Mini-Review

Dietary Sodium Intake and Serum Uric Acid: A Mini-Review

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Abstract

The aim of the present review is to summarize recent studies on the relationship between dietary sodium intake and serum uric acid concentration. In short-term dietary sodium intervention studies, including a recent further analysis of a previously published trial, high dietary sodium intake (200 mmol/day), compared with a low sodium diet (20–60 mmol/day), resulted in a significant reduction in serum uric acid, being approximately 20–60 $\mu\text{mol/L}$. This finding, though consistent across short-term studies, is in contradiction to the long-term observational evidence on the relationship between dietary sodium intake and serum uric acid. Indeed, in a population-based prospective study, high dietary sodium intake was associated with a higher serum uric acid concentration. If serum uric acid would be followed up, several currently ongoing long-term randomized dietary sodium intervention studies may shed some light on how dietary sodium intake interacts with serum uric acid in the development of hypertension.

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Uric acid is an end product of purine metabolism in humans. It is a well-recognized major antioxidant in the human body. However, it increases in hypertension and other cardiovascular diseases [1, 2]. Indeed, prospective studies demonstrated that hyperuricemia was associated with the incidence of hypertension [3] and cardiovascular mortality and morbidity [4, 5]. Some researchers believe that hyperuricemia may be a pathogenic factor for human hyper-

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tension [6]. There is some evidence that uric acid-lowering therapy may reduce the blood pressure in adolescents with hypertension [7] or prehypertension [8] in the presence of hyperuricemia [7, 8].

Despite epidemiological, experimental, and clinical trial evidence on the relationship between serum uric acid and human hypertension, the topic remains controversial [9]. One of the reasons is that serum uric acid lowering has very little or almost no blood pressure-lowering effect in hypertensive adults [10, 11] and no effect on endothelial function [9]. It is therefore postulated that the relationship between serum uric acid and hypertension may be mediated by other risk factors of hypertension rather than a direct causal one. After filtration of uric acid from the glomerulus, it may be reabsorbed in the renal tubules in parallel with sodium reabsorption. That is exactly the mechanism that thiazide diuretics increase serum uric acid via increasing sodium-uric acid reabsorption in the proximal tubule as a biofeedback of the thiazide-inhibited sodium reabsorption in the distal tubule [12]. Excessive dietary sodium intake is a major risk factor of human hypertension. Sodium intake and reabsorption is therefore most likely the mediator between serum uric acid and hypertension.

There is some prospective observational evidence on the interaction between sodium intake and serum uric acid in relation to the incidence of hypertension [13]. In a large ($n = 4,062$), population-based long-term follow-up (5–9 years) study, higher sodium intake at baseline was associated with a significantly higher increase in serum uric acid concentration during follow-up ($1.2 \mu\text{mol/L}$ per 1 g higher sodium intake at baseline, 95% confidence interval [CI] 0.2–2.6) and a significantly higher incidence of hypertension only in the top tertile of serum uric acid concentration at baseline (hazard ratio 1.09 per 1 g higher sodium intake, 95% CI 1.02–1.16) [13]. The investigators of the study interpreted the increased serum uric acid as a marker of endothelial dysfunction instead of a risk factor of hypertension. The observational nature of the study does not allow any causal inference. Nonetheless, the study clearly demonstrated some relationship between dietary sodium intake and the metabolism of uric acid.

There is a need of intervention trials to clarify the relationship between sodium intake and serum uric acid. A number of short-term (1 week to 1 month) intervention studies investigated effects of various levels of dietary sodium intakes on serum uric acid concentration (Table 1) [14–17]. The results of these studies were consistent. In these studies, high dietary sodium intake was approximately 200 mmol/day or 12 g of sodium chloride, and restricted low dietary sodium intake approximately 20 mmol/day or 1.2 g of sodium chloride. High dietary sodium intake, compared with low sodium intake, reduced the serum uric acid concentration by 20–60 $\mu\text{mol/L}$ (0.3–1.0 mg/dL) from approximately 300 to 400 $\mu\text{mol/L}$ (5.0 to 6.7 mg/dL) [14–17].

In a recent publication, Todd et al. [18] performed further analysis of the data from a previously published dietary sodium intervention study in 22 normotensive subjects and 30 hypertensive patients [19]. In a 4-week randomized cross-over study on high versus medium versus low levels of dietary sodium intakes, a moderate (150 mmol/day) and high (200–250 mmol/day) sodium diet, compared with a low sodium diet (60 mmol/day, mean $[\pm\text{SD}]$ serum uric acid concentration $300 \pm 70 \mu\text{mol/L}$), caused a statistically significant reduction in the serum uric acid concentration ($-22 \mu\text{mol/L}$, 95% CI -28 to -16 and $-24 \mu\text{mol/L}$, 95% CI -27 to -17 , respectively). High sodium intake was also associated with a higher urinary sodium/creatinine ratio, lower plasma renin activity, lower serum aldosterone concentration and aldosterone/renin ratio and a higher systolic and diastolic blood pressure [18].

