The ratio of urinary sodium and potassium and chronic kidney disease progression

Results from the KoreaN Cohort Study for Outcomes in Patients with Chronic Kidney Disease (KNOW-CKD)

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Abstract
The Na/K ratio in urine stands for the dietary of sodium and potassium intake in patients with chronic kidney disease remains unclear for the renal progression. We aimed to determine the risk of progression of chronic kidney disease based on the Na/K ratio in a 24-hour urine collection.

We determined the association between the progression of renal disease and 24-hour urinary sodium and potassium (Na/K) ratios in 2238 patients over a 5-year timespan using data obtained from the KoreaN cohort study for Outcomes in patients With Chronic Kidney Disease (KNOW-CKD). Renal events were defined as a 50% decrease in the glomerular filtration rate (GFR) below baseline, or the onset of end-stage renal disease (ESRD). Patients were divided into 4 groups based on the quartile range of the 24-hour urinary sodium and potassium ratio. We analyzed those variables in the 4 groups. Multiple logistic regression analyses were performed using the data of 1001 patients to identify the independent factors associated with renal events.

Age and male sex accounted for the greatest number of patients in the group with the highest values (group 4) of the 24-hour urinary Na/K ratio (≥3.85). There was no difference in the prevalence of hypertension or diabetes mellitus, the ratio of use of antihypertensive drugs, blood pressures, or estimated GFRs. In the group with the highest urinary Na/K ratio, the 24-hour urinary Na concentration mean ± standard deviation was 188.7 ± 70.6 mmol and that of urinary K was 39.9 ± 16.1 mmol. The urinary protein excretion was highest in the group with the highest urinary Na/K ratio. In the logistic regression analysis, the effect on renal events increased with increasing urinary Na/K ratios. After adjusting for other factors, the risk of renal events was 2.48 (95% confidence interval (CI) 1.30–4.90) in group 3, and 3.75 (95% CI: 1.35–11.27) in group 4. In the Kaplan–Meier analysis, the higher the urinary Na/K ratio, the higher the rate of CKD progression.

Based on our analyses, we concluded that the higher the urinary Na/K ratio, the greater the risk of CKD progression.

Abbreviations: ANOVA = analysis of variance, BMI = body mass index, CI = confidence interval, CKD = chronic kidney disease, DBP = diastolic blood pressure, eGFR = estimated GFR, ESRD = end-stage renal disease, FBS = fasting blood sugar, GFR = glomerular filtration rate, HDL = high-density lipoprotein, KDIGO = the Kidney Disease Improving Global Outcomes, KNOW-CKD = KoreaN cohort study for Outcomes in patients With Chronic Kidney Disease, LDL = low-density lipoprotein, MDRD = the Modification of Diet in Renal Disease, Na/K = sodium and potassium, SBP = systolic blood pressure, TG = triglyceride.

