Salt intake in kidney disease—a missed therapeutic opportunity?

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Abstract

Although significant progress has been made in the treatment of chronic kidney disease (CKD), treatment is not yet satisfactory, particularly when it is started in the late stages of the disease. Novel modes of intervention to mitigate the burden of disease are required. The reduction of dietary salt intake (which is high in the industrialized world) is one such option. Better understanding of the deleterious effects of salt on renal and cardiovascular health is necessary to raise awareness of the importance of reduction of the salt content in food products. Therefore, we (i) review pathways through which high salt intake exerts damaging effects, (ii) provide an assessment of recent observational studies linking dietary salt intake to the progression of renal and cardiovascular disease and (iii) discuss the interaction between salt intake and rennin–angiotensin–aldosterone-system inhibitors, i.e. the first choice antihypertensive agents for the treatment of CKD.

Keywords: chronic kidney disease; hypertension; rennin–angiotensin–aldosterone system; salt intake; sodium

Introduction

Recently, there has been considerable controversy concerning the most appropriate intake of salt [i.e intake of sodium chloride (Throughout the review the term 'salt' is used for sodium chloride. Two grams of sodium (the WHO recommended target) is equivalent to 5.1 g salt (sodium chloride). For reference, 100 mmol sodium chloride equals 5.8 g and 100 mmol sodium equals 2.3 g sodium] in the healthy population and particularly in individuals with cardiovascular disease. Most data contributing to this controversy come from cardiovascular studies and almost no information is available for kidney disease. The current controversial discussion on the issue of optimal salt intake has been triggered by several recent studies on type 1 and type 2 diabetes that came to the conclusion that low dietary salt intake was associated with higher morbidity and mortality [1, 2]. There must be a nadir, i.e. optimum of low salt intake, but the issue is whether it is reliably reflected by the available studies. To understand the controversy and the possible implications of recent studies, it is necessary to discuss the background and to take a critical look at the methodologies used in recent studies.

In the era of hunters and gatherers, salt intake was presumably <1.0 g/day. It was only after the agricultural revolution that salt consumption rose steeply. A recent survey across all European Member States (plus Norway and Switzerland) showed that daily salt consumption is between 8 and 12 g/day which is well above the World Health Organization recommended target of 5–6 g/day [3]. Table 1. Similar figures have been observed in the chronic kidney disease (CKD) population: the average daily salt consumption in all reported CKD studies to date was ~9–13 g/day [4]. Such data clearly illustrate that measures to restrict dietary salt consumption are not widely implemented in renal patients. To understand the high salt consumption and its impact on public health care, it is appropriate to ask: why is the current salt consumption so high? From a historical perspective, salt was primarily used to preserve food. With the introduction of freezers and refrigerators, salt lost its importance as a preservative. Nevertheless, salt intake has not decreased in the last decades because of its versatile role in influencing the characteristics of food and drinks in a positive way. Bread and cereals are the groups of food items (next to meat and fish) that contribute most to the daily salt intake in a Western diet. The addition of salt during the process of bread production improves the flavour and product texture, controls the growth of yeast and positively influences technological aspects of the production process such as mixing and baking [5]. Reducing the salt intake in bread thus faces technological barriers and involves food safety concerns. However, appropriate and cost-effective alternatives for each of the functions of salt during the bread production process have been offered so that technological hurdles can no longer be used as an argument not to reduce the salt content in bread, but also in other food products, e.g. meat and fish [5].

It had been known for decades that high salt intake increased blood pressure [6], reduced salt intake had beneficial effects in chronic kidney disease [7] and that salt has adverse effects on blood pressure, cardiovascular risk and survival. Yet the issue of the most appropriate salt intake in the general population, and particularly in
patients with chronic kidney disease, continues to be a bone of contention. Efforts to implement the reduction of salt intake may well also be counteracted by the habituation of the population to high salt intake, perpetuated by salt intake may well also be counteracted by the habituation of the population to high salt intake, perpetuated by

