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Dietary salt intake in chronic kidney disease. Recent studies and their practical implications

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Abstract

Epidemiological studies in the general population show that the level of dietary salt intake is associated with increases in blood pressure, cardiovascular events and mortality. Trial data show that reducing salt intake reduces blood pressure, cardiovascular events and mortality. On the basis of this evidence, the World Health Organization and other bodies recommend restricting salt intake. The association of salt intake with blood pressure and cardiovascular disease is also seen in CKD and trials of salt reduction in CKD have shown benefit by reducing blood pressure and cardiovascular events. However, these trials have typically used resource-intensive approaches to dietary salt reduction that are not suitable for routine clinical care and salt intake typically remains high in people with CKD. The OxSalt care

bundle is a low-cost intervention that was demonstrated in the OxCKD1 trial to help people with CKD to lower their salt intake and could be applied in routine clinical practice.

Key words

diet, intake, kidney, salt, sodium,

Introduction

Salt is unlikely to have been used as a food additive during human evolution, but over a relatively recent period of human history it has been used to preserve food, especially over the winter period.[1] The need for preservation of food with salt is now minimal due to the development of cold storage including freezing and the rapid transport of food from the site of production to that of consumption. Nevertheless, salt intake remains at very high levels in most regions of the world and this has been extensively documented over recent decades.[2] [3]

Taste and salt intake

The major mechanism of salt taste occurs through amiloride-sensitive ENaC sodium channels on type 1 taste receptor cells in fungiform papillae, although amiloride-insensitive pathways have also been identified in circumvallate and foliate taste buds.[4] There is considerable inter-individual variation in the sensation and palatability of saltiness.[5]

When people reduce their dietary salt intake, they often report that food seems bland and tasteless to them and this may discourage them from persisting with their attempts to lower their salt intake. A prolonged reduction in salt intake induces a change in taste perception such that foods taste saltier than they do when consuming a higher salt diet.[6] In a small study of healthy volunteers, those who had been on a low salt diet chose to add less salt to their food than those who had been on a higher salt diet.[7] Similarly, people on a low salt

diet rated foods as saltier than they had rated the same foods when they were on a high salt diet prior to reducing their salt intake.[8] This change in salt perception developed over weeks, but took several months to reach the maximal effect.

A more detailed understanding of salt taste perception may be useful in the design of strategies to help people to reduce their salt intake. For example, soup was perceived as less salty when served at 70 °C than when served at lower temperatures.[9]

Epidemiological studies of salt and health

There are extensive and wide-ranging studies of the relationship between salt intake and disease. [10] Salt intake is generally inferred from analysis of urinary sodium excretion as salt is the dominant source of dietary sodium. Some studies refer to salt and some to sodium and Table 1 provides the relevant conversion information.

A combined study of surveys of global sodium intake and a meta-analysis of 107 randomized interventions concluded that globally 1.65 million deaths from cardiovascular disease each year were attributable to sodium intake above the recommended level.[11] More recently, the Global Burden of Disease Study concluded that sodium was the major dietary risk factor for death and disability, resulting in 3 million deaths as well as the loss of 70 million disability adjusted life years in 2017.[12] Within the UK Biobank study of over 0.5 million individuals, adding salt to food at the table was associated with a hazard ratio of 1.28 for premature mortality.[13] In a pooled analysis of 4 large studies including over 10,000 participants with a median follow up of 8.8 years, salt intake, as assessed by multiple 24-hour urine collections, was associated in a dose-response manner with cardiovascular risk.[14]

A key observation made in the Intersalt study of over 50 communities globally is that the magnitude of the increase in blood pressure that occurs with age is correlated with sodium intake.[2] Both systolic and diastolic blood pressures are positively associated with sodium

intake in both hypertensive and non-hypertensive individuals and the correlation remains even after adjustment for age, sex, body mass, educational attainment, alcohol intake, current smoking and geographical region.[15]

Dietary salt intake may be declining in better resourced countries and has fallen by around 5% over the 13-year period to 2019 in the UK.[16] A reduction in salt intake has also been reported in people over 71 years of age in the US.[17] These changes may reflect various actions documented in some countries by the 2023 World Health Organization report and these actions typically include mandatory labelling of the sodium or salt content of food.[10]

