Low Dietary Sodium Intake Increases the Death Risk in Peritoneal Dialysis

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Background and objectives: To explore the correlation between dietary sodium intake and cardiovascular and overall mortality, and then determine whether this correlation can be explained by protein and energy intake paralleled with sodium intake in dialysis patients.

Design, setting, participants, & measurements: This single-center retrospective cohort study enrolled 305 incident patients who started peritoneal dialysis in our unit from July 2002 to February 2007. All patients were followed until death or until being censored in February 2008. Demographic data were collected at baseline. Biochemical, dietary, and nutrition data were examined at baseline and thereafter at regular intervals to calculate the average values throughout the study.

Results: Participants with the highest average sodium intake were more likely to be younger, male, and overweight. Patients in the high tertile of average sodium intake had higher albumin, prealbumin, and lean body mass levels, and more nutrient intakes paralleling with sodium intake. Low average sodium intake independently predicted the increased risk for overall and cardiovascular death after adjusting for recognized confounders. Further adjustment for dietary protein, energy, and other nutrient intakes individually had minimal impact on the association between average sodium intake and overall death, with hazard ratios varying between 0.35 and 0.44, and cardiovascular death, with hazard ratios varying between 0.06 and 0.11.

Conclusions: This study revealed that low dietary sodium intake independently predicts the high overall and cardiovascular mortality in dialysis patients. This correlation could not be entirely explained by deficient protein and energy intake.

Cardiovascular disease (CVD) has been extensively documented in patients with end-stage renal disease, including those undergoing peritoneal dialysis (PD) and hemodialysis (1,2), and CVD accounts for approximately 50% of the annual mortality in dialysis patients (3). Among the numerous risk factors for CVD, sodium has been a controversial one over the past half-century in the general population and among chronic kidney disease (CKD) patients (4–6). These controversies are partly due to an inconsistent relationship between sodium intake, estimated by either dietary intake or urinary removal, and overall and CVD mortality across the healthy, obese, and hypertensive populations (4,7–12). To some extent, the heterogeneity is due to the fact that sodium intake is parallel with protein and energy or other nutrient intakes. Accordingly, the correlation of sodium intake and mortality probably is confounded by the intake of these nutrients. For example, when sodium intake is positively correlated with energy intake (7,9), it predicts improved survival and vice versa (11,12,15). Deficient protein and energy intake and malnutrition are present in approximately 20% to 50% of the maintenance dialysis patients (16,17). Therefore, we hypothesized that dietary sodium intake may be negatively correlated with overall and CVD mortality because low sodium intake could be accompanied by deficient protein and energy intake in this population.

Therefore, we aim to explore the correlation of dietary sodium intake and overall and CVD mortality in dialysis patients, and to further determine whether this correlation can be explained by protein and energy intake through this retrospective cohort study. To our knowledge, this is the first study to address this issue in the dialysis population.

Materials and Methods

Subjects and Follow-Up

Our retrospective cohort study enrolled a total of 305 incident patients who started PD and lived longer than 6 months in our unit from

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July 2002 to February 2007. All patients could visit a physician at least once every 3 months. Demographic and clinical data collected within the week preceding PD catheter implantation included age, gender, body mass index (BMI), etiology of end-stage renal disease, diabetes (DM), and CVD (18). BMI higher than 23 kg/m² was defined as overweight according to the Asian standard (19). All patients were followed until death, transfer to hemodialysis, renal transplantation, or February 2008. Both CVD death and overall death were recorded. All patients were delivered lactate-buffered glucose PD solutions and had the twinbag connection system (Baxter Healthcare, Guangzhou, China). The study was approved by the Medical Ethical Committee of Peking University. Written informed consent was obtained from each patient.

Dietary Variables
A daily intake of no more than 2.3 g per day of sodium, at least 0.8 g/kg protein, and 25 kcal/kg energy have been recommended in terms of our previous data and guidelines from the European Best Practice Guidelines and International Society of Renal Nutrition & Metabolism at the initiation of PD treatment (18,20,21). During the follow-up, all patients completed 3-day dietary records before they visited the diettian. A dedicated dietitian checked the diary using food models. The dietary records would be invalid if they were recorded in less than 3 days or did not get checked successfully by the dietitian. Daily sodium, protein, energy, carbohydrate, fat, potassium, and fiber were calculated by using a computer software program (PD information Management System, Peritoneal Dialysis Center, Peking University, Beijing, China). The total caloric intakes include intake from dietary and dialysate sources. Both daily total protein and daily energy intakes were normalized for standard body weight. Sodium intake during the first 3 months was represented as the baseline sodium intake. All of the measurements during the study were averaged.