Long-term controlled studies (i.e. >2 years follow-up) on the effect of salt intake on blood pressure are limited in humans, but a 2-year study in chimpanzees by Walker showed that reducing the sodium intake from a standard diet of 250 mmol/day (14.6 g salt per day) to 125 mmol/day (7.3 g salt per day) significantly lowered systolic, diastolic and mean arterial pressures [10]. While the relation of salt intake to blood pressure is beyond doubt, the evidence for the relation of salt intake to endpoints in cardiovascular disease and chronic kidney disease is much less well documented. One of the problems in such studies is the methodology to assess salt intake, serum sodium concentrations and whole-body sodium stores, including osmotic and non-osmotic storage. The latter issue has recently become even more complex in view of recent findings by Titze, concerning the compartmentalization of sodium and novel methodologies to measure whole-body sodium [11]. This also raised the issue as to whether health effects of sodium intake are related to its effect on osmotic (i.e. extracellular volume) or non-osmotic sodium stores, or alternatively, as recently suggested, also to the effects on the plasma sodium concentration, or a combination of these.

### Table 1. Estimates of salt intake across EU countries

<table>
<thead>
<tr>
<th>Country</th>
<th>Adult men</th>
<th>Adult women</th>
<th>Year</th>
<th>Collection method</th>
<th>Sample size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Austria</td>
<td>9 g/day</td>
<td>8 g/day</td>
<td>2007</td>
<td>3-day dietary record, 24-h dietary record</td>
<td>3000</td>
</tr>
<tr>
<td>Belgium</td>
<td>10.5 g/day</td>
<td>10.5 g/day</td>
<td>2009</td>
<td>Urinary sodium for 24-h collections</td>
<td>280</td>
</tr>
<tr>
<td>Bulgaria</td>
<td>12.5–14.5 g/day</td>
<td>11.4–16.6 g/day</td>
<td>2004</td>
<td>24-h dietary recall</td>
<td>2282</td>
</tr>
<tr>
<td>Cyprus</td>
<td>~5 g/day</td>
<td>~5 g/day</td>
<td>2005–8</td>
<td>24-h dietary recall</td>
<td>1001</td>
</tr>
<tr>
<td>Czech R.</td>
<td>16.6 g/day</td>
<td>10.5 g/day</td>
<td>2003/4</td>
<td>Repeated 24-h dietary recall</td>
<td>2590</td>
</tr>
<tr>
<td>Denmark</td>
<td>~9.5 g/</td>
<td>~7.5 g/</td>
<td>2003–8</td>
<td>Dietary record, questionnaire</td>
<td>4431</td>
</tr>
<tr>
<td>Estonia</td>
<td>~10 g/</td>
<td>~10 g/</td>
<td>1997</td>
<td>Self-reported data</td>
<td>~1000</td>
</tr>
<tr>
<td>Finland</td>
<td>9.3 g/day</td>
<td>6.8 g/day</td>
<td>2007</td>
<td>24-h dietary recall (under-reporters excluded)</td>
<td>2039</td>
</tr>
<tr>
<td>France</td>
<td>9.6 g/day</td>
<td>7.3 g/day</td>
<td>2006/7</td>
<td>7-day dietary record (1 g was added for salting at meals)</td>
<td>2464</td>
</tr>
<tr>
<td>Germany</td>
<td>7.4 g/day</td>
<td>5.9 g/day</td>
<td>2007/8</td>
<td>Dishes (dietary history interview over 4 weeks retrospectively), dietary record</td>
