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The Interplay Between Dietary Sodium Intake and Proteinuria in CKD

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See Clinical Research on Page 1022

Kidneys play a crucial role in maintaining sodium balance by matching sodium intake with urinary sodium excretion, which is essential for regulating blood pressure.[1] However, in patients with chronic kidney disease (CKD), impaired renal excretion of sodium disrupts this steady state, making blood pressure more salt sensitive. Although multiple hypotheses have been generated to explain the mechanism by which salt intake raises blood pressure, recent studies have suggested that primary vascular dysfunction, primary sympathetic nervous system dysfunction, and immune activation play an essential role in addition to the capacity of kidneys to excrete sodium, as suggested by Guyton's hypothesis.[1]

A new paradigm for sodium regulation suggests that high sodium intake leads to an increase in the sodium content in the interstitium, which usually exceeds that of plasma content, indicating the presence of extrarenal regulatory mechanisms. This osmotically inactive sodium is associated with negatively charged glycosaminoglycans in the skin. The high sodium concentration in the interstitium activates T cells, leading to immune cell infiltration in the perivascular space and kidneys and resulting in vascular dysfunction and hypertension.[2]

High sodium intake can affect the kidneys via both direct and indirect mechanisms (Figure 1).[3] Previous studies have shown that an increase in salt intake leads to an increase in systolic blood pressure, glomerular filtration fraction, and urinary protein excretion, especially in hypertensive patients with salt sensitivity.[3] High blood pressure and proteinuria can cause vascular and kidney injuries, leading to the progression of kidney disease (Figure 2a). These findings suggest that salt sensitivity may be a marker for an increased risk of renal and cardiovascular complications.[4] The findings from preclinical and small human physiology studies are well-translated into extensive cohort studies. Urinary sodium has been shown to be a potent correlation of proteinuria in patients with CKD in the Chronic Renal Insufficiency Cohort study.[5] Multiple observational studies in the literature show an association between high salt intake and CKD progression. Most of these findings come from observational studies or *post hoc* analyses of randomized controlled trials.

We can conclude from the available evidence that high sodium intake can result in CKD progression and increased urinary protein excretion. Proteinuria is an independent risk factor for cardiovascular disease and CKD progression in patients with CKD. However, whether the effect of high sodium intake on the risk of adverse kidney outcomes modified by urinary protein excretion has yet to be explored. In this issue, Kim *et al*. explore this important question.[6] They studied this question by including 967 participants with available 24-hour urinary sodium estimation from 9 different tertiary care hospitals throughout Korea between 2011 and 2016 with CKD stages G1 to G5 from the Korean cohort study for outcome in CKD (KNOW-CKD). The main predictors of the study were urinary sodium and protein excretion. Sodium intake and urinary protein concentration were estimated using baseline measurements of 24-hour urine sodium and proteinuria excretion. The study's primary outcome was a composite outcome of estimated glomerular filteration rate decline >50% or end-stage kidney disease. In this cohort study, median urinary sodium excretion was 3.40 (2.46–4.51) g/d, above the guideline-recommended sodium intake of <2.3 g/d to prevent cardiovascular and kidney disease. Median urinary potassium excretion was