The results of these short-term studies are in line with the observation of a much earlier experimental study in a group of 24 normotensive and hypertensive subjects during the expansion of extracellular fluid volume with intravenous infusions of hypertonic saline [20]. In this study, acute sodium loading increased urinary excretions of sodium and uric acid

Table 1. Randomized cross-over trials on effects of dietary sodium intake on serum uric acid concentration

First author [ref]	Year of publication	Study subjects	Subjects, <i>n</i>	Intervention (sodium in mmol/day)	Follow-up time	Serum uric acid concentration at baseline or the end of follow-up (μmol/L)	Difference (95% CI) between low and high salt diet (μmol/L) ^a
Egan [14]	1991	White men with mild hypertension (<i>n</i> = 18) or normotension (<i>n</i> = 9)	27	20 vs. 200	7 days	404 ± 62 vs. 343 ± 49 ^b	-61.9 (-74.7 to -49.0)
Del Río [15]	1993	Diastolic blood pressure 90–104 mm Hg	30	48 vs. 200	2 weeks	380 ± 66 vs. 318 ± 57 ^b	-61.9 (-93 to -30.8)
Todd [16]	2010	Systolic blood pressure >130 mm Hg or diastolic blood pressure >85 mm Hg	35	60 vs. 150 vs. 200	4 weeks	330 ± 80 vs. 310 ± 60 vs. 290 ± 70 ^b	-20 (-40 to 10, medium) and -30 (-40 to -10, high) ^c
Juraschek [17]	2016	Systolic blood pressure 120–159 mm Hg or diastolic blood pressure 80–95 mm Hg	103	60 vs. 120 vs. 180	30 days	297.5 ± 77	-20.2 (-30.9 to -9.5, medium) and -25.6 (-34.5 to -16.7, high) ^c
Todd [18]	2017	Systolic blood pressure ≤130 mm Hg and diastolic blood pressure ≤85 mm Hg	25	60 vs. 150 vs. 200–250	4 weeks	300 ± 70	-22 (-28 to -16, medium) and -24 (-27 to -17, high) ^c

Studies are listed in the ascending order of the year of publication. ^a Negative values indicate a lower serum uric acid concentration on a high sodium diet. ^b Values at the end of follow-up. ^c Differences from low-salt diet.

Fig. 1. Possible mechanism for the increased urinary excretion of uric acid as a consequence of an increased sodium dietary intake and glomerular filtration into the renal tubules. (–), action of “inhibition”; (?), action “unknown”; URAT 1, urate transporter; MRP4, multidrug resistance protein; OAT, organic anion transporter.

(correlation coefficient 0.731) and resulted in a 36.9 $\mu\text{mol/L}$ (0.62 mg/dL) reduction in the serum uric acid concentration [20]. However, the results of the short-term studies seemed to be contradictory to the observational evidence from the abovementioned long-term prospective study [13]. To clarify this issue, long-term randomized dietary sodium intervention studies are required. In fact, several such studies are currently ongoing [21, 22]. If serum uric acid would be followed up, these studies might shed some light on the relationship between dietary sodium intake and urinary excretion of uric acid. Before such evidence is readily available, one of the speculative mechanisms might be that the increased urinary excretion of uric acid as a consequence of increased dietary sodium intake in the long run impairs kidney function and finally results in a high serum concentration of uric acid (Fig. 1). There is indeed abundant evidence on the detrimental effect of high urinary excretion of uric acid on kidney function [23] and on high serum uric acid as an indicator of impaired kidney function [24]. The urate salt, especially in the form of calcium salt, may become calculi or crystalline in the kidney and damage the function of the kidneys [23]. Impaired renal function may influence sodium metabolism and increase the risk of hypertension.

Other dietary factors or treatment with thiazide diuretics may also confound or contribute to the interaction between dietary sodium intake and the serum concentration and urinary excretion of uric acid. The currently ongoing long-term randomized dietary sodium intervention studies were not specifically designed to address this issue, and post hoc analyses can only be hypothesis generating.

Future research might have to rely on measurements of both serum concentration and urinary excretion of uric acid to investigate the role of uric acid in hypertension while accounting for sodium intake and excretion [25]. One research question may be whether to any extent long-term high dietary sodium intake would increase the blood pressure and the incidence of hypertension via increasing the urinary excretion of uric acid and impairing renal function. Another question is whether a high serum concentration of uric acid and high glomerular filtration of uric acid would influence tubular reabsorption of sodium in parallel with uric acid and induce the so-called sodium-sensitive hypertension. Because of the epidemic of a high-salt diet and high serum uric acid in almost all populations, it is important to illustrate the mechanisms for the interaction between sodium intake and the metabolism of uric acid in relation to hypertension, which is an increasing health burden in our modern society, regardless of high or low-middle incomes.

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