<td>16 371</td>
</tr>
<tr>
<td>Greece</td>
<td>Unavailable</td>
<td>Unavailable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hungary</td>
<td>17.5 g/day</td>
<td>12.1 g/day</td>
<td>2009</td>
<td>National survey, 3-day dietary record</td>
<td>1131</td>
</tr>
<tr>
<td>Ireland</td>
<td>8.7 g/day</td>
<td>8.0 g/day</td>
<td>2007</td>
<td>Food frequency questionnaire</td>
<td>10 364</td>
</tr>
<tr>
<td>Italy</td>
<td>11.2 g/day</td>
<td>9.4 g/day</td>
<td>1990</td>
<td>Urinary sodium for 24-h collections</td>
<td>149</td>
</tr>
<tr>
<td>Latvia</td>
<td>7.1 g/day</td>
<td>7.1 g/day</td>
<td>2007–9</td>
<td>24-h dietary recall, food frequency questionnaire</td>
<td>2000</td>
</tr>
<tr>
<td>Lithuania</td>
<td>13.5 g/day</td>
<td>10.5 g/day</td>
<td>1997/8</td>
<td>24-h dietary recall</td>
<td>3000</td>
</tr>
<tr>
<td>Luxembourg</td>
<td>Unavailable</td>
<td>Unavailable</td>
<td>2007/8</td>
<td>Food frequency questionnaire</td>
<td>1432</td>
</tr>
<tr>
<td>Malta</td>
<td>Unavailable</td>
<td>Unavailable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Netherlands</td>
<td>9.7–10.1 g/day</td>
<td>7.5–8.6 g/day</td>
<td>2006</td>
<td>Urinary sodium for 24-h collections, or food consumption data</td>
<td>333</td>
</tr>
<tr>
<td>Norway</td>
<td>9–10 g/day</td>
<td>8 g/day</td>
<td>2006</td>
<td>Urinary sodium for 24-h collections</td>
<td>208</td>
</tr>
<tr>
<td>Poland</td>
<td>14.7 g/day</td>
<td>8.6 g/day</td>
<td>2008</td>
<td>Household budget survey</td>
<td>4134</td>
</tr>
<tr>
<td>Portugal</td>
<td>12.3 g/day</td>
<td>12.3 g/day</td>
<td>2006</td>
<td>Urinary sodium for 24-h collections</td>
<td>426</td>
</tr>
<tr>
<td>Romania</td>
<td>12.5 g/day</td>
<td>10.2 g/day</td>
<td>2010</td>
<td>7-day dietary record in national survey</td>
<td>577</td>
</tr>
<tr>
<td>Slovak Republic</td>
<td>9.7 g/day</td>
<td>7.1 g/day</td>
<td>2009</td>
<td>24-h dietary recall and food frequency questionnaire</td>
<td>2880</td>
</tr>
<tr>
<td>Slovenia</td>
<td>12.4 g/day</td>
<td>12.4 g/day</td>
<td>2007</td>
<td>Urinary sodium for 24-h collections</td>
<td>600</td>
</tr>
<tr>
<td>Spain</td>
<td>11.5 g/day</td>
<td>8.4 g/day</td>
<td>2009</td>
<td>Urinary sodium for 24-h collections</td>
<td>418</td>
</tr>
<tr>
<td>Sweden</td>
<td>9 g/day</td>
<td>7 g/day</td>
<td>1997/8</td>
<td>7-day dietary record in national survey</td>
<td>1215</td>
</tr>
<tr>
<td>Switzerland</td>
<td>10.6 g/day</td>
<td>8.1 g/day</td>
<td>2004</td>
<td>Assessment of dietary salt intake from food items, urinary sodium for 24-h collections samples from 100)</td>
<td>13 355 (urine consumption survey)</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>9.7 g/day</td>
<td>7.7 g/day</td>
<td>2008</td>
<td>Urinary sodium for 24-h collections, food consumption survey</td>
<td>692</td>
</tr>
</tbody>
</table>

