.001
Total cholesterol, mg/dL	184.9±39.7	183.3±35.3	187.4±35.2	186.0±35.2	0.54
HDL cholesterol, mg/dL	47.5±12.1	47.8±11.4	48.1±11.8	48.4±11.7	0.80
Triglycerides*, median (range), mg/dL	108.6 (38–441)	105.5 (38–515)	104.3 (27–581)	106.1 (21–511)	0.73
FPG, mg/dL	105.9±24.2	108.2±27.4	109.7±30.0	112.1±33.4	0.069
AST, IU/L	20.9±12.0	19.4±8.2	19.7±10.8	19.7±.9.7	0.30
ALT, IU/L	13.7±10.6	13.0±8.9	13.6±11.5	14.1±9.4	0.56
Creatinine, mg/dL	1.0±0.21	1.0±0.24	1.0±0.21	1.1±0.28	0.11
eGFR, mL/min per 1.73 m^2	55.4±12.4	54.1±12.8	53.3±12.3	53.2±13.0	0.11
Uric acid, mg/dL	4.2±1.2	4.2±1.3	4.3±1.3	4.5±2.9	0.084
Urine, mL/24 h	1135.2±462.0	1302.8±419.9	1421.8±440.9	1655.9±512.1	<0.001
Urinary sodium excretion, g/24 h	4.28±1.71	5.39±1.55	6.14±1.91	7.37±2.59	<0.001
Sodium/potassium excretion	7.65±2.56	6.01±1.72	5.21±1.62	4.41±1.44	<0.001

Data are mean±SD, unless otherwise indicated. ALT indicates alanine aminotransferase; AST, aspartate aminotransferase; BP, blood pressure; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; and HDL, high-density lipoprotein.
*Logarithm-transformed values were used in analyses.

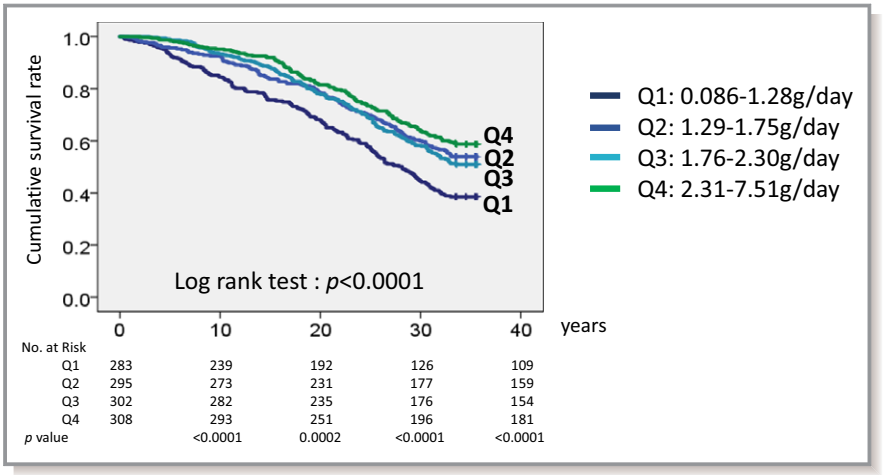

Figure. Kaplan-Meier survival curves for all-cause death stratified by the quartiles (Qs) of 24-hour urinary potassium excretion.

aminotransferase were significantly and positively associated with all-cause death, whereas 24-hour urinary potassium excretion was inversely associated with all-cause death (HR, 0.87; 95% CI, 0.78–0.97; *P*=0.01). However, 24-hour urinary sodium excretion was not associated with all-cause death (HR, 0.98; 95% CI, 0.94–1.02; *P*=0.29) (Table 2). The ratio of 24-hour urinary sodium and potassium excretion was not associated with all-cause mortality in the univariate Cox proportional hazards regression analysis (data are not shown).

HRs for All-Cause Death Stratified by 24-Hour Urinary Potassium Excretion Quartiles

We categorized the baseline 24-hour urinary potassium excretion levels into quartiles and calculated the HRs of all-cause death, using the lowest quartile as the reference (Table 3). The highest quartile of 24-hour urinary potassium excretion (quartile 4, ≥2.31 g/d) showed the lowest cumulative death rate. In the final model, using the significant factors shown in Table 2, a significant HR of 0.62 (95% CI, 0.48–0.79; *P*<0.001) for all-cause death was observed in the highest versus the lowest quartile of 24-hour urinary potassium excretion.

