Review

Sodium intake, RAAS-blockade and progressive renal disease

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ABSTRACT

Pharmacological blockade of the renin-angiotensin-aldosterone system (RAAS) by angiotensin converting enzyme inhibitors or angiotensin receptor blockers is the current standard treatment to prevent progressive renal function loss in patients with chronic kidney disease. Yet in many patients the renal protective effect of RAAS-blockade is incomplete. Short-term clinical studies have demonstrated that dietary sodium restriction potentiates the antiproteinuric effect of RAAS-blockade. More recently, it was shown that this effect is accompanied by a lower risk of end-stage renal disease and adverse cardiovascular outcomes. The modulation of RAAS-blockade efficacy by sodium intake is likely multifactorial, and is mediated by effects of sodium on local tissue RAAS in kidney, vasculature and brain, and by effects on the immune system. Despite the evidence showing the beneficial effects of even a moderate sodium restriction (~2.5 g/d), it remains difficult to realize in clinical practice. In an analysis based on 24-h urinary sodium excretion data from more than 10,000 CKD patients and renal transplant recipients, we found that sodium intake in these patients is on average 3.8 g/d, closely resembling the global general population (3.95 g/d). Behavioral approaches including the use of online dietary coaching (ehealth) and feedback using data from 24-h urine collections may be useful to successfully lower dietary sodium intake, aiming to improve cardio-renal outcomes in patients with CKD.

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Contents

1. Introduction 344
2. Sodium intake and cardiorenal outcomes 345
  2.1. Global sodium intake 345
  2.2. Sodium intake and cardiorenal risk in CKD 345
3. Sodium intake and RAAS-blockade efficacy 346
  3.1. Short-term effects (intermediate endpoints) 346
  3.2. Long-term effects (clinical endpoints) 347
  3.3. Molecular mechanisms 349
4. Management 349
  4.1. Quantification of sodium intake 349
  4.2. Strategies to lower sodium intake 349
5. Conclusion 349
Conflict of interest 349
Acknowledgements 349
References 349

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; NFAT5, nuclear factor of activated T cells 5; RAAS, renin-angiotensin-aldosterone system; SGK1, serum/glucocorticoid-regulated kinase 1; Th17 cells, interleukin (IL)-17 producing T helper cells.

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1. Introduction

Chronic kidney disease (CKD) affects 8–16% of the global population [1]. CKD is among the non-communicable diseases with a globally increasing age-standardized death rate: from 11.6 per 100,000 individuals in 1990–15.8 per 100,000 individuals in 2013 [2]. The high mortality rate in patients with CKD is for a considerable part attributable to the excessive cardiovascular risk in this population. In CKD, the presence of albuminuria is associ-
lated with an increased risk of progressive renal function loss and cardiovascular complications [3–7]. Pharmacological blockade of the renin-angiotensin-aldosterone system (RAAS) reduces albuminuria and blood pressure. Landmark clinical trials performed in the 1990s and early 2000s have demonstrated that through reduction of albuminuria and blood pressure, RAAS-blockade, i.e. angiotensin converting enzyme inhibition (ACEi) or angiotensin receptor blockade (ARB), subsequently retards renal function loss and reduces the risk of cardiovascular morbidity and mortality in patients with CKD [8–12]. In patients with diabetic nephropathy, treatment with the ARB irbesartan increased dialysis-free survival by 6 months on average (Fig. 1). Despite these encouraging results, RAAS-blockade is unable to halt the progression of CKD in a considerable proportion of patients. Residual albuminuria (or proteinuria), persisting despite optimally dosed RAAS-blockade, is strongly associated with adverse long-term renal and cardiovascular outcomes [13,14], and therefore considered a target for additional intervention. Dual RAAS-blockade using combined ACEi and ARB treatment, although further reducing albuminuria, has also been associated with a higher risk of adverse events (acute kidney injury, hyperkalemia) and should be used with caution in selected patients only, as reviewed elsewhere [15]. Additional pharmacological treatment modalities under investigation to lower residual albuminuria in CKD patients include other classes of RAAS-inhibitors such as mineralocorticoid receptor antagonists [16,17], vitamin D receptor activators [18–20], and dietary sodium restriction.

Here we will provide an overview of sodium intake in CKD patients as compared with the general population, address the mechanisms by which dietary sodium may influence the renoprotective efficacy of RAAS-blockade, and summarize evidence from clinical studies on this topic.

2. Sodium intake and cardiorenal outcomes

2.1. Global sodium intake

Global sodium intake is on average far above the recommendations by the American Heart Association (1.5 g/d) and the World Health Organization and United Nations (2 g/d) [21] in all parts of the world (Fig. 2). Nevertheless there is a considerable geographic variation in sodium intake, most likely resulting from socio-cultural differences. Sodium intake in various cohorts of CKD patients and renal transplant recipients, estimated by urinary sodium excretion in 24-h urine collections, revealed that average sodium intake in these patients is 3.8 g/d (9.5 g salt/d) (Table 1). Of note, this figure closely resembles the average sodium intake in the general population worldwide (Fig. 2), which is 3.95 g/d (9.9 g salt/d) [22].