The broad variety of dietary salt collection methodologies and wide range of sample sizes in the different EU countries highlight the need for more EU-wide standardized data collection. Data are derived from reference 3. (http://ec.europa.eu/health/nutrition_physical_activity/high_level_group/nutrition_salten.htm).
Obviously, the best parameter to estimate salt intake during steady state is 24-h urinary sodium excretion, despite the recent documentation of ultradian fluctuations of sodium excretion [Titze (personal communication)]. Several studies assessed sodium in the morning urine, but this is an imperfect reflection of 24-h excretion, given the circadian rhythm of salt excretion—rendering the measure basically flawed [12]. In addition, current standard laboratory measurements of sodium have a significant range of error. Improved methodologies to estimate the plasma sodium concentration allow a detailed assessment of salt loading on the plasma sodium concentration and its effect on blood pressure. Indeed, a recent study showed small but significant changes in plasma sodium, e.g. by 3.13 mmol/L in response to salted compared with unsalted soup, and the rise in plasma sodium was correlated with an increase in blood pressure [13].

Although a considerable number of older and recent studies addressed the role of salt intake in the genesis of hypertension and cardiovascular disease, the role of salt intake in kidney disease, specifically its evolution and response to treatment, has been little investigated in humans, although in animal models, the impact of salt restriction on the evolution of kidney disease has been clearly documented [14]. The lack of human studies on salt intake and its impact on kidney disease progression is the more remarkable, since the kidney is the major organ of salt excretion and plays a key role in the maintenance of sodium balance. Furthermore, no less than 10% of the population suffer from CKD and die prematurely. Although there is no evidence that the reduced life expectancy in CKD is directly linked to high sodium intake, studies in mice showed that a high sodium intake decreases dose-dependently the life expectancy from 26 to 6 months, highlighting the detrimental effects of high sodium intake on overall survival [15].

Pathomechanisms underlying salt-induced kidney damage

Mechanisms of salt-induced renal damage include hypertension, proteinuria, direct renal effects and effects on the response to therapy. Salt-induced kidney damage has been demonstrated in a wide range of rat models of renal disease, ranging from predominantly hypertensive, e.g. the DOCA-salt model, to primarily proteinuric, such as adriamycin nephrosis, documenting that high salt intake invariably aggravates the course of renal damage. In uninephrectomized spontaneously hypertensive rats, Benstein documented that salt-restricted diets are associated with less proteinuria and glomerulosclerosis [16]. Importantly, the benefit could not be achieved by the administration of hydrochlorothiazide, and the protective effect did not depend upon alterations in the plasma renin concentration or glomerular haemodynamics.

Furthermore, experimental studies have also shown the importance of an optimal salt intake during pregnancy. In view of the known higher renal risk in individuals with low birth weight and lower nephron endowment, it is of interest that, in pregnant rats, both high and low maternal salt intake affects kidney development in the offspring [17]. More recent studies have also shown that high salt intake in pregnant rats had long-lasting effects on the modelling of the vasculature in the offspring independent of the post natal salt intake or blood pressure. In these studies, high salt intake correlated with higher concentrations of marinobufagenin, the hormone known to mediate natriuresis and oxidative stress [18]. The existence of a link between a reduced number of nephrons and renal malfunction is further strengthened by the observation that rats with reduced nephron endowment develop elevated blood pressure when they are put on a high salt diet [19]. This has also been shown in other species as well, e.g. in sheep [20].

In view of the fact that epithelial-to-mesenchymal transition (EMT) is a major mechanism for the progression of kidney damage [21], it is of interest that, in the kidney, salt causes epithelial-to-mesenchymal transition via the sodium-induced signalling substance marinobufagenin [22].

The intra-renal pathways by which the adverse effect of high salt intake is mediated have not been studied in great detail. It is of interest that Rac1 GTPase in rodent kidneys is essential for salt-sensitive hypertension via a mineralocorticoid receptor-dependent pathway [23], although the role of Rac 1 GTPase on progressive kidney injury has not yet been fully clarified. Furthermore, salt-induced oxidative stress plays a role in salt-induced kidney damage, an ancient mechanism in evolution which is demonstrable even in the marigold [24]. The injurious pathways of high salt intake in the kidney, i.e. oxidative stress and renal expression of NADPH oxidase as well as super-oxide dismutase, have been documented in rat experiments [25]. Conversely, salt restriction has been shown to inhibit compensatory growth of nephrons and to reduce damage in rat kidney damage models [14]. Moreover, experimental studies have unambiguously shown that salt restriction enhances the renoprotective effects of pharmacological intervention by RAAS blockade [26].

Against the background of experimental data, what is the evidence of an injurious effect of high salt in human kidney disease?

In the REGARDS study, the highest quintile of dietary sodium was associated with an increased odds ratio for albuminuria in obese, but not in normal-weight, adults [27]. This is in line with corresponding data from the PREVEND study which demonstrate the robustness of the interaction between excess of weight and excess of sodium on end-organ damage [28]. A link between sodium intake and renal function decline was documented in the Nurses’ Health Study [29]. In this 14-year follow-up study, data were collected on 3296 nurses. After adjustment for other nutrients which were associated with eGFR decline, higher dietary sodium intake remained independently associated with eGFR decline amounting to ≥30% from baseline (OR 1.52, 95% CI 1.10–2.09). The results did not vary by diabetes or hypertension status. In patients with established primary kidney disease, e.g. autosomal dominant polycystic kidney disease, high dietary sodium intake again turned out to be one of the factors independently predicting growth in the total kidney
volume and progressive renal function loss over time [30].