Several steps were taken to ensure the reliability and stability of dietary sodium intake assessment: (1) each patient was asked to measure the amount of added salt by using a 1-g or 2-g salt spoon and soy sauce using a 5-ml little cup. (2) Patients avoided processed foods and eating out because the amount of hidden salt would be unknown. (3) Patients were taught to check the amount of salt labeled on snack or canned foods. (4) Patients ate foods separately from family members to ascertain how much salt they consumed. (5) Dietitian and primary nurses repeatedly highlighted the importance of recording dietary salt intake.

Measurement of Blood Pressure and Antihypertensive Medications
Systolic and diastolic BPs (SBP and DBP) were measured according to the standard method. Mean arterial pressure (MAP) was calculated. The dose of antihypertensive drugs was quantified by the defined daily dose (DDD) developed by the World Health Organization (22). The dose of antihypertensive drugs was quantified by the defined daily dose (DDD) developed by the World Health Organization (22). The dose of antihypertensive drugs was quantified by the defined daily dose (DDD) developed by the World Health Organization (22). The dose of antihypertensive drugs was quantified by the defined daily dose (DDD) developed by the World Health Organization (22). The dose of antihypertensive drugs was quantified by the defined daily dose (DDD) developed by the World Health Organization (22). The dose of antihypertensive drugs was quantified by the defined daily dose (DDD) developed by the World Health Organization (22).

Biochemical, Dialysis Adequacy, and Nutrition Variables
Biochemical indices, including hemoglobin (Hb), serum albumin (Alb), prealbumin (PA), blood urea nitrogen (BUN), serum creatinine (Scr), calcium (Ca), phosphate (P), bicarbonate, and LDL were examined using an automatic Hitachi chemistry analyzer at regular intervals. The product of Ca and P was calculated. Estimated GFR was calculated by a Chinese equation before PD catheterization (23). Biochemical indices during the first 3 months were represented as baseline values, and all of the measurements throughout the study were averaged.

Serum high-sensitive C-reactive protein (CRP) measured by immune rate nephelometric analysis during the first 3 months was represented as a baseline value. Dialysis adequacy was calculated by collecting dialysate and urine over the course of 24 hours to measure fluid and solute clearances. Weekly total, peritoneal, and renal Kt/V urea; weekly total, peritoneal, and renal creatinine clearance; and residual renal function were calculated using standard methods. Lean body mass (LBM) by creatinine kinetics method was used to reflect muscle protein stores (24,25) and also normalized by the square of height. Total sodium removal was the sum of urinary and dialysate sodium removal (26). The total Kt/V (Tkt/V), total creatinine clearance (Tccr), total sodium removal, and LBM during the first 6 months were represented as baseline values. All of the measurements throughout the study were averaged.

Statistical Analyses
Statistical analyses were performed using the SPSS software package (version 13.0; SPSS, Chicago, IL). Variables are expressed in a standard way. Average sodium intake was categorized by tertile based on the distribution among the study population. One-way ANOVA, Kruskal-Wallis, or the χ² test was used to compare the differences of variables between groups. Partial correlation analysis was used to analyze the correlation of sodium intake to nutritional and dietary variables adjusted for age and gender. Recognized confounders combined with the baseline and average sodium intakes, respectively, were evaluated by the Cox proportional regression model to determine the risk for CVD or overall mortality. When the baseline sodium intake was examined, the covariates included age, gender, BMI, the history of DM or CVD, baseline Tkt/V, Tccr, MAP, Alb, Hb, Ca × P, LDL, and CRP; when the average sodium intake was examined, the covariates included age, gender, BMI, the history of DM or CVD, average Tkt/V, Tccr, MAP, Alb, Hb, Ca × P, and LDL. Next, to examine the predicting role of average sodium intake in CVD and overall mortality, we included each dietary variable individually as a continuous variable in separate multivariate models to examine their impact on the hazard ratio (HR) estimate for the average sodium intake. Among these dietary variables, dietary energy intake instead of total energy intake was used. The final models contained the variables that remained in the model with a significance level of 0.05. The HRs and their 95% confidence intervals for mortality were shown in the final results. We accepted P < 0.05 as the indicator of statistical significance.

Results
Subject Demographics and Follow-up
We followed 305 incident PD patients (129 men, 176 women), mean age of 59.4 ± 14.2 years (range: 19–94 years), for 31.4 ± 13.7 months (range: 8–64 months); 42.3% (129 of 305) were men, 40.3% (123 of 305) had diabetes, and CVD was present in 61.6% (188 of 305).