Keywords: chronic kidney disease, urinary potassium, urinary sodium

1. Introduction
The excessive intake of salt directly leads to worsening of hypertension. In addition, high salt intake increases the excretion of protein in the urine, resulting in a decrease in renal function. There are some studies that provide evidence for such assertions. In an 11-year observational study of 2196 women with normal renal function, a higher intake of sodium based on questionnaire results showed a faster decline in glomerular filtration rate (GFR). In a study of the effects of ramipril in 500 patients with glomerulonephritis, elevated 24-hour sodium excretions resulted in the development of end-stage renal failure (ESRD). The same result was obtained after adjusting for proteinuria associated with deterioration of renal function. However, some studies have shown that sodium intake is not associated with deterioration of renal function. Approximately 800 nondiabetic patients with nephropathy participated in the Modification of Diet in Renal Disease (MDRD) study. There was no correlation between urinary sodium excretion and ESRD or all-cause mortality. The reason for the difference in the study
results was that the potassium intake was not adjusted. Because potassium intake increases the excretion of sodium thereby lowering blood pressure and reducing kidney damage, increased intake of potassium increases the excretion of sodium in the urine and decreases blood pressure. Increased potassium intake also increases Kallikrein secretion, reduces glomerulosclerosis, and inhibits tubular damage. The Na/K in urine stands for the dietary of sodium and potassium intake. Therefore, a study suggested that the relationship between the urine sodium/potassium (Na/K) ratio and blood pressure in the general population. When sodium intake was high, blood pressure increased, but if potassium intake was high, there was an increase in excretion of sodium into the urine. In particular the group who had higher sodium intake experienced a greater decrease in blood pressure with higher potassium intake. However, this study was conducted in the general population, and the results of the study in patients with chronic kidney disease were different. In an analysis of 24-hour urine sodium concentrations in 3939 patients with chronic kidney disease, renal outcomes such as the onset of ESRD and 50% decreases in the estimated GFR (eGFR) occurred more frequently with increased excretion of urine sodium and potassium. In this study, the renal outcome was poor when the potassium excretion was high, which was different from that of the general population in general. Therefore, we decided to conduct a study on the progression of renal disease and its relationship to results of 24-hour urine Na/K ratios in patients with chronic kidney disease.

2. Materials and methods

2.1. Study population and ethical considerations

The KoreaN cohort study for Outcomes in patients With Chronic Kidney Disease (KNOW-CKD) is a prospective cohort study of 2238 patients with nondialysis chronic kidney disease (CKD) stages 1 to 5 who were enrolled between February 2011 and January 2016 in Korea. The detailed design and methods of the KNOW-CKD were previously published. We excluded patients with a previous history of chronic dialysis or kidney transplantation, heart failure (NYHA class 3 or 4) or liver failure, past or current history of malignancy, and current pregnancy. The KNOW-CKD protocol was approved by the institutional review board at each participating hospital, including Seoul National University Hospital, Yonsei University Severance Hospital, Kangbuk Samsung Medical Center, Seoul St. Mary’s Hospital, Gil Hospital, Eulji Medical Center, Chonnam National University Hospital, and Busan Paik Hospital.

Of the 2238 patients, 1192 were excluded comprising 279 patients with missing urine sodium data and 956 with missing urine data. The outliers with respect to the urine Na/K ratio were also excluded (n=2). Ultimately, 1,001 patients were included in the final analysis (Fig. 1).

2.2. Data collection and definitions

Demographic data were collected from data registry including: age, sex, systolic blood pressure (SBP), diastolic blood pressure (DBP), body mass index (BMI), medical history of hypertension and diabetes, serum creatinine, 24-hour urine Na/K, total cholesterol, triglyceride (TG), high-density lipoprotein cholesterol (HDL cholesterol), low-density lipoprotein cholesterol (LDL cholesterol), fasting blood sugar (FBS), HbA1c, the presence or absence of metabolic syndrome, and antihypertensive medication history (angiotensin converting enzyme inhibitor, angiotensin receptor blocker, calcium channel blocker), estimated GFR, 24 hours urine protein.

CKD and its stages were defined from the Kidney Disease Improving Global Outcomes (KDIGO) 2012 guidelines. The eGFR was calculated using the 4-variable CKD-EPI equation. Metabolic syndrome was defined by the presence of 3 or more of the following: abdominal obesity >90cm in men or >80cm in women, triglyceride level ≥150mg/dL, taking medication such as lipid lowering agent, HDL-C level <40mg/dL in men or <50mg/dL in women, or taking medication, systolic blood pressure ≥130mm Hg and/or diastolic blood pressure ≥85mm Hg, or taking medication, and fasting plasma glucose level ≥100mg/dL, or taking medication. Thresholds for abdominal obesity were defined based on the Asian population. We defined renal events as a 50% decrease of the GFR from baseline and/or the start of renal replacement therapy.