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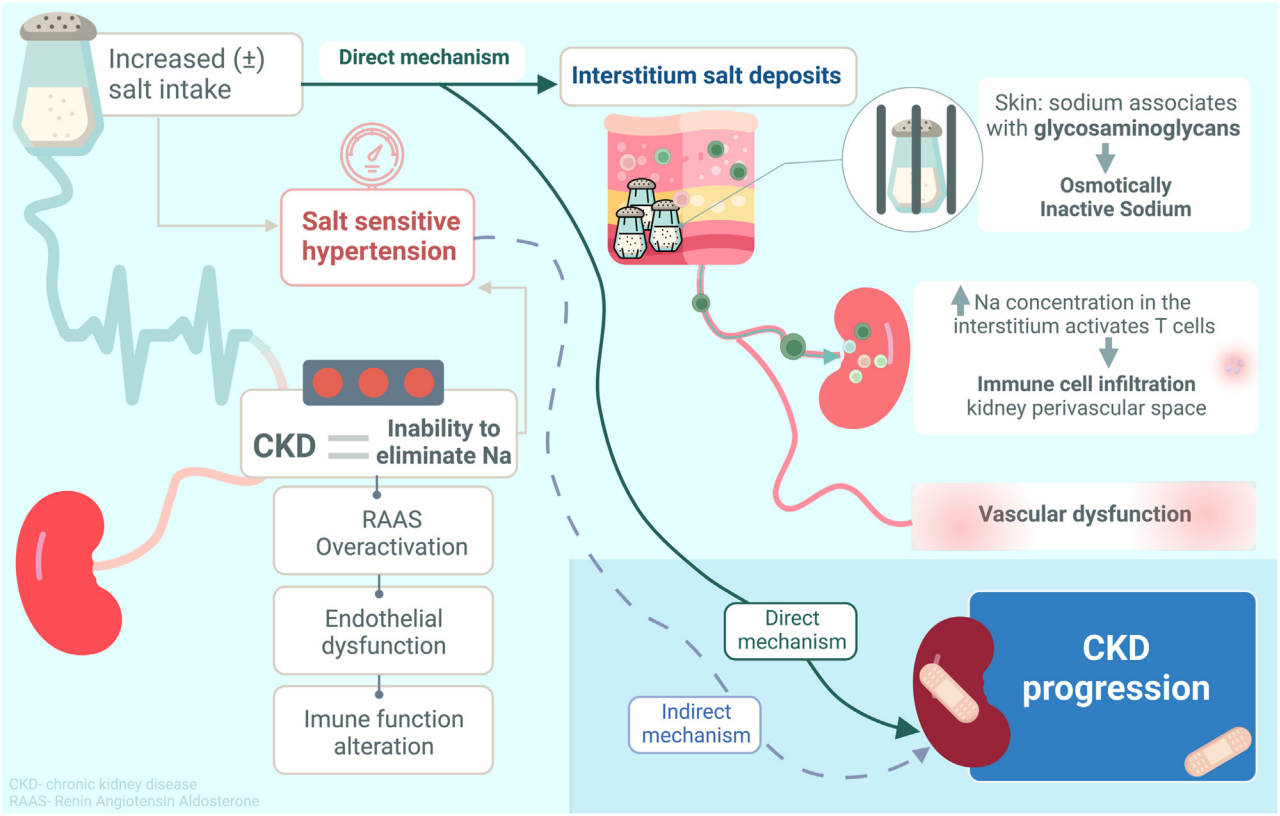

Figure 1. The pathophysiology of sodium-induced CKD progression. CKD, chronic kidney disease.

1.95 (1.44–2.57) g/d, below the recommended potassium intake to prevent cardiovascular and kidney disease. The median urinary protein excretion was 0.56 (0.19–1.58) g/d. In this study, 24-hour sodium excretion was independently associated with proteinuria, expanding on findings from the Chronic Renal Insufficiency Cohort. During a median follow-up period of 4.1 years, the primary outcome events occurred in 287 participants (29.7%). The primary hypothesis was tested using a multivariable Cox-proportional hazard model. The authors used 24-hour urinary sodium and protein excretion as a continuous variable to test statistical interaction. There was a significant statistical interaction between proteinuria and sodium excretion for the primary outcome ($P = 0.006$). A significant finding of the study was that proteinuria modified the association between 24-hour urinary sodium excretion and adverse kidney outcomes. In patients with proteinuria <0.5 g/d, sodium excretion was not associated with the primary outcome. However, in patients with proteinuria ≥0.5 g/d, a 1.0 g/d increase in sodium excretion was associated with a 29% higher risk of adverse kidney outcomes in a fully adjusted model.

The authors explored the joint association between urinary sodium and potassium excretion with adverse kidney outcomes. They created 4 groups by dividing urinary sodium and protein excretion by median concentration. In this study, patients with urinary sodium excretion >3.4 g/d and urinary protein excretion >0.5 g/d had a 5.7-fold risk for adverse kidney outcomes compared with patients with urinary sodium excretion <3.4 g/d and urinary protein excretion <0.5 g/d in a fully adjusted model. One interesting finding in joint group analysis is that the group with urinary protein excretion >0.5 g/d and urinary sodium excretion <3.4 g/d had a 2.32-fold high risk for adverse kidney outcomes, suggesting proteinuria being such a strong risk factor compared to sodium intake for kidney disease progression.

