Salt and nephrolithiasis

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ABSTRACT

Dietary sodium chloride intake is nowadays globally known as one of the major threats for cardiovascular health. However, there is also important evidence that it may influence idiopathic calcium nephrolithiasis onset and recurrence. Higher salt intake has been associated with hypercalciuria and hypocitraturia, which are major risk factors for calcium stone formation. Dietary salt restriction can be an effective means for secondary prevention of nephrolithiasis as well. Thus in this paper, we review the complex relationship between salt and nephrolithiasis, pointing out the difference between dietary sodium and salt intake and the best methods to assess them, highlighting the main findings of epidemiologic, laboratory and intervention studies and focusing on open issues such as the role of dietary salt in secondary causes of nephrolithiasis.

Keywords: hypercalciuria, nephrolithiasis, salt, urinary calcium, urinary sodium

INTRODUCTION

Excessive salt intake has been focused on in the last few years as one of the main elements that influence health status. In particular, salt is linked to hypertension and cardiovascular disease, and therefore many professional organizations have...
issued strong recommendations to reduce salt intake [1–4]. The relationship between salt and nephrolithiasis is perhaps less popular, but in the same way well established. The purpose of this manuscript is, therefore, to review the current knowledge and to address the main controversies about salt intake and kidney stones.

FULL REVIEW

DIETARY ISSUES

In the medical literature, there is some confusion between salt and sodium intake. By dietary salt we mean the intake of sodium chloride. Dietary sodium, on the other hand, refers to the total amount of Na⁺ ions contained in foods. Naturally, salt is by far the main dietary source of sodium, but one must consider that foods generally contain small amounts of sodium bicarbonate and sodium citrate as well. There is some evidence that sodium is harmful for kidney stone disease only when it is accompanied by the ion chloride [5]. Therefore, from a nutritional point of view, it is important to consider salt intake and not sodium intake.

In a typical Western diet, salt is mainly supplied through processed foods (70–80% according to some estimates) [6]. About 10–15% of the whole salt intake is naturally contained in food composition, while only a small percentage (<10%) is discretionaly added to foods [6, 7]. Therefore, an effective program to reduce global salt intake must be primarily aimed at reducing the salt content of processed foods. On the other hand, voluntary avoidance of discretionary salt affects global salt intake in a limited way [8].

The simplest way to assess a patient’s salt intake is a dietary diary. Recent reports have shown a sufficient degree of accuracy of both a 24-h dietary recall and a food-frequency questionnaire in estimating the real salt intake [9, 10], but these methods actually lack objectivity and may be complex to carry out [11]. Better accuracy may be obtained through direct measurement of renal sodium excretion. Although some studies suggest that sodiuria underestimates actual salt intake by 16–40% [12–14] and others show that there is a 7–30% overestimation [15, 16], 24-h sodiuria has entered clinical practice as the gold standard for salt intake assessment [3]. Twenty-four hour urine collection is generally considered necessary because there may be some daily variations in sodium output; however, an estimation using a casual urine specimen can sometimes be acceptable for monitoring or research purposes [17].

World Health Organization recommendations state that daily salt intake should not exceed 5 g (Na⁺ 85 mEq) [3]. Modern diets in industrialized countries contain an excessive amount of salt. For example, the mean intake in an Italian cohort was 10.9 g/day (186 mEq/day) in men and 8.5 g/day (145 mEq/day) in women [18]; in a Spanish cohort, it was 9.8 g/day (167 mEq/day) [19] and in large epidemiologic studies set in the USA, it was 8.4 g/day (143 mEq/day) [20]. Actually, during the Paleolithic era, diet contained very low amounts of salt, estimated in ~1 g/day (17 mEq/day), so kidneys, from an evolutionist’s perspective, are not used to handle so much salt as what is generally present in modern diets [21].

EPIDEMIOLOGICAL CONNECTION BETWEEN SALT AND NEPHROLITHIASIS

The most convincing epidemiologic proof that salt intake is linked to nephrolithiasis comes from a large American prospective study conducted on >90 000 healthy middle-aged women, showing a clear increasing trend in the relative risk of developing stones as the quintiles of salt intake rise [maximum RR 1.30 for a salt intake >10.3 g/day (176 mEq/day)] [22]. However, other large prospective studies failed to demonstrate such a correlation, especially in younger women and men [23–25]. These studies, however, evaluated dietary habits at baseline and kidney stone prevalence was detected after many years of follow-up, so that salt intake might have changed at the time of stone formation. Moreover, they were based on food-frequency questionnaires, which may not always be sufficiently precise in estimating the actual salt intake [26], thus introducing a possible bias. In any case, the existence of age- and gender-related differences in the epidemiological connection between salt intake and nephrolithiasis cannot be excluded, also because of difficulties in estimating the actual sodium intake.