At the end of study, 187 patients were still being maintained on PD, 74 had died, 16 had transferred to hemodialysis, 24 had undergone renal transplantation, and four had transferred to other hospitals. The causes of death were cardiovascular diseases in 32 patients, systemic infection in 32, severe malnutrition in four, and unknown causes or multiple organ failure in six. A total of 43.2% (32 of 74) of all deaths were due to cardiovascular causes.

Average Total Sodium Intake and Baseline Characteristics
The average sodium intake was 1.82 g/d (0.76–5.53 g/d) in our cohort. The baseline characteristics of the study population
tertiled by the average sodium intake are given in Table 1. Participants with the highest intake of sodium were more likely to be younger, male, overweight, and have lower CRP levels \((P < 0.05)\). The prevalence of DM and CVD, and baseline estimated GFR, Hb, and Alb levels were not significantly different between groups. The average sodium intake in the high tertile group tended to have higher sodium removal \((P < 0.001)\) and slightly higher DBP \((P = 0.07)\). No significant differences in average SBP, MAP, and DDD levels were observed between groups (Table 2).

**Average Sodium Intake, Dietary, and Nutritional Variables**

The comparison of nutritional and dietary variables showed that patients in the high tertile of average sodium intake have significantly higher Alb, PA, LBM, and LBM/height (27) levels \((P < 0.001 \sim 0.05)\), as well as higher protein, energy, fat, carbohydrate, fiber, and potassium intake compared with patients in low tertile or both low and middle tertile groups (Table 3). Partial correlation analysis revealed that average sodium intake was significantly correlated with LBM, dietary protein, energy, fat, carbohydrate, potassium, and fiber intake, with \(r\) values of 0.13 \((P = 0.02)\), 0.3 \((P < 0.001)\), 0.29 \((P < 0.001)\), 0.31 \((P < 0.001)\), 0.21 \((P < 0.001)\), and 0.19 \((P = 0.001)\) respectively. There was no correlation between average sodium intake and Hb, Alb, and PA levels.

**Predictive Value of Sodium Intake for Overall and CVD Mortality**

The relationship between baseline or average sodium intake and mortality was analyzed respectively. The baseline low sodium intake was significantly associated with overall mortality after adjusting for age, gender, BMI, DM and CVD history, MAP, Hb, Alb, Ca \(\times P\), LDL, Kt/V, Tccr, and CRP, with an HR of 0.45 \((0.23 \sim 0.90)\) \((P = 0.02)\), and showed a trend to be correlated with CVD mortality, with an HR of 0.33 \((0.10 \sim 1.10)\) \((P = 0.07)\) (Table 4). Similarly, average sodium intake was correlated with overall mortality, with an HR of 0.44 \((0.20 \sim 0.95)\) \((P = 0.04)\), and CVD mortality, with an HR of 0.11 \((0.03 \sim 0.48)\) \((P = 0.003)\), after adjusting for above covariates besides CRP (Table 5).

**Table 1. Baseline demographic and clinical characteristics of study subjects according to tertile of average sodium intake**

<table>
<thead>
<tr>
<th>Basic Characteristic</th>
<th>Tertile of Average Sodium Intake</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low</td>
<td>Middle</td>
</tr>
<tr>
<td>Follow-up, mo</td>
<td>30.59 (\pm) 11.31</td>
<td>32.88 (\pm) 13.82</td>
</tr>
<tr>
<td>Age, yr</td>
<td>63.08 (\pm) 12.8^a</td>
<td>61.07 (\pm) 13.02^a</td>
</tr>
<tr>
<td>Male gender, % ((n))</td>
<td>20.8 ((21/101)^a)</td>
<td>42.2 ((43/102)^c)</td>
</tr>
<tr>
<td>BMI, kg/m^2</td>
<td>22.63 (\pm) 3.59^ed</td>
<td>23.89 (\pm) 3.71</td>
</tr>
<tr>
<td>Diabetes, % ((n))</td>
<td>33.7 ((34/101))</td>
<td>46.1 ((47/102))</td>
</tr>
<tr>
<td>Cardiovascular disease, % ((n))</td>
<td>64.4 ((65/101))</td>
<td>61.8 ((63/102))</td>
</tr>
<tr>
<td>Urine volume, ml</td>
<td>808.97 (\pm) 425.80^a</td>
<td>822.31 (\pm) 435.93^c</td>
</tr>
<tr>
<td>eGFR, ml/min per 1.73 m^2</td>
<td>6.64 ((1.8 \sim 21.4))</td>
<td>6.97 ((2.4 \sim 21.7))</td>
</tr>
<tr>
<td>Hb, g/L</td>
<td>100.70 (\pm) 16.82</td>
<td>102.75 (\pm) 16.33</td>
</tr>
<tr>
<td>Alb, g/L</td>
<td>35.82 (\pm) 4.86</td>
<td>35.32 (\pm) 4.32</td>
</tr>
<tr>
<td>CRP, mg/L</td>
<td>4.11 ((0.17 \sim 292))</td>
<td>2.31 ((0.17 \sim 90.7))</td>
</tr>
<tr>
<td>Bicarbonate, mmol/L</td>
<td>24.04 (\pm) 2.51</td>
<td>24.36 (\pm) 2.32</td>
</tr>
</tbody>
</table>