Several mechanisms in humans have been documented through which high salt induces renal damage, either dependent or independent of blood pressure.

- First, renal damage may be induced by high salt intake as a result of its interaction with aldosterone. Interaction was demonstrated in individuals with resistant hypertension: in increasing tertiles of urinary sodium excretion proteinuria was progressively higher in subjects with high plasma aldosterone concentrations for any given blood pressure [31]. These data suggest that high sodium could amplify the risk of progressive renal function loss by non-blood pressure-dependent direct, e.g. pro-fibrotic, effects of aldosterone.

- Second, potential mediators of salt-induced kidney damage in chronic renal failure are the Na/K-ATPase inhibitors marinobufagenin and endogenous ouabain. These substances are implicated in sodium regulation and also exert pro-fibrotic effects. In patients with chronic kidney disease, plasma marinobufagenin concentration was significantly higher when compared with healthy controls [32].

- Third, high sodium intake can activate the local RAAS in vessels as well as the kidney [33]. In a clinical study, Boddi documented enhanced conversion from angiotensin I to angiotensin II during high salt intake (23 g sodium chloride per day) consistent with increased tissue RAAS activity [34]. These data are in line with rat studies showing that high sodium intake abrogates the effects of angiotensin-converting enzyme (ACE) inhibition on the conversion from angiotensin I to angiotensin II in vascular tissues [35].

- Fourth, high sodium intake induces hyperfiltration as documented in essential hypertension, where it was also associated with albuminuria in otherwise healthy overweight men [36, 37]. Hyperfiltration in turn can cause renal damage as demonstrated in numerous animal studies. Whether these data also apply to the renal damage in diabetic nephropathy is still debated. In animal models of type I diabetes, and in normoalbuminuric subjects with type I diabetes, a low salt diet induces a rise in filtration fraction [38, 39]. This fuelled Vallon’s hypothesis of a salt paradox in diabetes, explained by increased sodium re-absorption (along with glucose re-absorption) in the proximal tubule, with consequently reduced delivery of sodium at the macula densa [40]. As a result, the tubulo–glomerular feedback would elicit afferent vasodilation, unbalanced by efferent vasodilation, with a consequent rise in filtration pressure and an increased glomerular filtration rate—which can be considered unfavourable in patients with diabetes. This has led to reluctance among clinicians to prescribe salt restriction in diabetic patients. However, whether these findings in diabetes, obtained in the absence of renal damage, are also relevant in the clinical setting of diabetic nephropathy has not yet been established. In this clinical setting where most patients suffer from type II diabetes and are by default treated with RAAS blockade, the possible effects of lower salt intake on the tubulo-glomerular feedback might well be balanced and outweighed by the effects on blood pressure and proteinuria.

The right balance between too little and too much salt?

Public awareness about a potentially adverse role of high sodium chloride consumption was first raised by a study in Finland [41]. In that prospective study on 1173 men and 1263 women, 24-h urinary sodium excretion was measured at baseline. A 17-year follow-up documented that a high sodium intake predicted mortality, particularly in males and overweight individuals [41].

Unfortunately, there is a paucity of high-quality prospective randomized controlled intervention trials investigating whether a lower than currently usual level of dietary salt intake improves long-term outcome. Only two prospective intervention trials have been conducted. Long-term follow-up data of these trials provided evidence that reducing salt intake confers cardiovascular protection. In the TOPH I and TOPH II trials [Trial of Hypertension Prevention] (32) 3126 men and women received comprehensive education and counselling on reducing salt intake. The participants were randomized to intervention, i.e. dietary sodium reduction or usual care, for a duration of 18 months (TOPH I) or 36–48 months (TOPH II). In TOPH I, a net reduction in the daily sodium excretion of 44 mmol/24 h (2.6 g sodium chloride) was achieved and in TOPH II a reduction of 33 mmol/24 h (1.9 g sodium chloride). Although the effect on blood pressure during the intervention was unimpressive, after a 10–15-year follow-up, the risk of cardiovascular events was 25% lower in the intervention group (95% CI 0.57–0.99, P = 0.04) [42].