![Figure 1](image-url)

Figure 1. Algorithm for selecting study subjects from the KNOW-CKD cohort. KNOW-CKD = KoreaN Cohort Study for Outcomes in Patients With Chronic Kidney Disease.
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studied. Systolic and diastolic blood pressures were significantly reduced in 104 patients with moderate essential hypertension studied. Systolic and diastolic blood pressures were significantly reduced in 104 patients with moderate essential hypertension.

| Table 1 | Baseline characteristics of patients according to quartile of 24-hour urinary Na/K ratio. |
|-----------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| Variable        | < 0.29 (n=229) | 0.29–2.58 (n=229) | 2.59–2.96 (n=229) | ≥2.96 (n=229) |
| Age, years      | 55.4 ± 10.9   | 54.9 ± 11.6       | 55.3 ± 12.1       | 53.7 ± 12.6 |
| Min. %          | 118 (20.8)    | 147 (25.0)        | 149 (26.2)        | 153 (26.9)  |
| Current smoking, % | 8 [6.2]      | 36 [27.0]         | 38 [29.4]         | 47 [36.4]  |
| Hypertension, % | 217 [24.8]    | 220 [25.2]        | 222 [25.4]        | 214 [24.5] |
| Diabetes, %     | 66 [27.1]     | 60 [24.6]         | 57 [23.4]         | 60 [24.6]  |
| Cause of CKD    |                      |                      |                      | 0.077 |
| Hypertension    | 45 (16.0)     | 41 (16.4)         | 49 (19.5)         | 59 (23.6)  |
| ADPKD           | 39 (15.6)     | 42 (16.8)         | 30 (12.0)         | 23 (9.2)   |
| Diabetic nephropathy | 75 (30.0) | 62 (24.8)         | 62 (24.7)         | 66 (26.4)  |
| Glomerulonephritis | 78 (31.2) | 80 (32.0)         | 95 (37.8)         | 80 (32.0)  |
| Others          | 13 (5.2)      | 25 (10.0)         | 15 (6.0)          | 22 (8.8)   |
| Antihypertensive medication, % |                     |                      |                      | |
| ACEI            | 16 [15.3]     | 26 [25.0]         | 26 [25.0]         | 36 [34.6]  |
| ARB             | 186 [25.1]    | 192 [25.9]        | 186 [25.1]        | 176 [23.7] |
| CCB            | 80 [23.0]     | 83 [23.9]         | 92 [26.5]         | 92 [26.4]  |
| Diuretics, %    | 65 [23.0]     | 67 [23.7]         | 73 [25.8]         | 77 [27.3]  |
| Loop diuretics  | 40 [16.5]     | 45 [20.8]         | 50 [28.8]         | 52 [32.5]  |
| Thiazide diuretics | 15 [23.0] | 17 [33.0]         | 13 [25.1]         | 21 [41.4] |
| Aldosterone antagonist | 10 [8.0] | 6 [8.1]          | 0 [0.0]           | 5 [5.0]    |
| SBP, mm Hg      | 128 ± 15.5    | 127 ± 16.0        | 129 ± 14.4        | 127 ± 17.0 |
| DBP, mm Hg      | 71.1 ± 10.6   | 76 ± 10.7         | 76 ± 10.5         | 76 ± 12.4  |
| eGFR mean, mL/min/1.73 m² | 50.7 ± 27.5 | 54.6 ± 32.2       | 50.4 ± 28.4       | 48.8 ± 28.8 |
| Total cholesterol, mg/dL | 170.3 ± 39.3 | 175.6 ± 45.3      | 174.2 ± 36.5      | 175.1 ± 42.0 |
| TG, mg/dL       | 145.4 ± 83.2  | 169.5 ± 106.5     | 160.3 ± 101.4     | 175.2 ± 112.5 |
| HDL, mg/dL      | 48.4 ± 14.0   | 48.6 ± 15.5       | 48.7 ± 14.2       | 48.2 ± 14.5 |
| LDL, mg/dL      | 194 ± 31.2    | 197.4 ± 33.9      | 196.2 ± 51.1      | 198.4 ± 53.3 |
| Fasting blood sugar, mg/dL | 115.6 ± 47.0 | 113.8 ± 41.1      | 109.1 ± 31.0      | 118.8 ± 45.2 |
| HbA1c, %        | 7.0 ± 1.5     | 7.1 ± 1.4         | 6.7 ± 1.0         | 6.9 ± 1.4  |
| Urinary potassium mmol/24h | 106.5 ± 54.6 | 160.1 ± 105.2     | 170.7 ± 60.8      | 190.9 ± 72.3 |
| eGFR mean, mL/min/1.73 m² | 63.9 ± 36.7 | 61.8 ± 43.2       | 51.1 ± 18.3       | 41.0 ± 16.4 |
| eGFR mean, mL/min/1.73 m² | 50.7 ± 27.5 | 54.6 ± 32.2       | 50.4 ± 28.4       | 48.8 ± 28.8 |
| Group 2 (reference) | 25 (23.1) | 36 (33.3)         | 28 (25.9)         | 29 (17.3)  |
| Group 3         | 45 (25.7)     | 44 (25.1)         | 47 (26.8)         | 39 (22.2)  |
| Group 4         | 43 (27.3)     | 42 (25.4)         | 34 (20.6)         | 46 (27.8)  |
| Group 5         | 58 (26.0)     | 43 (20.0)         | 59 (27.4)         | 55 (25.5)  |
| Group 6         | 48 (22.4)     | 58 (27.1)         | 49 (22.8)         | 59 (27.5)  |
| Urine protein mg/24h | 10 (26.3) | 6 [15.7]          | 12 [31.5]         | 10 [26.3]  |
| eGFR mean, mL/min/1.73 m² | 1104 ± 228 | 2209 ± 8590      | 1555 ± 2346       | 1510 ± 2119 |