2.2. Sodium intake and cardiorenal risk in CKD

In patients with CKD, blood pressure is usually sodium sensitive. Furthermore, proteinuria is strongly associated with dietary sodium intake. As a result, a moderate dietary sodium restriction in itself reduces both blood pressure and proteinuria in CKD patients [23,24], and may also reduce the long-term risk of cardiovascular events as shown in patients with prehypertension [25]. Interestingly, the antiproteinuric effect of sodium restriction remained upon adjustment for blood pressure [24]. In line, in another study in healthy volunteers, sodium restriction reduced albuminuria in the normal range, without a detectable effect on blood pressure [26]. These findings suggest that the capacity of sodium restriction to reduce proteinuria is not only mediated by blood pressure, but additionally by renal-specific effects.

Several mechanisms may underlie the adverse cardio-renal effects of high sodium intake. High sodium intake induces intrarenal and vascular RAAS-activation, in contrast with the systemic suppression of RAAS activity, as observed in several animal studies [27–30]. Furthermore, high sodium intake may promote a pro-inflammatory and pro-fibrotic state, as reflected by biomarkers such as connective tissue growth factor and N-acetyl-seryl-aspartyl-lysyl-proline [31,32]. Recent studies underline the role of the immune system as an important mediator of adverse renal outcome due to high sodium intake. Two recent studies elegantly demonstrated that high dietary salt intake induces pathogenic interleukin (IL)-17 producing CD4+ T helper cells (Th17 cells) through activation of p38 mitogen-activated protein kinase, the osmosensitive transcription factor nuclear factor of activated T cells 5 (NFAT5) and its target serum/glucocorticoid-regulated kinase 1 (SGK1) [33,34]. The newly identified population of Th17
cells plays a crucial role in the development of auto-immune diseases [35]. Even more important, Th17 cells are also well known to play a pathogenic role in inflammatory renal diseases [36–38]. Recently Th17 lineage-specific regulatory T cells (Treg17) were indentified that depend on activation of the transcription factor Stat3 [39]; Stat3/STAT3-dependent Treg17 cells were subsequently shown to specifically target Th17 cells in murine and human crescentic glomerulonephritis [40]. Taken together, these data indicate that the induction of Th17 cells by salt not only induces auto-immunity as demonstrated in a model of experimental autoimmune encephalomyelitis [33], it is also likely to contribute to the progression of inflammation-driven types of CKD including glomerulonephritis.

Sodium is not the only dietary component that has been linked with cardiorenal risk in CKD patients. The beneficial effects of potassium supplementation on blood pressure and kidney function were already recognized in the 1950s [41]. More recently, several large cohort studies including the PURE study (including >100,000 subjects) showed inverse relationships between urinary potassium excretion, blood pressure, and cardiovascular outcome [42,43]. Furthermore, three large observational studies specifically addressed the role of dietary potassium in patients with CKD, two of which showed a striking association between higher urinary potassium excretion (as proxy for dietary intake) and slower progression of CKD [44,45]. Interestingly, emerging evidence suggest interaction between sodium and potassium intake, which could be the primary target for intervention in the treatment of hypertension [46].

3. Sodium intake and RAAS-blockade efficacy

3.1. Short-term effects (intermediate endpoints)

The short-term effects of sodium restriction on RAAS-blockade efficacy were first demonstrated over 25 years ago. Restricting dietary sodium intake potentiates the efficacy of RAAS-blockade to reduce blood pressure and proteinuria in patients with hypertension, and non-diabetic and diabetic CKD [24,47–49]. Dietary sodium restriction enhances the efficacy in terms of blood pressure and proteinuria reduction of all types of RAAS-blocking agents, including ACEi [50], ARB [24], their combination [47], and renin-inhibition [51]. Interestingly, lowering of sodium intake also increases the antiproteinuric efficacy of non-RAAS blocking agents including neprilysin inhibitors [52] and vitamin D receptor agonists [53]. It is important to note that the efficacy of RAAS-blockade can already be substantially improved by using a moderate sodium restriction, i.e. to ∼100 mmol/d (∼2.5 g/d) [47]. This alleviates the concerns on excess mortality with overzealous salt restriction [54,55].
Table 1
Sodium intake in patients with chronic kidney disease (CKD) and in renal transplant populations. Overview of major cohort studies and randomized controlled trials reporting sodium intake by 24-h urinary collections. Abbreviations: DM-CKD: chronic kidney disease with diabetes mellitus, non-DM-CKD: chronic kidney disease without diabetes mellitus.