*Values are mean \(\pm\) SEM, median (minimum to maximum), or absolute numbers with percentages.

^a^ \(P < 0.001\) compared to high-tertile group.

^b^ \(P < 0.001\) compared between three groups.

^c^ \(P < 0.05\) compared to high-tertile group.

^d^ \(P < 0.001\) compared to middle-tertile group.

^e^ \(P < 0.05\) compared between three groups.
These data further support our hypothesis that sodium intake per se is closely correlated with protein and energy intake, and the correlation of sodium intake and mortality is confounded by these nutrient intakes. Indeed, low sodium intake also is linked to lower nutrient intakes in the general population. In the National Health and Nutrition Examination Survey (NHANES) I study, subjects in the lowest quartile of sodium intake had the lowest calorie intake (7). In the NHANES II study, subjects with a lower sodium intake also had lower dietary calories and potassium levels (9). Both studies showed the inverse correlations between sodium intake and cardiovascular outcome similar to ours. By contrast, a statistically significant direct association of sodium with CVD and overall mortality was observed in a Finnish community sample (12) and an inverse correlation of sodium intake and mortality is linked to lower nutrient intakes in the general population.
the overweight subgroup of the NHANES I study (11), with stroke in a community sample in Japan (15). Among these three studies, subjects with the lowest sodium intake or sodium-to-energy ratio had relatively high BMI (12), adequate protein, and/or energy intake (11,15).

Our finding provided another example of “reversal epidemiologic” phenomenon, which has already existed in the relationship between a couple of CVD risk factors and outcome in dialysis population (28). In fact, a “U”- or “J”-shaped curve with a horizontal axis of sodium intake and a vertical axis of overall or cardiovascular mortality can well describe their relationship in the general population (29). In our study, low and middle tertiles of average sodium intake (that is, 1.41 g/d and 1.8 g/d) might fall in the down slope of this curve. Therefore, in the case of dialysis patients, harm may outweigh benefit if low-sodium diet came from anorexia and deficient nutrient intakes. We need to cautiously recommend sodium restriction if patients on dialysis treatment already suffer from deficient nutritional intake and protein-energy malnutrition.

Of interest, low sodium intake is significantly related to overall and CVD mortality despite adjusting for protein, energy, and other nutrient intakes in our cohort. This result indicates that the other potential mechanisms linking low dietary sodium to poor outcome are unknown. Sodium restriction did generate undesirable effects in previous studies, including increased insulin resistance (30), activation of the renin-angiotensin system (23), and increased sympathetic nerve activity (32). On the other hand, the positive correlation of sodium intake and mortality is supposed to be built on the direct link of sodium intake to hypertension, which did not exist in our specific population. One possible reason is that patients with higher sodium intake also had higher sodium removal and numerically higher DDD. In summary, the health effects of low sodium intake in this cohort ultimately depend on the sum of these recognized (nutrient deficiency, worse nutrition, activation of endocrinal hormone, no advantage in BP) and probably other unrecognized intermediate effects (4).

Table 4. Baseline sodium intake and adjusted variables associated with overall and cardiovascular mortality in Cox proportional-hazard regression

<table>
<thead>
<tr>
<th>Overall Mortality</th>
<th>Cardiovascular Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>β</strong></td>
<td><strong>P</strong></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Age-, gender- and BMI-adjusted</td>
<td></td>
</tr>
<tr>
<td>Sodium intake, g/d</td>
<td>-0.14</td>
</tr>
<tr>
<td>Age, yr</td>
<td>0.04</td>
</tr>
<tr>
<td>Multivariate-adjusteda</td>
<td></td>
</tr>
<tr>
<td>Sodium intake, g/d</td>
<td>-0.79</td>
</tr>
<tr>
<td>DM</td>
<td>1.28</td>
</tr>
<tr>
<td>Alb, g/dl</td>
<td>-0.15</td>
</tr>
<tr>
<td>CRP</td>
<td>0.03</td>
</tr>
</tbody>
</table>

CI, confidence interval.
aAdjusted for age, gender, BMI, DM, and CVD history, baseline MAP, Hb, Alb, Ca × P, LDL, Kt/V, Tccr, and CRP.

