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COMMENT

Sodium-to-potassium ratio and renal functional decline

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I read with great interest the article by Takase and colleagues published in Hypertension Research [1]. In their longitudinal study including individuals who participated in annual health check-up programs, urinary sodium-to-potassium (Na/K) ratio was found to be independently associated with incidence of chronic kidney disease defined as an estimated glomerular filtration rate (eGFR) of < 60 mL/min/1.73 m^2 and an annual eGFR decline.

The urinary Na/K ratio varies widely per measurement, and it has a strong regression toward the mean [2]. Hence, the longitudinal associations between the Na/K ratio and changes in clinical markers were challenging to validate. We reported that the use of single measurement of spot urinary Na/K ratio may be difficult to use as a prognostic marker of longitudinal blood pressure changes and renal functional decline [3]. On this issue, Takase et al. used the mean Na/K ratios measured in three different years as a baseline value, a simple method to weaken the regression toward the mean effect, and observed a significant association between Na/K ratio and eGFR decline. Several studies have shown the possible association between Na/K ratio and eGFR decline [4]. However, this may be the first study confirming such an association using repeated measures of urinary Na/K ratio as a baseline value.

The mechanism by which urinary Na/K ratio is associated with eGFR decline is not fully elucidated. The authors suggested that high blood pressure is a mediating factor between baseline urinary Na/K ratio and eGFR decline. Individuals who were regularly taking high sodium diet, which may accelerate blood pressure elevation independent of baseline blood pressure, were more likely to show a decrease in eGFR during the follow-up period. If blood pressure change during the follow-up period was a confounding factor, baseline Na/K ratio itself did not have a direct effect on renal function. To validate this issue, an analysis using time-dependent variables, such as linear mixed model analysis and time-dependent Cox proportional-hazards analysis [5], may be helpful. If a high baseline Na/K ratio itself is a cause of renal functional decline, then this association remains significant if time-dependent changes in blood pressure, Na/K ratio, and other covariates were included in the model. I believe such an analysis is possible in this large-scale study with a long follow-up period, and I hope the results will be provided by the authors in the future.

According to the authors, they used an overnight urine sample, which was collected by instructing the participants to collect their urine sample on the morning during the day of the health check-up. However, the sample was not necessarily an overnight sample because several participants had urinated during sleeping hours. Salt sensitivity is a cause of increased sleep blood pressure because natriuresis is carried over during sleep in individuals with salt sensitivity that have difficulty excreting enough sodium prior to sleep. Therefore, individuals who experience nocturia are likely to be salt-sensitive, have decreased renal function, and may a have lower Na excretion rate in the morning [6]. In the study of Takase, the eGFR did not differ significantly based on the Na/K ratio quartiles. However, because patients in the lowest quartile were younger than those in other quartiles, adjusting for age might have resulted in a lower eGFR in this group. Considering this physiology, analysis using a morning urine sample may weaken the true association between Na/K ratio and eGFR decline if salt sensitivity was not considered. Older adults are likely to be more salt-sensitive. Thus, an age-stratified analysis may shed light on this issue. Sex-separated analysis can also be helpful because men urinate more frequently at

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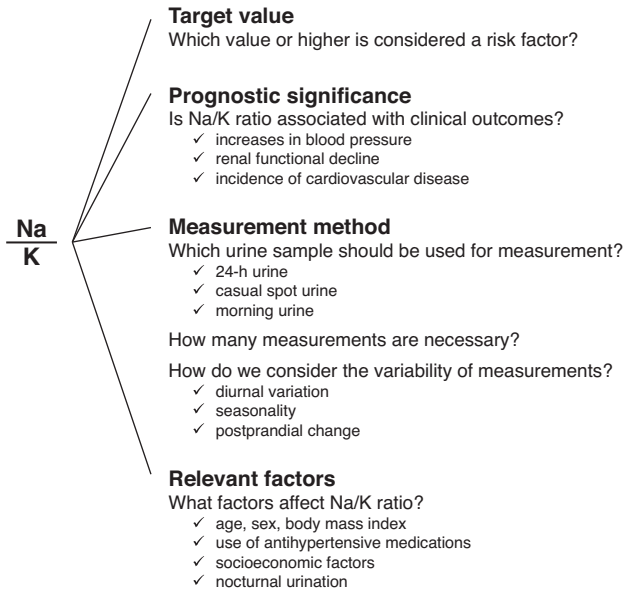

Fig. 1 Issues that must be validated prior to the use of Na/K ratio in community health care settings

night than women. I believe that the sample size of this study is large enough to perform a stratified analysis.

Further, whether Na/K ratio is superior to Na or K alone in relation to eGFR decline has been an interesting topic. Na/K was more closely related to blood pressure than Na or K alone or salt intake estimated from Na values [7]. Thus, further studies should be performed to determine whether the superiority of Na/K ratio can be extrapolated into the association with eGFR decline. The Na/K ratio can be easily assessed using a simple device [8] without laboratory measurement because it does not require creatinine value. If Na/K ratio is strongly associated with eGFR decline, the results can support the potential use of Na/K ratio in community health care settings. Furthermore, an optimal cutoff value for individuals who are at risk should also be determined.

I hope that Takase et al. can assess the abovementioned issues (Fig. 1) in future studies to facilitate the use of Na/K ratio as a novel risk marker.

Compliance with ethical standards

Conflict of interest The author declares no competing interests.

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