Some studies focusing on dietary habits of idiopathic calcium stone formers have clearly demonstrated that these individuals have a significantly higher daily intake of salt and a more frequent consumption of salty foods, such as sausages and ham, than healthy controls, especially among younger females [27, 28]. Salt intake in subjects with idiopathic hypercalciuria is, furthermore, higher than in stone formers with a normal calcium excretion [29]. Calcium stone formers also showed significantly different intakes of other nutrients, thus the specific contribution of salt and salty foods in stone formation is not known.

The uncertainties in this field are, however, counterbalanced by a large number of studies showing that high salt intake does affect other urinary parameters of lithogenic risk and that a low-salt diet may be effective in kidney stone prevention.

EFFECTS OF SALT ON URINARY PARAMETERS OF LITHOGENIC RISK

In 1964, Kleeman et al. first reported an association between salt intake and calcium excretion, documenting a dramatic rise in calciuria (+82%) after the shift from a very-low-sodium diet [1.1 g/day (19 mEq/day)] to a very-high-sodium diet [24.5 g/day (419 mEq/day)] [30]. Since then, a large number of interventional studies have reported a linear association between salt intake and calcium excretion in healthy subjects, even for more modest levels of salt intake [31]. It has been suggested that a dietary increase of 6 g/day (103 mEq/day) in salt intake may result in a 40 mg/day (1 mmol/day) increase in urinary calcium [32]. Moreover, a 3.5 g (60 mEq/day) increase in salt intake leads to a 1.63-fold increase in the relative risk for hypercalciuria, while healthy subjects with a daily salt intake >10 g (171 mEq) have a 21.8% prevalence in hypercalciuria, compared with a 3.9% prevalence in those with a lower intake [33].
The same relationship has also been demonstrated in idiopathic calcium stone formers, regardless of the levels of calcium intake [30, 34–37]. The levels of calcium excretion are generally higher in stone formers than in healthy subjects with the same sodium intake, so that a 6 g/day (103 mEq/day) rise in salt intake may result in a 80 mg/day (2 mmol/day) increase in urinary calcium in stone formers [38] versus 40 mg/day in non-stone formers.

At the Kidney Stone Clinic of Parma University Hospital, Parma, Italy, we analyzed 24-h urinary excretion of calcium and sodium of all patients who underwent a full urinary profile of lithogenic risk from 1986 to 2011 (1952 subjects: 1192 males and 760 females). We actually found that calciuria (in mg/day) is dependent on sodiuria (in mEq/day) in a linear regression model, both in males (\(y = 0.7721x + 131.68, R^2 = 0.15, r = 0.4, P < 0.001\)) and females (\(y = 0.9482x + 80.524, R^2 = 0.22, r = 0.47, P < 0.001\)), as shown in Figures 1 and 2. The relationship persisted after categorization of patients for hypertensive or hypercalcicuric status. Moreover, from the analysis of a subset of 743 male and 429 female normotensive calcium stone formers compared with 179 male and 292 female healthy controls from the Parma area, we also found that stone formers of both genders have higher levels of calcium excretion for each category of salt intake, as shown in Figure 3.

This relationship may be explained on the basis of renal physiology. In the renal proximal tubule, calcium handling is strongly dependent on sodium. A high dietary salt intake induces a high-sodium load to the kidney and a status of relative hypervolemia. According to the mechanisms of glomerulotubular balance, this condition diminishes the efficacy of sodium and water reabsorption in proximal tubule [39, 40]. At the same time, the reabsorption of calcium, whose handling is passively coupled with sodium and water, is less effective. Since in the distal sections of nephron calcium reabsorption is unrelated to volume status, this condition leads to higher urinary calcium excretion [41]. On the other hand, a low dietary salt intake induces relative hypovolemia, thus promoting directly sodium and indirectly calcium reabsorption in the proximal tubule, and subsequently lower calciuria.

A high level of urinary calcium is notoriously one of the main risk factors for developing kidney stones. The salt-induced rise in calciuria actually results in higher levels of urinary supersaturation indexes for calcium phosphate and uric acid, but probably not for calcium oxalate, which is by far the most common component of stones [42]. Recent hypotheses have, however, assigned a primary role to calcium phosphate supersaturation in the early phases of calcium oxalate lithogenesis [43, 44]. Moreover, excessive salt intake is associated with lower levels of the upper limit of metastability for calcium oxalate, which means that salt affects lithogenesis through different and more complex mechanisms than a simple calciuric effect [42, 45].

It should also be considered that the relationship between sodium intake and calcium excretion is influenced by hormonal factors. In fact, there are some reports demonstrating that calcium excretion is higher in postmenopausal women than in pre-menopausal women at any level of salt intake [46, 47]. Hormonal replacement therapy surprisingly seems to enhance, rather than mitigate, the calciuric effect of salt intake [48].