Controversy around very low dietary salt intake

Sodium intake is generally assessed by measurement of the sodium content of urine. For this purpose, 24-hour urine collections can be used, but necessarily rely on the participant collecting all their urine during this time period. In some population studies, spot urine collections have been used to estimate sodium intake, but substantial error can arise from spot urine collections.[18]

In meta-analyses of some population datasets, a J-shaped curve has been observed in the relationship between urinary sodium excretion and cardiovascular events or mortality.[15] This has raised questions about whether a very low salt intake is causative of increased mortality and the significance of this observation has been debated.[19] [20] [21] The large population studies on which these analyses have been undertaken typically rely on estimates of sodium intake based on spot urine tests, which may not provide a reliable index of sodium intake.[4] The potential for misunderstanding and over interpretation of the J-shaped curve has been extensively critiqued and potential problems with such conclusions identified.[20] [18] Notably, when sodium intake was estimated in the Trials of Hypertension Prevention follow up data a J-shaped relationship was seen between sodium intake modelled on the

standard spot urine method and mortality, but when the average multiple measured values for sodium excretion from 24-hour urine collections were used the relationship was linear.[22] Spot urine collections have been shown to perform poorly at estimating sodium intake in CKD.[23]

When tested against Hill's criteria, a causative relationship between low salt intake and increased mortality was found to lack credibility for multiple reasons.[20] Sodium intake is derived from food and almost all food has significant sodium content, so at low levels, sodium intake can correlate with food intake. Therefore, increased mortality in people with very low sodium intake could represent reverse causation with frail or unwell people having a low food intake and so a low sodium intake. Evidence supporting this explanation comes from a detailed study from the Netherlands which found that the increase in mortality with low salt intake only occurred in people with a low protein intake and not in people with a healthy protein intake.[24]

Trials of lowering salt in the general population

Multiple studies have investigated the health outcomes from lowering salt intake. A meta-analysis of 103 trials concluded that a reduction of 100 mmol sodium (2.3 g of sodium or 5.8 grams of salt, see Table 1) per day lowered systolic blood pressure by 3.74 mmHg in normotensive individuals and that this rose to 5.84 mm Hg in those aged 70 and was increased by 1.87 mmHg in people with hypertension.[11] In a further meta-analysis of prospective cohort studies and randomized controlled trials a mean differences of systolic and diastolic blood pressures of 3.39 and 1.54 mmHg respectively was observed when sodium intake was higher versus lower than 2 grams per day.[25] From an analysis of over 133 studies including 12,197 participants, there was a significant correlation between the reduction in sodium intake and the reduction in blood pressure and this relationship was

stronger for older populations, non-white population and those with higher blood pressure. [26]

A major challenge with dietary intervention studies is to ensure that the intervention is adhered to and various approaches have been used to optimize uptake of the intervention including the direct provision of low salt food. Within the DASH trial, participants were assigned to eat either standard or healthy diets that were provided for them and within these groups they spent time in random order consuming the allocated diet with either low, intermediate or high sodium content of 60-70, 100-110 and 140-150 mmol sodium per day respectively).[27] With either the standard or the healthy diet, there were progressive reductions in both systolic and diastolic blood pressure as sodium intake was reduced to the intermediate and low levels. Kitchens catering for resident retired veterans in Taiwan were randomized to use normal salt or a potassium-enriched salt substitute.[28] Over a mean of nearly 3 years there was a significantly lower rate of cardiovascular deaths in the low sodium group. In a large study in China, 600 villages were cluster randomized to use regular salt or a potassium-enriched salt substitute and over nearly 5 years of follow up systolic blood pressure was reduced and rates of stroke, major cardiovascular events and death were all significantly lower in the low sodium group.[29]

Guidance on salt intake for the general population

On the basis of the current evidence, there is a clear consensus that for the general population sodium intake is associated with increases in blood pressure and with increases in cardiovascular events and overall mortality. This has led to guidance from the World Health Organization and other bodies to reduce sodium intake; the World Health Organization guidance is to reduce intake to less than 2 g sodium per day which is equivalent to 87 mmol sodium or 5 g salt per day (Table 1).[3] Guidance from the European Society of