Discussion

In this relatively large and long-term prospective cohort study, we have investigated the association between 24-hour urinary sodium or potassium excretion using 24-hour urine collection and mortality in a community-dwelling Japanese population. We found that the cumulative survival rate was significantly decreased in the lowest quartile (quartile 1) compared with the other higher groups (quartile 2–quartile 4). After adjustment for age and sex, the Cox proportional hazard regression analysis revealed that 24-hour urinary potassium excretion was inversely associated with all-cause mortality.

Table 2. Multivariate Cox Proportional Hazards Regression Analysis of All-Cause Death Adjusted for Age and Sex

Variables	HR	95% CI	*P* Value
Weight	1.00	0.99–1.01	0.36
Body mass index	0.98	0.96–1.01	0.19
Systolic BP	1.01	1.01–1.01	<0.001
Diastolic BP	1.02	1.01–1.03	<0.001
Pulse pressure	1.01	1.00–1.01	0.002
Smoking (0, no; 1, yes)	1.23	0.98–1.52	0.07
Alcohol (0, no; 1, yes)	0.86	0.71–1.05	0.15
Total protein	1.03	0.86–1.22	0.78
Albumin	0.86	0.68–1.09	0.19
Total cholesterol	1.00	0.99–1.00	0.52
HDL cholesterol	1.00	0.99–1.01	0.47
Triglycerides*	1.00	0.99–1.00	0.81
FPG	1.01	1.00–1.01	<0.001
AST	1.02	1.01–1.02	<0.001
ALT	1.01	1.01–1.02	<0.001
Creatinine	1.00	0.67–1.49	1.00
eGFR	1.00	0.99–1.01	0.81
Uric acid	0.99	0.95–1.02	0.36
24-h urinary sodium excretion	0.98	0.94–1.02	0.29
24-h urinary potassium excretion	0.87	0.78–0.97	0.01

ALT indicates alanine aminotransferase; AST, aspartate aminotransferase; BP, blood pressure; CI, confidence interval; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HDL, high-density lipoprotein; and HR, hazard ratio.
*Logarithm-transformed values were used in analyses.

Table 3. HRs and 95% CIs of All-Cause Death Stratified by 24-Hour Potassium Excretion Quartiles at Baseline

Models	Quartiles of 24-h Urine Potassium Excretion (g/d)			
	Quartile 1 (0.09–1.28)	Quartile 2 (1.29–1.75)	Quartile 3 (1.76–2.30)	Quartile 4 (2.31–7.51)
Total no.	321	319	325	324
No. of deaths	190	147	160	134
Model 1	Reference	0.64 (0.51–0.80)*	0.68 (0.54–0.85)*	0.54 (0.43–0.68)*
Model 2	Reference	0.77 (0.61–0.97)†	0.81 (0.65–1.02)	0.72 (0.57–0.91)‡
Model 3	Reference	0.72 (0.56–0.92)‡	0.74 (0.59–0.94)†	0.62 (0.48–0.79)*

Model 1: not adjusted. Model 2: adjusted for age and sex. Model 3: adjusted for age, sex, systolic blood pressure, aspartate aminotransferase, and fasting plasma glucose. CI indicates confidence interval; and HR, hazard ratio.
*$P<0.001$.
†$P<0.05$.
‡$P<0.01$.

After further adjustment for confounding factors, a significant HR of 0.62 (95% CI, 0.48–0.79; $P<0.001$) for all-cause death was observed in the highest versus the lowest quartile of 24-hour urinary potassium excretion.

Potassium Excretion and All-Cause Mortality

Only a few studies have ever examined the relationship between urinary potassium excretion and all-cause mortality for long-term follow-ups.

In the PURE (Prospective Urban Rural Epidemiology) study, compared with <1.50 g/d of estimated potassium excretion, higher potassium excretion was associated with a lower risk of death and cardiovascular events.[21] In other studies, higher estimated potassium excretion was associated with a reduced risk of stroke.[22–24] The systematic reviews with meta-analyses suggested that increased potassium intake lowers blood pressure in adults with and without hypertension,[25–28] suggesting the increased potassium intake may reduce the risk of death through the effects of blood pressure lowering.

Next, the relationship between potassium intake and diabetes mellitus was further examined in prospective cohort studies.[8,9] Potassium's role in the control of blood glucose is grounded in its function at a cellular level, where potassium-induced cell depolarization causes insulin secretion from pancreatic β cells.[29]

On the basis of these findings, potassium has been identified as a shortfall nutrient by the Dietary Guidelines for Americans 2010 Advisory Committee.[28] Data from many countries indicated that the average potassium consumption is 1.7 to 3.7 g/d.[5] The present study indicated that the mean 24-hour urinary potassium excretion was 1.85±0.82 g/d in Tanushimaru in 1980. Currently, the potassium consumption has been reported as 2.30±0.92 g/d (mean±SD) in Japan in 2015.[30] However, the World Health Organization recommended a potassium consumption of at least 90 mmol/d (3.5 g/d) for adults.