Table 5. Average sodium intake and adjusted averaged variables associated with overall and cardiovascular mortality in Cox proportional-hazard regression

<table>
<thead>
<tr>
<th>Overall Mortality</th>
<th>Cardiovascular Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>β</strong></td>
<td><strong>P</strong></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Age-, gender- and BMI-adjusted</td>
<td></td>
</tr>
<tr>
<td>Sodium intake, g/d</td>
<td>-0.69</td>
</tr>
<tr>
<td>Age, yr</td>
<td>0.03</td>
</tr>
<tr>
<td>Multivariate-adjusteda</td>
<td></td>
</tr>
<tr>
<td>Sodium intake, g/d</td>
<td>-0.83</td>
</tr>
<tr>
<td>MAP</td>
<td>-0.29</td>
</tr>
<tr>
<td>Alb, g/dl</td>
<td>-0.27</td>
</tr>
<tr>
<td>Hb, g/l</td>
<td>-0.03</td>
</tr>
</tbody>
</table>

CI, confidence interval.
aAdjusted for age, gender, BMI, DM, and CVD history, average MAP, Hb, Alb, Ca × P, LDL, Kt/V, and creatinine clearance.
dietary recall, food frequency questionnaire, or 24-hour urine sodium output. However, 24-hour urine sodium output cannot reflect the actual sodium intake in CKD and chronic heart failure patients (33), although it was thought a gold standard for measuring sodium intake in healthy subjects. In the dialysis population, sodium removal consists of urine and dialysate sodium output. Sodium removal through drained dialysate depends on the convection through the peritoneal membrane; therefore, it also cannot reflect the actual sodium intake in PD patients even though they lose the urine (26). Of interest, although we tried to achieve a precise estimation by repeatedly educating and training patients, we finally found the sodium intake was actually less than the sodium removal in our patients. So far, only three studies simultaneously present sodium intake and sodium removal data in PD patients showing the similar results as we do; namely, sodium removal higher than sodium intake (34–36). Obviously, a well-designed sodium balance study need to be done in the dialysis population to figure out the gap between sodium intake and sodium removal. On the other hand, the actual sodium intake in this study is markedly lower than the average levels of 6 g/d for the general population in Beijing, northern China (37). The energy and protein intake are even low in the highest tertile of sodium intake. We cannot preclude that some degree of underreporting may have occurred even if subjects were well-educated. Memory can be faulty, estimates of portion size can be mistaken, and diet can change from day to day. However, to the extent that such variation was random, it would tend to mute the relation of exposure (sodium) to outcome (death).

This study has several strengths. To our knowledge, this is the first study to verify that both the baseline and average sodium intakes can predict the overall and CVD mortality. Of note, all of the observational studies assessed exposure to dietary sodium only once at baseline throughout the long follow-up periods, the longest being up to 20 years (4). We realized a single baseline assessment of dietary sodium is inappropriate in the dialysis population because that population’s sodium intake probably changed over time as the result of salt-restricted education, or it fluctuated because of intermittent gastrointestinal symptoms. In addition, the patients were thoroughly examined with nutritional and dietary variables during the follow up, which gave us the unique chance to determine the impact of nutrients on the relationship between sodium intake and mortality.

We realize the limitations of this study. The dietary recall of sodium intake was probably underestimated even if subjects were well-educated, as discussed above. We cannot preclude an unrecognized factor confounds the observed associations by being associated with both exposure and outcome. Accordingly, we cannot further speculate on the potential mechanisms of increased death risk of low sodium intake because of the lack of information on insulin resistance, renin-angiotensin system, sympathetic nerve activity, or other aspects.

**Conclusions**

Our study revealed that low sodium intake was closely correlated with nutrient deficits and poor muscle protein stores. Both the baseline and average low sodium intakes were significantly independent predictors of high overall and CVD mortality despite adjusting for recognized confounders and dietary nutrient intake. The potential mechanisms on the independent impact of sodium intake on survival are to be determined. Although our observational data
cannot change therapeutic recommendations for dialysis patients (27,38), we reveal for the first time that low sodium intake is not necessarily a good thing if it comes from anorexia and protein-energy malnutrition in dialysis patients. How to prescribe the low-sodium diet for patients with various degrees of malnutrition is challenging.

Acknowledgments
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Disclosures
None.

References