Urinary protein excretion in the study meets the definition of an effect modifier; the effect of urinary sodium excretion on adverse kidney outcomes is different in patients with different urinary protein excretion (<0.5 and >0.5 g/d). The authors used a single measurement of 24-hour urinary sodium excretion as a predictor in this study. Single 24-hour urinary sodium excretion may not reflect dietary sodium intake and its variable by the day. However, the authors did a sensitivity analysis using an average of 24-hour urinary sodium excretion and protein

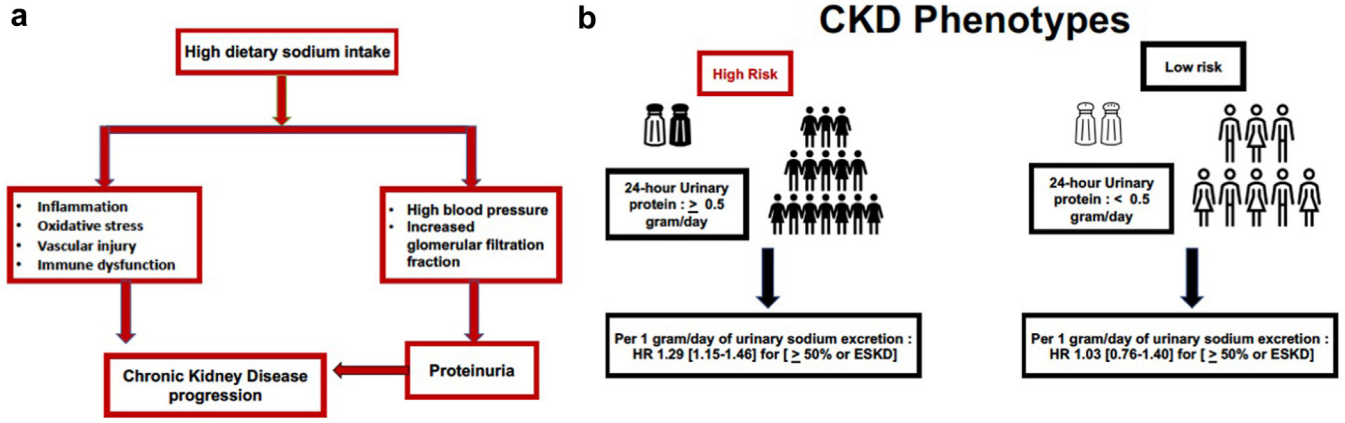

Figure 2. (a) Mechanism of high dietary sodium intake and kidney disease progression; (b) CKD phenotypes according to dietary sodium intake and urinary protein excretion. CKD, chronic kidney disease; ESKD, end-stage kidney disease; HR, hazard ratio.

excretion from baseline and the third year in 465 patients and arrived at the same conclusion. We should be cognizant of the secondary analyses considering the small sample size leading to loss of statistical power. The authors also did multiple secondary analyses using different cut points for urinary protein and sodium excretion. The findings were similarly qualitative.

A previous study using the same cohort of KNOW-CKD explored the association between 24-hour urinary sodium excretion and adverse kidney outcomes.[7] Interestingly, that study included 1254 participants in the analysis compared with 967 participants. In a subgroup analysis of the previous study, baseline proteinuria had no effect modification. The flow diagrams of the present study are different from those in the previous study, with the exclusion of 287 participants because of missing baseline laboratory data, including 24-hour urinary protein excretion. In the previous study, urinary protein excretion of 3.5 g/d was used for subgroup analysis. The baseline characteristics of both study populations are very different. The difference in the results from these 2 studies using the same cohort may be due to different final study populations. Previous studies using more than 1 measurement of 24-hour urine sodium collection did not explore questions regarding the effects of modification by proteinuria, even in secondary and subgroup analysis.[8,9]

The study's findings should be interpreted in the context of this study. In this study, about 43% of participants had glomerulonephritis and polycystic kidney disease as primary renal disease, making them a very different phenotype of CKD compared to patients with diabetes and hypertension. Because of the observational study design, this study is prone to residual confounding. The study had participants who missed 24-hour urinary potassium excretion, a critical covariate-adjusted in Cox-proportional hazard models. The primary hypothesis was tested using only 1 measurement of 24-hour urinary sodium, which does not reflect dietary sodium intake accurately. Duration of the use of antiproteinuric medications was unknown given that these agents can modify urinary protein excretion. Finally, the study included only participants of Asian ethnicity, making results not generalizable to other patient populations. These results should be further validated in cohorts with a common form of CKD.