From different quarters, concerns have been raised about potential adverse effects of low salt, e.g. activation of the sympathetic system, activation of the renin–angiotensin–aldosterone system, reduced insulin sensitivity and increased LDL cholesterol. In humans, such concerns of adverse effects of dietary salt restriction have been summarized and documented in a Cochrane Collaboration Report [43]. A total of 167 studies up to the year 2012 were analysed. In normotensive Caucasians, sodium reduction produced an average reduction in systolic blood pressure of −1.27 mmHg, but there was also a significant increase in renin (P < 0.0001), aldosterone (P < 0.0001), noradrenalin (P < 0.0001), adrenalin (P < 0.0002), cholesterol (P < 0.001) and triglycerides (P < 0.0008) on low compared with high sodium intake. In general, the duration of the studies included in the meta-analysis was short, however. Previous studies had shown that an abrupt reduction of sodium intake caused an increase of renin, aldosterone and adrenalin, but this was an acute compensatory short-term reaction in response to the acute changes in extracellular volume. Indeed, longer-term studies with moderate salt reduction showed at best a small increase in plasma renin and no appreciable
changes in sympathetic nerve activity, glucose tolerance or insulin sensitivity [44].

Considerable concern for a potential adverse effect of low salt intake has recently been raised by two studies in type 2 and type 1 diabetes, respectively. In a prospective cohort study, Ekinçi evaluated 638 type 2 diabetic patients; 24-h urinary sodium excretion was measured at a single visit, and the patients were followed for 10 years [1]. Baseline urinary sodium excretion was 184 ± 73 mmol/24-h (10.7 g sodium chloride/day). After 10 years of follow-up, 175 deaths were observed, 43% of which were of a cardiovascular cause. The main finding of this study is that all-cause mortality was lower by 28% for every 24-h sodium excretion higher by 100 mmol; cardiovascular mortality also significantly and inversely correlated to sodium excretion (hazard ratio 0.65 per 100 mmol higher 24-h sodium excretion). This finding has been interpreted as evidence that lowering salt intake may cause adverse effects. Before accepting this conclusion, one has to consider that patient characteristics across the range of urinary sodium excretion were not balanced. The low salt group had a longer duration of diabetes, lower body mass index (presumably less calorie intake), lower eGFR, higher frequency of macrovascular disease, received considerably less RAAS blockade and insulin treatment more frequently. All these factors may explain a more adverse outcome.

Of more concern is another recent nationwide multicentre study (FinnDiane Study) on 2807 adult type 1 diabetic patients [2]. In this study with a 10-year follow-up, the main finding was that urinary sodium excretion was non-linearly associated with all-cause mortality: both low and high urinary sodium excretion were associated with higher mortality. The nadir of mortality was at a consumption of 100 mmol sodium /24-h (5.8 g sodium chloride per day). The association was independent of confounders such as age, gender, duration of diabetes, eGFR or albuminuria. For the interpretation, it is important to take into consideration that in the low salt cohort there were more females; the individuals had a lower BMI, required less anti-hypertensive medication and had macrovascular disease more frequently—all these findings would be consistent with a higher cardiovascular risk. Before accepting the conclusion that, in these studies, low dietary sodium intake was the cause of higher mortality, this finding should ideally be replicated in prospective randomized controlled trials. One must realize, however, that it will be extremely difficult to provide such ‘gold standard’ information, as long-term maintenance of dietary sodium reduction in a clinical trial environment will be difficult to achieve. In the absence of gold standard evidence, it appears sensible (i) to avoid excessively low as well as excessively high salt intake and (ii) to optimize intake according to the target of 5–6 g/day recommended by the World Health Organization. It is also of note that the low sodium excretion rates reported in the studies of patients with type 1 and type 2 diabetes are extremely rare in the non-morbid general population. As a consequence, extrapolation of these study results to healthy individuals is not justified.