<table>
<thead>
<tr>
<th>First author</th>
<th>PMID</th>
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<td>1671</td>
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<td>57</td>
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3.2. Long-term effects (clinical endpoints)

Two post-hoc analyses from large randomized controlled trials have shown that the potentiation of albuminuria reduction by low sodium intake is associated with improved clinical outcomes (Fig. 3). In a re-analysis of the Ramipril Efficacy In Nephropathy Study II (REIN) trial by tertiles of baseline sodium intake, Vegter et al. found that proteinuria reduction was not only less effective in the higher tertiles of sodium intake, but higher sodium intake was also associated with worse long-term renal outcome [56]. In the tertile with the highest sodium intake 60% of patients, all of whom had non-diabetic CKD, reached end-stage renal disease whereas in the lowest sodium tertile 20% reached the renal end-point, after four years of follow-up (Fig. 3A). In a post-hoc analysis of combined data from the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan Study (RENAAL)/Irbesartan Diabetic Nephropathy Trial (IDNT) studies, performed in patients with diabetic nephropathy, similar results were found [57]. In patients treated with an angiotensin receptor blocker, the risk of a renal or cardiovascular event was approximately two-fold higher in patients in the highest tertile than those in the lowest tertile (Fig. 3B). Of note, the design of the REIN trial, as well as RENAAAL/IDNT, included titration of blood pressure to target levels (140/90 mmHg). Accordingly, blood pressure was similar across the tertiles of sodium intake in both analyses. This further supports the notion that the renoprotective effects of sodium restriction are at least in part through blood pressure-independent intrarenal effects.

3.3. Molecular mechanisms

Sodium restriction shifts the top of the dose-response curve for RAAS-blockade, increasing the maximum renoprotective efficacy that could be achieved, i.e. the capacity to reduce proteinuria, blood pressure and glomerulosclerosis, in an experimental model of proteinuric nephropathy [58]. The interaction between sodium status and the pharmacological efficacy of RAAS-blockade is likely multifactorial. First, the impaired vascular conversion of angiotensin I in rats treated with a high sodium diet in combination with an ACEI [28] implies that sodium intake influences RAAS-blockade efficacy at the level of the vasculature, possibly by induction of tissue ACE [59,60]. Furthermore, the rise in angiotensin I normally occurring during RAAS-blockade is potentiated by sodium restriction. This is relevant as angiotensin I is not only a precursor of angiotensin II, but also of angiotensins with vasodilator and antifibrotic properties, such as angiotensin (1–7). During RAAS-blockade, sodium restriction further shifts the balance between vasoconstrictor and vasodilator angiotensins towards a vasodilator profile [51]. Third, an interaction between the brain and kidney RAAS may also play a role. Interestingly, a recent study demonstrated that in the 5/6 nephrectomy model, a high-sodium diet induced renal and cerebral, but not systemic RAAS-activation [30]. Of interest, high sodium intake also increased the activity of renal sympathetic nerves and neurons in the forebrain of 5/6 nephrectomized rats. Moreover interventions targeting the central nervous system (intracerebroventricular tempol, losartan, or clonidine, or renal denervation) reduced renal fibrosis that was exacerbated by the high sodium diet [30]. Together, these findings connect the detrimental renal effects of high sodium intake with deregulations in the central nervous system, which seem to be mediated by the intracerebral RAAS.

Finally, the pro-inflammatory effects of high sodium intake may influence RAAS-blockade efficacy. This was demonstrated in an elegant study showing that mycophenolate mofetil, an antilymphocyte agent, strongly enhanced the renoprotective efficacy of
the ACE inhibitor lisinopril in the rat 5/6 nephrectomy model, i.e. a primarily nonimmune model [61]. The effects of mycophenolate mofetil were apparently beyond the anti-inflammatory effects of ACE inhibition in itself, among others by reducing proteinuria [62]. Similar findings were obtained in the same model using a combination of enalapril (or candesartan) and tacrolimus: the combination of these drugs provided more powerful renoprotection than each individual treatment [63]. These preclinical studies provide a mechanistic basis for the effect of immunosuppressive treatment of CKD patients with nephrotic range proteinuria. Several clinical trials have provided evidence that pharmacological anti-T cell therapies such as calcineurin inhibitors may be used as an adjunct to RAAS-blockade, for example in patients with membranous nephropathy [64,65] and focal segmental glomerulosclerosis [66]. The fact that anti-T cell therapy seems to enhance renoprotection by RAAS-blockade, combined with the specific effects of sodium intake on pathogenic Th17 development, as reviewed above, suggests that sodium intake modulates RAAS-blockade-induced renoprotection for an important part through modulation of the immune system. This is in agreement with the observation that intrarenal inflammation blunts or annihilates the renal protective effects of RAAS-blockade [67], whereas both dietary sodium restriction [68]
and anti-inflammatory treatment [61] can restore the susceptibility to the protective effects of RAAS-blockade.