ACEI = angiotensin-converting enzyme inhibitor, ADPKD = autosomal dominant polycystic kidney disease, ARB = angiotensin receptor blocker, BMI = body mass index, CCB = calcium-channel blocker, CKD = chronic kidney disease, DEP = diastolic blood pressure, eGFR = estimated glomerular filtration rate, HbA1c = glycated hemoglobin, HDL = high-density lipoprotein, HN = hypertension, LDL = low-density lipoprotein, Na/K ratio = sodium-to-potassium ratio, SBP = systolic blood pressure, TG = triglyceride, WC = waist circumference.

The relationship between the urinary Na/K ratio and renal function in patients with CKD was not well known.  In our study, we found that the greater the excretion of urine sodium, the less the urinary potassium excretion, that is, the greater the reduction in eGFR by a constant amount of decrease in urinary sodium, the greater the increase in eGFR.
24-hour urine Na/K ratio, the higher the blood pressure and the faster the impairment of renal function.

In addition, if the GFR was <15 mL/min/1.73 m², it may have affected potassium excretion into the urine. In our study, we excluded patients with a GFR of <15 mL/min/1.73 m² and the results were the same.

There is a plethora of research on the recommended daily allowance of sodium. There is a report that the intake of 1.787 to 2.391 g sodium per day lowers cardiovascular disease.\(^\text{19}\) Intake of <2.3 g of sodium per day is likely to maintain adequate blood pressure.\(^\text{20}\) However, the intake of sodium in Korea based on the 24-hour urine analysis was 3,910 mg per 242 people in Pohang City in 2013.\(^\text{21}\) The excretion of potassium is known to be significantly correlated with potassium intake. The potassium intake should be such that the ratio of sodium to potassium is close to 1, that is, the daily potassium intake is 70 to 80 mmol (2.74–3.13 g).\(^\text{22}\) Dietary sodium and potassium intervention studies in 1906 Chinese people showed that low sodium and high potassium interventions correlated with blood pressure. People who are sensitive to sodium intake showed more effective blood pressure lowering when they consumed a diet with low sodium and high potassium intake.