Important additional information has also been provided by two studies in patients at high cardiovascular risk: the ONTARGET and TRANSCEND trials, comprising 28 880 individuals. In these patients, urinary sodium was measured in morning urine samples and the authors extrapolated from these morning samples the estimated 24-h sodium excretion [45]. After a median follow-up of 56 months, 2057 CV death events were recorded. In the reference group with an estimated sodium excretion of 4–5.99 g/day (equals 10–15 g sodium chloride/day), 6.3% of the cohort experienced cardiovascular death. Higher baseline sodium excretion increased the risk of CV death (hazard ratio 1.53 for 7–8 g sodium per day (equals 18–20 g sodium chloride per day). Lower sodium excretion was also associated with increased risk of CV death (hazard ratio 1.19). The authors rightfully did not consider sodium excretion in isolation and appropriately evaluated K⁺ excretion as well. A higher K⁺ excretion was associated with a reduced risk of stroke. This study highlights the difficulty of the methodology to address this issue. The result has been interpreted to indicate that the risk of cardiovascular death starts to rise at sodium chloride consumptions below as well as above 10 g/day. It should be emphasized, however, that the authors used a first morning void urine sample to assess sodium excretion (as an estimate of daily intake). Owing to the circadian rhythm of sodium, only 24-h urine samples (with no collection errors!) can provide an accurate estimate of sodium consumption. The authors corrected for their sampling method using the Kawasaki formula to estimate 24-h sodium excretion. The Kawasaki formula has been established in Japanese, however, and may somewhat overestimate daily sodium chloride consumption in Europeans. Taken together, it is likely that the nadir of 10 g of sodium chloride per day observed in ONTARGET and TRANSCEND trials is an overestimate, but the conclusion that both too low and too high salt intakes raise the CV risk is absolutely plausible. The results of prospective intervention studies using 24-h urinary sodium (and potassium) excretion have to be awaited before definitive conclusions are drawn. An additional concern of a more theoretical nature is that the optimum for cardiovascular patients may not be completely appropriate for the general population. Yet, controlled intervention studies in animals support the notion that vigorous restriction of dietary sodium, in combination with RAAS blockade can elicit profound interstitial damage both in healthy rats and nephrotic rats. These data suggest that lower is not always better and imply the likely existence of a nadir for the optimum of salt intake [46]. The challenge is to find out the optimal level!

Impact of salt intake on the response to renoprotective intervention—in particular renin-angiotensin-aldosterone inhibitors

In the debate over the possible merits of low sodium intake, it might be useful to distinguish between the effects of diet as such in subjects without medication, and the effects of low dietary sodium as an amplifier of the benefit of well-established treatments, e.g. renin–angiotensin–aldosterone system blockade and others. As RAAS...
blockade is evidence-based first-line treatment in CKD as well as in heart failure, and a main treatment in essential hypertension, this issue deserves more consideration in the salt debate.

It has been known for many years that the blood pressure-lowering capacity of antihypertensive drugs can be amplified by concomitant dietary sodium restriction [47, 48]. In this respect, the efficacy of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers (ARB) to lower blood pressure and proteinuria is potentiated by dietary sodium restriction in hypertensive diabetic and non-diabetic populations. Recently, in patients on an ACE inhibitor (lisinopril 40 mg/day), Slagman compared the efficacy of an additional salt-restricted diet (salt intake 6 g/day, estimated from 24-h sodium excretion) versus adding an ARB (valsartan 320 mg/day). The combination of the ACE-inhibitor with moderate dietary salt restriction reduced proteinuria and blood pressure to a markedly greater extent than the combination of ACE inhibitor with an ARB [49]. Interestingly, in a similar set-up, N-terminal pro-brain natriuretic peptide (NT-proBNP) levels predicted both the blood pressure and anti-proteinuric response to dietary sodium restriction and/or diuretic (but not to adding the ARB); this observation suggests that—at least in patients with normal cardiac function—NT-proBNP can be used as a tool to identify subjects in whom salt reduction can improve blood pressure and proteinuria [50]. Whether the effect of dietary salt restriction can be reproduced by a diuretic was investigated by Vogt [51]. They showed that sodium restriction and hydrochlorothiazide were equally effective in reducing blood pressure and proteinuria when added on top of losartan treatment (Figure 1). However, the combination of both measures (salt restriction and hydrochlorothiazide) produced the greatest reduction in blood pressure and proteinuria, indicating that both measures are required to achieve maximal reduction in blood pressure and proteinuria.