However, little is known on how salt intake influences the actual lithogenic risk in postmenopausal women. Salt is not the only nutrient with a calciuric effect. Animal protein intake is in fact related to calcium excretion and kidney stone risk [23, 49, 50]. There is some evidence in the literature that high-salt and high-protein diets influence urinary calcium excretion in an additive way. For example, when a subject on usual diet [8 g/day (137 mEq/day) of salt intake and 1 g/kg/day of protein intake] shifts to a high-salt diet [12 g/day (205 mEq/day)], urinary calcium increases by 50 mg/day (1.25 mmol/day), but if protein intake rises to 2 g/kg/day too, urinary calcium increases by 100 mg/day (2.5 mmol/day) [51].

Moreover, a high intake of salt has been linked to a lower urinary excretion of citrate, which is one of the main inhibitors of lithogenesis. A rise in salt intake from 2.9 to 14.5 g/day (50–248 mEq/day) resulted in a significant decrease in urinary citrate from 593 mg/day (3.14 mmol) to 476 mg/day (2.52 mmol) in a small cohort of healthy volunteers [42]. A concomitant rise in protein intake may result in a further decrease in citrate excretion, strengthening the hypothesis that salt and protein intake concur in determining a rise in lithogenic risk [51]. A diet with a high salt or protein content impairs citrate excretion by inducing a subclinical intracellular and extracellular acidosis [52]. This condition promotes the conversion of trivalent citrate\(^3^-\) to bivalent citrate\(^2^-\) in the lumen of the renal proximal tubule, with the latter form more efficiently reabsorbed by
sodium-dependent dicarboxylate transporter (NaDC-1) that cotransports $3\text{Na}^+\cdot\text{citrate}^2^\text{−}$. Moreover, acidosis promotes the institution of a luminal-cellular electrochemical gradient for citrate reabsorption because it is transformed into bicarbonate in the mitochondria of epithelial cells [53]. This mechanism is sodium chloride-specific, because some reports state that sodium bicarbonate can actually promote citrate excretion [54, 55]. This is probably one of the reasons why a recent epidemiologic study demonstrated that there is a positive correlation between sodium and citrate excretion, contradicting classical physiologic findings [56].

Salt intake can influence nephrolithiasis also indirectly, by inducing and maintaining hypertension. Salt-sensitive hypertension is the most frequent type of primary arterial hypertension, consisting in an exaggerated increment in blood pressure driven by a salt load [57]. The pathophysiology of this condition, not yet fully understood, depends on renal mechanisms, such as water retention due to the high-sodium load, and extra-renal pathways, such as a salt-induced increase in sympathetic nerve activity that underlies a complex neurohormonal interplay [58]. Both males and females with stable primary hypertension have higher levels of urinary calcium and oxalate excretion than normotensive controls without kidney stones, resulting in a 5-fold increased risk for incident nephrolithiasis after 5 years of follow-up [59]. Moreover, large epidemiological studies have demonstrated that a past history
of nephrolithiasis without hypertension is a risk factor for hypertension development [60, 61], thus suggesting that a renal damage caused by stones or by urinary stone risk factors may play an important role in hypertension development. Hypertensive kidney stone formers generally have higher calciuria [62] and urinary acid excretion [63] than normotensive stone formers, while hypertension has also been proved to be a major determinant of recurrence for stone formers [64].

As shown above, the majority of scientific evidence highlights a harmful role for salt intake in kidney stone onset. However, there are also some reports showing that in selected populations, a higher salt intake is linked to a decrease in calcium oxalate supersaturation [65] and that dietary salt supplementation may benefit calcium stone formers in some cases, by leading to a higher voluntary fluid intake [54]. It should also be noted that high salt intake, by increasing the number of molecules dissolved in urine, produce an increase in ionic strength, thus resulting in a decrease of activity of the ionic species involved in saturation [66]. This means that, at any level of calcium concentration in urine, the crystallization and precipitation of lithogenic salts is less likely when there is a high concentration of sodium chloride, which may in this way exert a protective action against nephrolithiasis. However, the precise clinical significance of these mechanisms is still uncertain and current state of art does actually support the need for a reduction of salt intake for idiopathic kidney stone prevention.

### INTERVENTIONAL STUDIES REDUCING SALT INTAKE

The first interventional study assessing the effects of dietary salt reduction on nephrolithiasis, set in 1959 by Hills et al. [67], showed that a 3.8 g/day (65 mEq/day) decrease in two healthy subjects resulted, after 4 days, in a 23 mg/day (0.58 mmol/day) reduction in calcium excretion. These findings are surprisingly very similar to those by Lin et al. [68], who, 40 years later, tested the effects of a salt intake reduction and of a Dietary Approaches to Stop Hypertension (DASH) diet approach on a larger cohort of healthy volunteers for a longer period of time (one month), although in this case it was difficult to discern the consequences of salt reduction and of fruit and vegetable increase. Salt reduction can also prevent the calciuric effect of dietary potassium depletion in a cohort of healthy volunteers [69].