Potassium is commonly found in a variety of unrefined foods, especially fruits and vegetables. However, the amount of potassium can be reduced in processed food,[31] which may reflect the low intake of potassium in modern society. The successful implementation of these recommendations would have an important public health impact through the improvement of morbidity, mortality, and quality of life for millions of people, associated with substantial reductions in healthcare costs.[32,33]

Sodium Excretion and All-Cause Mortality

Our study indicated that the mean 24-hour urinary sodium excretion was 5.80±2.28 g/d, and it was equivalent to 13.6±5.3 g/d salt excretion. In 1980, the average salt intake was 13.0 g/d in Japan.[34] Although it has markedly decreased over the years, it still remains high. The mean level of worldwide sodium consumption was 3.95 g/d, indicating that 99.2% of the adult population in the world exceeds the World Health Organization recommendation of 2.0 g/d.[35]

Urinary sodium excretion was associated with the risk of hypertension.[36] In this situation, there was a direct linear association between average sodium excretion and mortality.[37] However, the association between sodium excretion and all-cause mortality is still controversial.

In the PURE study, an estimated sodium excretion between 3 and 6 g/d was associated with a lower risk of death and cardiovascular events than either a higher or lower estimated level of the excretion.[21] In another study, sodium excretion of >7 g/d compared with 4 to 5.99 g/d was associated with an increased risk of all cardiovascular events, and a sodium excretion of <3 g/d was associated with increased risk of cardiovascular mortality and hospitalization for congestive heart failure.[22] On the contrary, it has been also reported that lower sodium excretion was associated with higher cardiovascular mortality[38] and that lower 24-hour urinary sodium excretion was paradoxically associated with increased

all-cause and cardiovascular mortality in patients with type 2 diabetes mellitus.[39] Although the precise mechanisms in this issue remain unknown, this might be because the reduced sodium consumption is associated with the activation of metabolic and neurohormonal pathways, including the sympathetic nervous system and the renin-angiotensin-aldosterone system.[40] Reduced sodium consumption is also associated with the increase in total and low-density lipoprotein cholesterol[40] or the reduced peripheral insulin sensitivity,[41] which should be clarified in the near future.

The Ratio of Sodium/Potassium Excretion and All-Cause Mortality

The Japanese diet is characterized with high sodium and low potassium intakes.[42] The combination of dietary potassium and sodium should be beneficial for blood pressure lowering.[43] Lower potassium/sodium intake ratios strongly associated with the increased all-cause mortality.[44]

In our cohort, the ratio of 24-hour urinary sodium and potassium excretion was 5.8±2.2, which was much higher than the ratio in recent reports.[44] However, the current study showed no significant association between 24-hour urinary ratio of sodium/potassium excretion and all-cause mortality.

Limitations

The present study has several limitations. First, we were not able to exclude subjects with hypertension. Urinary excretion is influenced by many factors, particularly antihypertensive medications (eg, diuretics, angiotensin-converting enzyme inhibitors, and angiotensin II receptor blockers). We have no information about medication, but angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers were not available in the market at baseline. Second, we measured urinary electrolytes only at baseline; thus, we cannot negate the possibility of misclassification of the participants' levels during the follow-up. Third, the total number of deaths from cancer or cardiovascular death was small and limited the statistical power for these outcomes, which is causatively more relevant. Finally, because of the lack of dietary data, we were unable to compare 24-hour urinary sodium or potassium excretion with dietary intake.

Strengths

One of the major strengths of the study is the use of 24-hour urine collections rather than spot or overnight timed urine samples. The 24-hour urine collection is the most reliable method to evaluate potassium excretion amounts.[12,13] Other strengths are the relatively large number of enrolled participants, outcomes, and long-term follow-up of almost 30 years, with a high follow-up rate.

Perspectives

We have investigated the effect of increased potassium excretion on cause-specific mortality in a Japanese community-based survey using 24-hour urine collection. Clinical usefulness of 24-hour urine collection may expand the values as the predictor of mortality in the population-based survey.

Conclusion

In conclusion, this is the first report demonstrating that 24-hour urinary potassium excretion, but not sodium excretion, was significantly associated with all-cause mortality in the general Japanese population.

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Disclosures

None.

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