Until recently, all studies investigating the amplification of RAAS inhibition by dietary salt restriction were short-term and long-term hard outcome data were lacking. Recently, two post-hoc studies, one on non-diabetic renal patients and the other on diabetic nephropathy provided important insights on the long-term effect of dietary sodium consumption during RAAS blockade. Vegter assessed the rate of progression to ESRD and the interaction between salt intake and proteinuria during Ramipril treatment in patients with non-diabetic nephropathy in a post-hoc analysis of the REIN trial [52]. The authors divided the population post-hoc into individuals with low (<100 mEq/g creatinine), medium (100 ≤ 200 mEq/g) or high (>200 mEq/g) sodium excretion based on urinary sodium throughout follow-up. After a follow-up of >4.2 years, 18.4% of the patients developed ESRD, and this was strongly related to sodium excretion with 6.1% versus 7.9% and 18.2% per 100 patient-years for increasing categories of sodium excretion (P < 0.001; Figure 2). The authors documented a linear association between sodium intake and risk of ESRD. They did not identify a sodium threshold below which the risk of ESRD was no longer sensitive to further lowering of sodium intake. Moreover, the association between sodium intake and ESRD was independent of blood pressure, probably due to the stringent blood pressure titration in the primary trial. This indicates that even when blood pressure is well controlled, high sodium intake increases ESRD risk! As a potential mechanism, the authors pointed out that the high sodium intake blunted the anti-proteinuric effect of ACE inhibition despite blood pressure titration. The risk of ESRD was increased by a factor of 1.61 per 100 mEq/g higher urinary sodium/creatinine ratio—but this relation was lost after adjustment for changes in proteinuria. This finding implies that the renoprotective effect of low sodium is explained, and potentially mediated by, its anti-proteinuric effect. Interestingly, another recent study documented similar results in diabetic patients. In a combined analysis of two large trials in patients with advanced diabetic nephropathy (the RENAAL and IDNT trials), Lambers Heerspink showed that treatment with ARB (losartan 100 mg/day or irbesartan 300 mg/day) compared with non-RAAS intervention produced the greatest long-term effects on renal and cardiovascular events in the lowest tertile of sodium intake (Figure 2) [53]. These two studies extend the previous short-term studies and indicate that a
moderation of dietary sodium intake enhances the renal and cardiovascular protective effects of first-choice antihypertensive therapies in patients with diabetic and non-diabetic kidney disease. The findings in diabetic patients, moreover, demonstrate that the ‘salt-paradox’ should not be extrapolated to the setting of renoprotective intervention in overt diabetic nephropathy. Interestingly, the protective effects of lower sodium were demonstrated for a range of sodium intake that was relatively high, suggesting that even small reductions from habitual intake in CKD may have substantial health benefits.

Finally, the benefits of dietary sodium reduction appear to go beyond renal and cardiovascular disease. In the elderly population, which constitutes a major cohort of patients with chronic kidney disease, low sodium intake has also beneficial effects on the preservation of cognitive performance—illustrating that one has to look at the patient in his or her entirety and not simply at one organ or one disease [54].

What conclusions can be drawn for patients with CKD from the above incomplete data?

The issue of optimal salt intake in the general population, and particularly in patients with CKD, is highly controversial. Given the evidence currently available, ‘dogmatic ex cathedra’ statements are certainly not appropriate. As in the general population, there is currently no evidence to assume that reducing salt intake to 5–6 g/day causes harm or adverse effects in cardiovascular patients and patients with CKD. In the above-mentioned studies, no systematic adverse effects were noted with this intake. Having said this, it is wise to pay attention to some practical points. In all patients, sodium excretion should be monitored in 24-h urine collections, blood pressure control should be performed in the sitting and standing position (the latter because this might point to hypovolaemia). Higher salt intake may be appropriate during episodes of, or in patients with, sodium loss, e.g. diarrhoea, vomiting etc.

Controlled gold standard evidence has not been provided by prospective controlled trials documenting less cardiovascular or renal events as a result of reducing dietary salt intake per se. Nevertheless, convincing studies show that reduction of sodium intake (in association with other manipulations, particularly a concomitant change of potassium intake) lowers blood pressure in essential hypertension.

In renal patients, even a modest reduction of dietary sodium is associated with lower blood pressure, proteinuria and better outcome. Information on the impact of salt intake on the course of kidney disease is fragmentary, but points to the direction that high salt aggravates long-term outcomes. All these data taken together support the call to avoid excessive high salt intake and underscore efforts to reduce dietary salt intake to recommended targets in CKD patients.

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References


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