A salt-reduction strategy has proven to be effective in lowering calcium excretion also in postmenopausal women [46] and in idiopathic calcium stone formers [37, 70]. The size of calciuria reduction was particularly impressive in calcium stone formers. For example, in one study, a 11.3 g/day (193 mEq/day) salt intake reduction resulted in an average of 343 mg/day (8.5 mmol/day) reduction in calcium excretion [70]. In another larger study, a 7.7 g/day (132 mEq/day) reduction in salt intake diminished calcium excretion by 109 mg/day (2.7 mmol/day) after only 3 days [37].

Another study from our research group randomized a cohort of male idiopathic stone formers prospectively followed up for 5 years to receive a low-salt low animal protein diet versus a low-calcium diet (with unrestricted salt intake), confirming that the reduction in salt intake lowers calciuria and demonstrating that the low-salt low animal protein diet is associated with a significantly lower rate of stone recurrence rate (unadjusted RR 0.49) [71]. Thus, salt reduction does not only lead to decreased calciuria, but also to an improvement in the disease course. These findings have been more recently indirectly supported by Taylor et al. [72], who found that a DASH-style diet (i.e. with low intake of sodium and high intake of fruits and vegetables) is associated with lower rates of kidney stone onset and recurrence.

However, in these studies, the effects of low salt intake are not fully discernible from the effects of other nutritional elements, such as proteins, fruits and vegetables. However, some recent research clearly demonstrates that a mere reduction in salt intake of ~8 g/day (137 mEq/day) is able to correct hypercalciuria in a hypertensive individual cohort of both genders prospectively followed up for 3 months [73]. Therefore, salt reduction alone may actually be effective in preventing kidney stone recurrence.

### CONTROVERSIAL ISSUES

It is plausible, as seen in clinical practice, that dietary salt restriction may not be effective in reducing calcium excretion in all patients, because some subjects may be unresponsive or less responsive to dietary intervention. The concepts of salt-sensitivity and -resistance are actually well established in the hypertension field. The existence of these concepts also in idiopathic calcium stone formers has not been investigated properly so far. However, there are some reports indicating that salt-sensitive hypertensive subjects exhibit higher levels of calcium excretion after a standard sodium chloride load than salt-resistant hypertensive subjects [74–76]. More recent studies carried out on animal models (Dahl rats) of salt-sensitivity and -resistance showed that the calciuric response to salt is influenced by the status of salt-sensitivity only in females [77, 78], suggesting that there may be gender-related factors influencing how the kidneys handle calcium excretion after a salt load. Actually, some human genetic markers of salt-sensitive hypertension may affect renal calcium handling [79], thus establishing a possible connection between salt-sensitivity, -resistance, hypertension and kidney stone risk.

Very few studies investigated the role of salt intake in patients with a well-established cause of hypercalciuria. In primary hyperparathyroidism, calcium excretion is generally thought to be independent from diet, because normally high levels of parathyroid hormone and subsequent hypercalciuria are sufficient to explain hypercalciuria. However, there are some data suggesting that salt intake is very important to modulate the calciuric response to high parathyroid hormone levels. For example, the comparison between a low salt intake [4.6 g/day (79 mEq/day)] and a high salt intake [11.7 g/day (200 mEq/day)] in a small cohort of subjects with primary hyperparathyroidism showed significantly lower levels of calciuria in the low-salt group [304 versus 424 mg/day (7.6 versus 10.6 mmol/day)] [80]. These findings are partially contradicted by some unpublished data from our research group, showing that a median 5 g/day (85 mEq/day) reduction in salt intake
(from an average of 10–5 g/day) in a cohort of 23 female patients with primary hyperparathyroidism awaiting for elective parathyroidectomy did not result in significant changes in calcium excretion after a median 8-week follow-up (438 ± 120 versus 413 ± 120 mg/day). Further research is, however, needed to confirm if there are behavioral factors, such as dietary salt intake, that can modulate calcium excretion in primary hyperparathyroidism.

**CONCLUSION**

Most scientific evidence suggest that excessive salt intake is associated with a higher risk for hypercalciuria and thus for idiopathic nephrolithiasis onset or recurrence. Limiting salt intake may be an effective preventive measure. However, the complex interplay between salt intake and other dietary manipulations is far from being fully understood. Moreover, few data are available on the role of salt restriction in secondary types of hypercalciuria and on the determinants of salt-sensitivity and -resistance. Further research is needed to address these issues and to raise awareness of the harmful effects of salt also in this setting of human pathology.

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