Hypertension, endorsed by the International Society of Hypertension and by the European Renal Association, highlights the frequent presence of fluid volume retention in people with hypertension and the proven value for blood pressure control of restricting sodium intake to less than 2 g sodium or 5 g salt per day.[30] This dietary guidance to reduce salt intake is likely to be particularly relevant for people with resistant hypertension.[31] [32]

Dietary salt intake in CKD

A key question is whether epidemiological studies of general populations which demonstrate increased cardiovascular risk with increased salt intake are applicable to people with chronic kidney disease (CKD) and multiple studies have addressed this. The Chronic Renal Insufficiency Cohort (CRIC) study enrolled nearly 4,000 people with CKD across 7 locations in the US and at around 10 years of follow up there was a significant and relatively linear association between high 24-hour urinary sodium excretion and increased risk of cardiovascular disease.[33] After adjustment for multiple variables associated with modifiable cardiovascular risk factors, the hazard ratios for the highest quartile of urinary sodium excretion compared to the lowest were 1.36, 1.34 and 1.81 for composite cardiovascular events, heart failure and stroke respectively. Analysis of CKD progression in the CRIC study showed a hazard ratio of 1.54 for CKD progression in the highest sodium excretion quartile compared to the lowest sodium excretion quartile.[34] Analysis of nondiabetic participants in the Ramipril Efficacy in Nephropathy (REIN) trial estimated that there was a 1.61-fold increase in the risk of end stage kidney failure with a 100 mmol/g increase in urinary sodium to creatinine ratio.[35] High sodium intake also reduced the anti-proteinuric effect seen with ramipril use.

Multiple studies have tested the benefits of lowering salt intake in CKD. A randomized trial of sodium restriction in patients with CKD and hypertension reported reductions of 10

mmHg in systolic and 4mm Hg in diastolic blood pressure indicating that that the benefits in CKD might be substantial.[36] By delivering intensive personalized dietary advice and the providing low-sodium foods this study achieved notable reductions in sodium from 168 mmol/day (3.9 g sodium or 9.8 g salt) in the high salt group to 75 mmol/day (1.7 g sodium or 4.4 g salt) in the low salt group. In a non-blinded UK trial of 56 participants, reductions of ambulatory systolic and diastolic blood pressures of 8 and 2 mmHg respectively were associated with a reduction in sodium excretion from 260 (6 g sodium or 15.2 g salt) to 103 (2.4 g sodium or 6 g salt) mmol/ day.[37] When moderate salt restriction was added to an angiotensin-converting enzyme inhibitor in patients with nondiabetic CKD (target daily salt intake 2.9 g, achieved 6.2 g), this reduced proteinuria and BP more than the addition of an angiotensin receptor blocker.[38] A small study in transplant recipients who were already on an angiotensin converting enzyme inhibitor or angiotensin receptor blocker demonstrated a reduction in blood pressure with reduced sodium intake.[39] Reductions in blood pressure were also seen with reductions in sodium excretion in the Effects of Self-monitoring on Outcome of Chronic Kidney Disease (ESMO) trial.[40] A study of 58 people with stage 3-4 CKD demonstrated significant reductions in both blood pressure and whole body extracellular volume when 24-hour sodium excretion was reduced by 57 mmol/day (1.3 g sodium or 3.3 g salt).[41]

The intensive and personalized nature of the interventions used to lower salt intake have meant that most of these trials are relatively small in size, often having only around 50 participants in total. Nevertheless, a Cochrane review and meta-analysis of 21 studies of lowering salt intake involving 1197 participants with CKD concluded that there was high certainty evidence that salt reduction lowered blood pressure in CKD.[42]

Guidance on salt intake for people with CKD

In the light of the evidence in CKD, guidelines for the care of people with CKD generally include recommendations around sodium intake.[43] [44] [45] The Kidney Disease Outcome Quality Initiative guidelines recommend a reduction to less than 2 g per day of sodium or 5 g of salt or 90 mmol of urinary sodium excretion.[43] However, there is evidence that targets for salt intake may be the least achieved management targets in the care of people with CKD.[46] [47] This is borne out by the high sodium excretion seen in control groups in many of the studies considered above. In a cross sectional analysis of potentially modifiable cardiovascular risk factors in Italian patients with CKD, urinary sodium excretion was elevated at around 150 mmol/ day (3.5 g sodium or 8.8 g salt) across CKD stages 3-5.[46] Similarly, in a study of cardiovascular risk factors in people with CKD in the Netherlands, levels of around 155 mmol/ day (3.6 g sodium or 9.1 g salt) were identified.[47]