4. Management

4.1. Quantification of sodium intake

From the studies summarized above, it becomes clear that a moderate dietary sodium restriction to 100 mmol/d (2.5 g/d sodium or 6.3 g/d salt) is probably sufficient to provide a clinically meaningful effect. The gold standard to assess sodium intake is by well-collected 24-h urine samples. In contrast, it is notoriously difficult to estimate salt intake from dietary questionnaires. As an additional advantage, 24-h urine collections provide a wealth of additional information on dietary factors including proteins [69], potassium [70], and magnesium [71]. Creatinine excretion not only serves as a useful marker of completeness of the 24-h urine collection, it is also a marker of physical fitness and a predictor of mortality risk [72].

4.2. Strategies to lower sodium intake

From the data in Table 1 it becomes apparent that, without exception, no CKD or renal transplant population is able to meet the recommended sodium intake of 2 g/d on average. Even a moderate sodium restriction towards 2.5 g/d, which already strongly potentiates the efficacy of RAAS-blockade [47], seems difficult to achieve. How can this gap between recommendations and daily practice be bridged? First, governments and food industry should take further actions to reduce the sodium content of food products [73], and specific approaches are needed for high-risk patient categories including CKD patients [74]. Moreover, it is essential to develop improved strategies for lifestyle management in patients with CKD. This should include monitoring of dietary sodium (as well as other relevant dietary factors) from 24-h urine, as well as integration of behavioral approaches into regular care. KDIGO guidelines do not provide suggestions for the frequency of 24-h urine collections. We ask patients to collect 24-h urines before each outpatient clinic visit, to monitor proteinuria and to give feedback on adherence to dietary sodium restriction. We explain that the renoprotective medication is not effective when dietary sodium intake is too high (based on Ref. [56]), and provide counseling by a dietician at the first visit, and subsequently upon indication. Furthermore, support strategies should be implemented to target specific needs of patients in changing and maintaining a sodium restricted diet. Such strategies include support to set sodium-related goals, strengthening of intrinsic motivation, the delivery of comprehensive and practical information (for example about “hidden salt” in food products), increasing social support, stimulating the self-monitoring of sodium intake and disease progression (using 24-h urine collections), and building a supportive patient-healthcare professional relationship, encompassing shared decision making and coaching [75].

Importantly, dietary intervention strategies should not be restricted to targeting sodium intake. Several other dietary factors may also importantly contribute to an increased cardioenal risk in CKD patients. These include potassium deficiency, as discussed above, and high protein intake, although specifically dietary acid load may be most relevant [76]. Interestingly, phosphate also seems to interfere with RAAS-blockade efficacy as suggested by a post-hoc analysis of the REIN trial [77]; the phosphaturic hormone fibroblast growth factor 23 may play a role in this interplay [78,79]. Notably, there seems to be concordance in dietary phosphate and sodium intake across CKD populations, and targeting sodium intake also has a small but detectable effect on phosphate intake [80].

Together, these findings underline the importance of an integrated dietary approach aiming for reduction of deleterious factors including sodium, and simultaneously promoting the intake of beneficial factors such as potassium. To this extent, the 24-h urine collection is also helpful since it provides data on potassium and protein intake (by 24-h urea excretion) as well.

5. Conclusion

Dietary sodium intake modulates the efficacy of RAAS-blockade, the cornerstone therapy for patients with CKD, to lower blood pressure and proteinuria. The effect on proteinuria seems to be partly independent of blood pressure, pointing towards a specific renal effect, which could be related to local RAAS-activation and to activation of the immune system. The potentiating effect of a low sodium diet on the antiproteinuric effect of RAAS-blockade is accompanied by beneficial long-term renal and cardiovascular outcomes, and was clearly present with only moderately restricted sodium intake (2.5 g/d). Currently, even this goal seems difficult to achieve in daily practice (Table 1). The data summarized in Table 1 are even likely to be an optimistic representation, as part of these patients were selected to participate in clinical trials. The inability to meet recommendations on lower sodium intake is striking, given the limited (or even absent) efficacy of RAAS-blockade-based therapy during high sodium intake (Fig. 3), and requires further action. Behavioral approaches including shared decision making and coaching, taking advantage of feedback derived from 24-h urine collections, should be implemented in daily clinical care to improve adherence to sodium restriction, optimize RAAS-blockade efficacy, and ultimately improve outcomes in patients with CKD.

Conflict of interest

Dr. Navis is advisor for AstraZeneca. Dr. De Borst has no conflict of interest related to this work.

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