EClinicalMedicine 33 (2021) 100803

Contents lists available at ScienceDirect

EClinicalMedicine

journal homepage: https://www.journals.elsevier.com/eclinicalmedicine

Commentary

Low sodium intake increases plasma renin activity

Conor Judge, Martin O'Donnell*

Health Research Board Clinical Research Facility Galway, National University of Ireland Galway, University Road, Galway H91 TK33, Ireland

ARTICLE INFO

Article History:
Received 3 March 2021
Accepted 3 March 2021
Available online xxx

Reducing sodium intake to low levels (<2 g/day, 5 g/day of salt) is recommended in the entire adult population by the WHO [1], which will require substantial reductions in mean sodium intake globally (current mean: 3·9 g/day). The recommended low sodium intake target is based on short-term randomized clinical trials, reporting a reduction in blood pressure with reductions in sodium intake to low intake levels. It is assumed, but unproven, that sustained low sodium intake will translate into reductions in cardiovascular events, on the premise that reducing sodium intake will not have adverse effects.

Over the past decade, a series of prospective cohort studies have failed to report a reduction in cardiovascular events associated with low sodium intake (compared to moderate/average intake, 2.3–4.6 g/day) and many studies have reported a higher risk of cardiovascular events and death associated with low sodium intake [2]. Overall, evidence from prospective cohort studies supports a *J*-shaped association of sodium intake with cardiovascular disease, with the lowest risk observed at a moderate intake range. While some suggest that the increased risk in those consuming low sodium intake may be attributable to reverse causation or residual confounding [3], others advance the argument that extreme reductions in an essential electrolyte may have adverse consequences that offset benefits of modest blood pressure lowering [4].

The results of a meta-analysis by Graudal et al. [5] published in *EClinicalMedicine* provides evidence that lowering sodium intake, from moderate to low intake levels, results in an increase in plasma renin activity, in short-term clinical trials, and suggest a larger effect in normotensive populations than in hypertensive populations. In contrast, the authors reported no effect of reducing sodium intake from high to moderate intake on plasma renin levels. An increase in renin activity with low urinary sodium excretion was described almost 50 year ago in a cross-sectional study [6]. Increases in renin are associated with increases in blood pressure secondary to angiotensin-II-mediated vasoconstriction and aldosterone-mediated sodium retention in the kidney. Increases in plasma renin activity have been associated with an increased risk of cardiovascular events, first described 30 years ago, and replicated in numerous prospective studies [7]. However, some antihypertensive agents (e.g. thiazide diuretics) also increase renin but are effective in reducing cardiovascular events in patients with hypertension, suggesting a contextual pattern of association and consequence.

Sodium is essential to numerous physiologic processes, and subject to negative feedback loops to maintain homeostasis [4]. An assessment of compensatory physiologic mechanisms provide key insights into establishing a 'deficient' state, analogous to the approach taken in determining adequate thyroid hormone replacement, which is based on thyroid stimulating hormone levels. Therefore, the point at which reducing sodium intake evokes a compensatory effect on plasma renin activity may inform the location of a lower limit of the 'normal' range of sodium intake [4]. Activation of compensatory mechanisms likely explain the observation that blood pressure reduction with reducing sodium intake diminishes at lower sodium intake ranges. It also provides a biological rationale for increased cardiovascular risk associated with low sodium intake, where activation of plasma renin may offset the potential benefits of blood pressure lowering in this sodium intake range. In contrast, reductions in sodium intake from high to moderate intake ranges are not associated with changes in plasma renin activity, a range where associations with blood pressure and cardiovascular risk are consistent. A limitation in the available evidence, reported by Gradual et al., is the relatively short duration of clinical trials (4–42 days), precluding an assessment of the long-term effect of changing sodium intake on plasma renin activity.