The results of this study have sound biological plausibility, because in previous studies, increased sodium intake is associated with increased urinary protein excretion and CKD progression. High dietary sodium has been shown to abate the antiproteinuric benefits of angiotensin-converting enzyme therapy.[S1] Moreover, a randomized trial has shown that reducing sodium intake can reduce urinary protein excretion. A recent Cochrane review showed that salt reduction reduced blood pressure in people with CKD and albuminuria in people with earlier stages of CKD in the short term. If a reduction can be maintained, it can translate into clinically significant reductions in CKD progression and cardiovascular events.[S2]

This study is an excellent addition to the literature showing the importance of dietary sodium restriction in a patient with a high amount of proteinuria. However, this study cannot prove causality. Patients with high dietary sodium intake and urinary protein excretion will have a high risk for CKD progression per this study

(Figure 1b). The high-risk group may benefit from interventions like salt reduction, the implementation of antiproteinuric therapies, and blood pressure monitoring to reduce risk for CKD progression. In the future, there is a need to study the impact of high dietary sodium on the efficacy of antiproteinuric therapies like sodium-glucose cotransporter-2 and nonsteroidal mineralocorticoid receptor agonists and the long-term effects of sodium-restricted diet in patients with CKD. In conclusion, though an observational study with no proven causality, this study asked an essential question relevant to day-to-day clinical practice.

DISCLOSURE

All the authors declared no competing interests.

REFERENCES

1. Ellison DH, Welling P. Insights into salt handling and blood pressure. *N Engl J Med*. 2021;385:1981–1993. https://doi.org/10.1056/NEJMra2030212
2. Kirabo A. A new paradigm of sodium regulation in inflammation and hypertension. *Am J Physiol Regul Integr Comp Physiol*. 2017;313:R706–R710. https://doi.org/10.1152/ajpregu.00250.2017
3. Wright JA, Cavanaugh KL. Dietary sodium in chronic kidney disease: a comprehensive approach. *Semin Dial*. 2010;23:415–421. https://doi.org/10.1111/j.1525-139X.2010.00752.x
4. Weir MR, Dengel DR, Behrens MT, Goldberg AP. Salt-induced increases in systolic blood pressure affect renal hemodynamics and proteinuria. *Hypertension*. 1995;25:1339–1344. https://doi.org/10.1161/01.hyp.25.6.1339
5. Weir MR, Townsend RR, Fink JC, et al. Urinary sodium is a potent correlate of proteinuria: lessons from the chronic renal insufficiency cohort study. *Am J Nephrol*. 2012;36:397–404. https://doi.org/10.1159/000342966
6. Kim HJ, Jung C-Y, Kim HW, et al. Proteinuria modifies the relationship between urinary sodium excretion and adverse kidney outcomes: findings from KNOW-CKD. *Kidney Int Rep*. 2023;8:1022–1033. https://doi.org/10.1016/j.ekir.2023.02.1078
7. Kang M, Kang E, Ryu H, et al. Measured sodium excretion is associated with CKD progression: results from the KNOW-CKD study. *Nephrol Dial Transplant*. 2020;36:512–519. https://doi.org/10.1093/ndt/gfaa107
8. He J, Mills KT, Appel LJ, et al. Urinary sodium and potassium excretion and CKD progression. *J Am Soc Nephrol*. 2016;27:1202–1212. https://doi.org/10.1681/ASN.2015010022
9. Ogata S, Akashi Y, Sakusabe T, et al. A multiple 24-hour urine collection study indicates that kidney function decline is related to urinary sodium and potassium excretion in patients with chronic kidney disease. *Kidney Int*. 2022;101:164–173. https://doi.org/10.1016/j.kint.2021.10.030