![Figure 2](image2.png)

**Figure 2.** The event-free survival probability of the KM analysis in the urinary Na/K groups. (A) All patients, (B) patients with eGFR 10–90 mL/min/1.73 m². eGFR = estimated glomerular filtration rate, KM = Kaplan–Meier.

![Figure 3](image3.png)

**Figure 3.** Cox regression analysis of renal outcomes and risk factors. (A) All patients, (B) patients with eGFR 10–90 mL/min/1.73 m². BMI = body mass index, CI = confidence interval, eGFR = estimated glomerular filtration rate, HbA1c = glycated hemoglobin, UNAK = urine Na/K.
pressure, increased potassium intake in people with high salt sensitivity is reported to be more effective for controlling blood pressure. In our study, the urine Na/K ratio in group 3 was more associated with renal impairment. For people at the same level as group 2, the average daily intake of sodium should be <160.1 ± 103.2 mmol/day, and potassium should be consumed in excess of 61.6 ± 42.2 mmol/day to decrease the negative effects on renal function. Sodium should be consumed in amounts <3680 ± 2418 mg, and potassium should be consumed in amounts >2407 ± 1649 mg per day. This includes the WHO recommended Na/K 1:1 intake. When sodium is converted to salt, it should be consumed at <9.2 ± 6.0 g, and potassium should be consumed at the recommended daily dose of 3000 mg. Additionally, if GFR is decreased, potassium should be consumed with caution.

After the use of a diuretic, the sodium resorption in the thick ascending limb is decreased, urinary sodium is increased, and urinary potassium excretion also increases. If the use of diuretics is not confirmed, the results of the study may be limited. In our study, there was no difference in diuretic use among the 4 groups in the 24-hour urine Na/K ratio. There was no significant difference in the GFR that affected the excretion of potassium among the groups. Also, there was no difference in the percentage of CKD among the groups. All the factors that might affect urinary sodium and potassium excretion were adjusted. After that, it was confirmed that if the urine sodium was high and the potassium was low, the renal function would deteriorate quickly.

Among the factors that could affect the deterioration of renal function, age, sex, smoking status, blood pressure, BMI, dyslipidemia, hyperglycemia, and proteinuria were different among the urinary Na/K ratio groups. In a regression analysis of renal outcomes, BMI, HbA1c, creatinine and proteinuria, and 24-hour urinary Na/K ratios were significant. In the Cox analysis, groups 3 and 4 showed more renal outcome than the other groups. The level of the ratio of urinary sodium and potassium in group 3 and 4 was also found to have exacerbated the worsening of renal function compared to the other factors exclude the eGFR below 15 mL/min/1.73 m².

The limitations of this study include the relatively short observation period and the fact that other factors affecting renal function deterioration were not properly evaluated. A re-analysis should be performed with a longer observation period. The collection of the 24-hour urine was not well evaluated, and there may have been an error in its interpretation. The amount of urine proteinuria may have affected the degree of deterioration of renal function. There is a study that divided urine proteinuria by 1 g. We did not analyze it separately, so an accurate assessment of the impact of proteinuria could not be made. However, our study was conducted by collecting 24-hour urine specimens for more than 1000 patients with CKD.

Unlike previous studies, the 24-hour urine Na/K ratio was analyzed. The benefit of this method was that both effect of sodium and potassium was considered. Also the GFR, which affects potassium excretion, was excluded, except in cases where it was <15 mL/min/1.73 m². In our study, we found that low sodium intake and high potassium intake could delay the deterioration of renal function. However, additional analysis is needed after evaluating the 1:1 ratio of urinary sodium and potassium before and after accurate urine volume assessments, and increasing the observation period.

5. Conclusion

In patients with CKD, the higher the ratio of urine sodium and potassium over a 24-hour period, the faster the deterioration of renal function.

Author contributions

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