The optimal range of sodium intake for human health has been a subject of considerable debate. The case for recommending low sodium intake (< 2 g/day) necessitates an exclusionary focus on the association of sodium intake and blood pressure, while the case for recommending a moderate range (i.e., reducing sodium intake in those consuming intakes above 4·6 g/day) is based on the additional inclusion of evidence from prospective cohort studies and physiologic effects of low sodium intake, such as reported by Graudal et al. It is proposed that resolving the controversy will require a large Phase III randomized clinical trial, comparing the effect of moderate to low sodium intake on cardiovascular events and mortality. However, a major challenge to such a trial is maintaining sustained low sodium intake in a large cohort of community-dwelling individuals, which has not been achieved in longer-term trials, even those employing intensive dietary counselling [8,9]. This inability to

DOI of original article: http://dx.doi.org/10.1016/j.eclinm.2021.100750.
* Corresponding author.
E-mail address: martin.odonnell@nuigalway.ie (M. O'Donnell).

https://doi.org/10.1016/j.eclinm.2021.100803

achieve sustained low sodium intake in populations may also relate to neurohormonal control mechanisms governing the maintenance of sodium homeostasis, and disputes the feasibility of low sodium intake in the general population [10].

The meta-analysis by Gradual et al. provides summary evidence that low sodium intake may not be a physiologically 'normal' intake range and adds further support to the contention that public health policy should target a moderate range of sodium intake [2].

Declaration of Competing Interest

The authors declared no conflict of interest.

Author contribution

Both authors wrote the commentary and approved the final version of the manuscript.

Acknowledgments

CJ was supported by the Irish Clinical Academic Training (ICAT) Programme, supported by the Wellcome Trust and the Health Research Board (Grant Number 203930/B/16/Z). MOD is supported by the European Research Council COSIP Grant 640580.

References

[1] World Health Organization (WHO). Guideline: sodium intake for adults and children. World Health Organization (WHO); 2012. Geneva http://www.who.int/nutrition/publications/guidelines/sodium_intake_printversion.pdf (accessed Nov 19, 2018).
[2] O'Donnell M, Mente A, Alderman MH, et al. Salt and cardiovascular disease: insufficient evidence to recommend low sodium intake. Eur Heart J 2020;41:3363–73.
[3] Cobb Laura K, Anderson Cheryl AM, Paul Elliott, et al. Methodological issues in cohort studies that relate sodium intake to cardiovascular disease outcomes. Circulation 2014;129:1173–86.
[4] Heaney RP. Sodium: how and how not to set a nutrient intake recommendation. Am J Hypertens 2013;26:1194–7.
[5] Graudal N, Hubeck-Graudal T, Jurgens G. Influence of sodium intake and change in sodium intake on plasma-renin in man. EClinicalMedicine 2021;0. doi: 10.1016/j.eclinm.2021.100750.
[6] Weidmann P, Beretta-Piccoli C, Ziegler WH, Keusch G, Glück Z, Reubi FC. Age versus urinary sodium for judging renin, aldosterone, and catecholamine levels: studies in normal subjects and patients with essential hypertension. Kidney Int 1978;14:619–28.
[7] Alderman MH, Madhavan S, Ooi WL, Cohen H, Sealey JE, Laragh JH. Association of the renin-sodium profile with the risk of myocardial infarction in patients with hypertension. N Engl J Med 1991;324:1098–104.
[8] Whelton PK, Appel LJ, Espeland MA, et al. Sodium reduction and weight loss in the treatment of hypertension in older persons: a randomized controlled trial of nonpharmacologic interventions in the elderly (TONE). TONE collaborative research group. JAMA 1998;279:839–46.
[9] Cook NR, Cutler JA, Obarzanek E, et al. Long term effects of dietary sodium reduction on cardiovascular disease outcomes: observational follow-up of the trials of hypertension prevention (TOHP). BMJ 2007;334:885.
[10] McCarron DA, Geerling JC, Alderman MH. Urinary sodium excretion measures and health outcomes. Lancet 2019;393:1294–5.