Challenges around reducing salt intake in CKD

Overall, there is strong evidence demonstrating the value of lowering salt intake in CKD, but it is also evident that salt intake remains elevated in populations with CKD. Why is this? In general populations, some studies lowering salt intake have used potassium-enriched salt substitutes, but this approach is less suited to CKD where problems with hyperkalemia may be more common and more serious. Studies that have sought to test the effect of lowering salt intake in CKD have used a wide range of interventions. These have typically been labor-intensive and resource-intensive interventions as illustrated in the following examples. The provision of information by physicians was combined with personalized dietary advice and individualized dietary counseling from dieticians in a study from the Netherlands.[38] The ESMO study had a team of 4 personal coaches (3 health psychologists and 1 dietician) supporting an intervention group of 67 participants and this was supplemented with further

education, an online food diary and a cookbook of appropriate recipes.[40] In a UK study with 26 participants in the intervention group, there was input from a study dietician, follow up telephone calls and practical cooking sessions involving hands-on food preparation and education sessions, both of which were attended by a researcher.[37] In a further study, feedback on salt intake from the results of 24-hour urine sodium excretion was combined with individualized dietary counselling in an intervention group of 22 participants.[39] Unfortunately, CKD is a common long term condition and the cost and nature of these personalized intensive interventions makes them neither affordable nor feasible for large scale use in routine clinical care of people with CKD, even in countries with relatively well-funded healthcare services.

The OxSalt intervention

Although there is a significant body of evidence demonstrating the health benefits for people with CKD of reducing their salt intake, there has been very little, if any, evidence about practical interventions that could be implemented in routine clinical practice to help people with CKD to lower their salt intake in accordance with guideline recommendations. This makes it extremely challenging for people with CKD to lower their salt intake. To address this evidence gap, we developed a simple low-cost intervention designed to help people with CKD to reduce their dietary salt intake. This intervention was developed by a multidisciplinary team involving nephrologists, primary care physicians, nurses, dieticians, patients, and members of the public; we termed the intervention the OxSalt care bundle.[48] [49] The underlying premise of the intervention was that it should help to empower people to make the changes in their diet that would help them to lower their salt intake. Three principles guided the development of the intervention, and these were to empower people to 1) understand the health benefits of reducing salt intake, 2) understand how to evaluate the

salt contents of food and 3) understand how to select or prepare food that is appetizing and low in salt content. The information provided included information about the time it can take for taste to adapt to less dietary salt intake. The intervention lasted only 4 weeks and started with a set of self-explanatory slides to look over on a device with a screen and these covered the benefits of reducing salt intake, how to evaluate the salt content of foods and how to select or prepare appetizing food that is low in salt content. Written information was also provided including a booklet about the topics covered in the slides, a credit-card sized reminder about food labelling and salt content, tips for selecting lower salt foods and for using non-salt flavoring. The intervention also included access to a website making all this information easily accessible. This was supplemented at minimal cost with reminders about salt that were sent as automated phone text messages and emails. Details of the intervention and its components are available online.[49]

The OxCKD1 trial to evaluate the OxSalt intervention

The randomized controlled OxCKD1 trial recruited 201 participants with CKD to evaluate the OxSalt care bundle compared to standard routine clinical care.[48] Multiple 24-hour collections were used to assess sodium excretion and so salt intake. Baseline urinary sodium excretion was 130.2 mmol/24 hours (3 g of sodium or 7.6 grams of salt). Recruitment was conducted at multiple centers and participants were randomized with minimization.[50] The primary outcome was a reduction in salt intake as assessed by 24-hour urine sodium excretion after 4 weeks of the intervention and at this time point the mean sodium excretion was 92.9 mmol/24 hours (2.1 g sodium or 5.4 g salt) in the intervention group compared to 118.9 mmol/24 hours (2.7 g sodium or 6.9 g salt) in the control group (*P =0.001*). The mean change in individual 24-hour sodium excretion was -32.4 mmol/24 hours (-0.7 g sodium or -1.9 g salt) for the intervention group compared to -6.3 mmol/24 hours (-0.1 g sodium or 0.4

