Sodium and Potassium Intake: A New Statistical Model to Test Their Effects on Health Outcomes

To the Editor: In their article "Urinary Sodium-to-Potassium Ratio and Blood Pressure in CKD," Alencar de Pinho et al.[1] report a significant association between urinary sodium and blood pressure among patients with chronic kidney disease from the REIN cohort study. This is an additional piece of evidence in favor of the deleterious effect of sodium intake on blood pressure among patients with chronic kidney disease while this relationship is well documented in numerous populations.[2]

In this study, urinary sodium-to-potassium ratio was associated with blood pressure whereas potassium was not. It can be puzzling to conclude for the significance of a ratio when one of its components is not significant. A similar result was observed in the CoLaus study in which a significant association was observed between urinary sodium and urinary sodium-to-potassium ratio with age-related kidney function decline. Indeed, the authors faced a similar situation when finding no association for urinary potassium.[3]

We propose a new regression model able to solve this issue and to separate the intrinsic effect of sodium and potassium from their respective interaction: one could build a unique regression model with sodium, potassium, and the interaction between each other. The interpretation is greatly facilitated. If the interaction is nonsignificant, the effects of sodium and potassium are additive, whereas if the interaction is positive or negative, the effects are nonadditive. Moreover, this model, which is an alternative to the sodium-to-potassium ratio, is compatible with the physiological literature that suggests that these effects could be nonadditive.[4]

1. Alencar de Pinho N, Kaboré J, Laville M, et al. Urinary sodium-to-potassium ratio and blood pressure in CKD. *Kidney Int Rep.* 2020;5:1240–1250.
2. Huang L, Trieu K, Yoshimura S, et al. Effect of dose and duration of reduction in dietary sodium on blood pressure levels: systematic review and meta-analysis of randomised trials. *BMJ.* 2020;368:m315.
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4. Gritter M, Rotmans JI, Hoorn EJ. Role of dietary K+ in natriuresis, blood pressure reduction, cardiovascular protection, and renoprotection. *Hypertension.* 2019;73:15–23.

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The Authors Reply: We thank Deriaz et al.[1] for their proposal to use a regression model including sodium, potassium, and an interaction term between the two rather than sodium-to-potassium ratio, to determine whether or not this interaction is significant. We repeated our analysis in the CKD-REIN cohort,[2] using a linear model that included spot urinary sodium-to-creatinine (uNa/Cr), potassium-to-creatinine (uK/Cr), and an interaction term to estimate the effect on systolic blood pressure, while adjusting for potential confounders. In Table 1, we show the adjusted mean difference in systolic blood pressure expressed in mm Hg by quartiles of uNa/Cr for a median uK/Cr, by quartiles of uK/Cr for a median uNa/Cr, and by quartiles combining increasing uNa/Cr quartiles with decreasing uK/Cr quartiles to estimate joint effects.

As in our primary analysis,[2] systolic blood pressure significantly increased across spot uNa/Cr quartiles ($P = 0.003$), up to 5.12 (3.15 to 7.10) mm Hg between the fourth (Q4) and the first quartile (Q1), while it decreased, although

Table 1. Adjusted variations in systolic blood pressure by quartiles of spot urine sodium-to-creatinine and potassium-to-creatinine ratios

	Mean difference in systolic blood pressure (mm Hg)
Spot uNa/Cr (mmol/g) at median uK/Cr	
Q1 <69.6	Ref
Q2 (69.6–102.3)	1.31 (0.79 to 1.83)
Q3 (102.3–142.7)	2.61 (1.59 to 3.63)
Q4 ≥142.7	5.12 (3.15 to 7.10)
Spot uK/Cr (mmol/g) at median uNa/Cr	
Q1 <36.0	Ref
Q2 (36.0–46.9)	−0.28 (−0.91 to 0.34)
Q3 (46.9–61.1)	−0.53 (−1.70 to 0.64)
Q4 ≥61.1	−0.98 (−3.16 to 1.20)
Joint effects of spot uNa/Cr and uK/Cr	
Q1 of uNa/Cr and Q4 of uK/Cr	Ref
Q2 of uNa/Cr and Q3 of uK/Cr	1.59 (0.31 to 2.87)
Q3 of uNa/Cr and Q2 of uK/Cr	3.09 (1.01 to 5.16)
Q4 of uNa/Cr and Q1 of uK/Cr	5.89 (2.67 to 9.13)

uK/Cr, urine potassium-to-creatinine ratio; uNa/Cr, urine sodium-to-creatinine ratio; Ref, reference.
Model adjusted for age, gender, education level, estimated glomerular filtration rate, albuminuria category, history of diabetes, heart failure, dyslipidemia, body mass index, and number of antihypertensive drug classes.

nonsignificantly, across spot uK/Cr quartiles ($P = 0.256$). The interaction between spot uNa/Cr and uK/Cr was not statistically significant ($P = 0.121$). As a result, the size of the joint effect was modest as reflected by a mean difference of 5.89 (2.67–9.13) mm Hg in systolic blood pressure between Q4 (combining high spot uNa/Cr and low uK/Cr) and Q1 (low uNa/Cr and high uK/Cr), just above that observed for spot uNa/Cr alone. However, we would caution against a risk of bias of such a model due to colinearity between the 2 urinary markers (rho = 0.30). As shown by Yoo et al.,[3] even moderate correlations between 2 covariates may impact regression estimates.

Our conclusions about the preponderant role of sodium in blood pressure control, and the marginal, if any, role of potassium, in patients with moderate to severe chronic kidney disease seem robust to model specification.

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2. Alencar de Pinho N, Kaboré J, Laville M, et al. Urinary sodium-to-potassium ratio and blood pressure in CKD. *Kidney Int Rep.* 2020;5:1240–1250.

3. Yoo W, Mayberry R, Bae S, et al. A study of effects of multicollinearity in the multivariable analysis. *Int J Appl Sci Technol.* 2014;4:9–19.

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Comments on "Supervised Exercise Intervention and Overall Activity in CKD" by Pike *et al.*

To the Editor: We read with interest the study by Pike et al.[1] whereby patients with stages 3 to 4 chronic kidney disease were submitted to supervised exercise and calorie restriction and assessed for a hypothetical increase in overall weekly physical activity. Nevertheless, we call attention to possible baseline differences between groups. The exercise group seems to have a lower sedentary time. The authors should have conducted an intergroup comparison to ensure that no baseline differences existed on physical activity. Moreover, the authors have adopted too tight eligible criteria, such as body mass index ≥25 kg/m² and do not require insulin therapy. This might not have included the real picture of the disease and could potentially skew the enrollment to a healthier and more active sample.

Our research group has recently conducted a clinical trial (UTN: U1111-1173-6199) with intradialytic cycling and resistance exercises and verified its effects on weekly physical activity by pedometry. Interestingly, we also found no differences between moments and groups (Figure 1). Although previous studies have shown improvements in weekly physical activity after exercise interventions in both hemodialysis and