g/day) for control group. As shown in Figure 1, there remained a significant reduction in 24-hour sodium excretion in the intervention group, but not the control group at 2 months and 11 months after the end of the intervention. The aim of the study was not to evaluate the effect of lowering sodium intake, as this is already well established, but rather to determine whether the OxSalt intervention could empower people to lower their salt intake. Compared to the control group, the intervention group had lower mean systolic ($P = 0.05$) and diastolic blood pressures ($P = 0.04$) at 1 month. The results demonstrate that this simple and low-cost intervention helps people with CKD to cut their salt intake significantly. The intervention was only tested for 4 weeks and the longer-term results indicate that there may be benefit from further 'booster' intervention elements beyond the 4 week period.

Conclusions

There is strong evidence in the general population that salt intake is associated with increased blood pressure and increased risk of cardiovascular events and mortality. Trials of reducing dietary salt intake have resulted in reductions in blood pressure, cardiovascular events and mortality. It can take some time for taste to adjust to a lower salt intake. In CKD, salt intake is also associated with increased blood pressure and increased cardiovascular events and mortality. Although trials of reducing sat intake in CKD show benefit, these trials have typically used resource-intensive approaches to reduce salt intake and such approaches are not feasible for widespread use in routine clinical practice. The OxSalt care bundle is a simple low-cost intervention that lasts only 4 weeks and was shown in the OxCKD1 trial to help people with CKD to lower their salt intake significantly. It could be applied at scale for people with CKD.

Article information

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Conflict of interest None declared.

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Table 1. Sodium and Salt values

Sodium (mmol)	**Sodium (g)**	**Salt (g)**
25	0.6	1.5
50	1.2	2.9
75	1.7	4.4
87	2.0	5.1
100	2.3	5.8

125	2.9	7.3
150	3.5	8.8
175	4	10.2
200	4.6	11.7
225	5.2	13.1
The World Health Organization recommended maximal intake is shown in red. To convert mmol of sodium to grams of sodium multiply by 0.023. To convert mmol of sodium to grams of salt multiply by 0.058. To convert grams of sodium to grams of salt multiply by 2.54. to convert grams of sodium to mmol of sodium multiply by 43.5. To convert grams of salt to grams of sodium multiply by 0.393. To convert grams of salt to mmol of sodium multiply by 17.1		

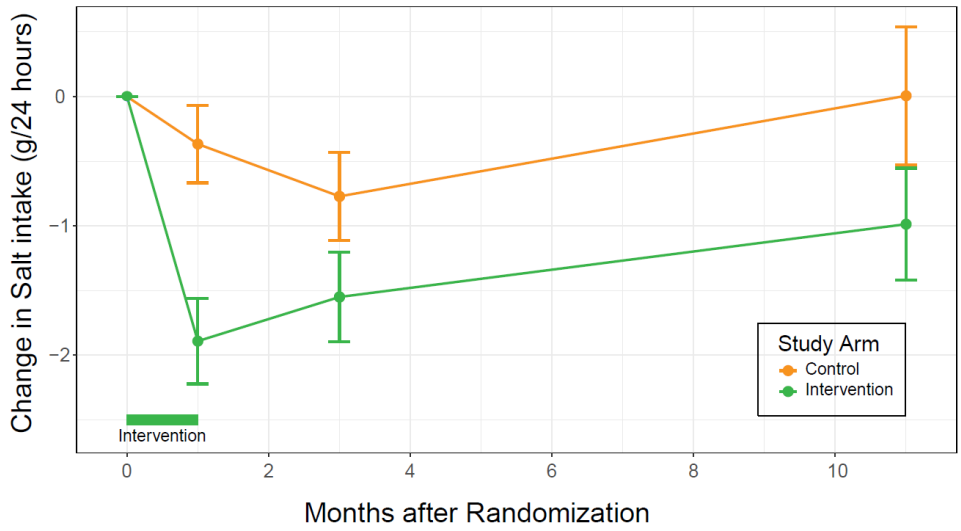

Figure 1 Results of the OxCKD1 study.[48] Salt intake was assessed by measuring the sodium content of 24-hour urine collections. After a simple, low-cost intervention lasting for 4 weeks, there was a significant reduction in salt intake in the intervention, but not the control group and this effect persisted beyond the period of the intervention.

Short title: Salt intake in CKD