European Journal of Internal Medicine xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Review Article

The role of sodium intake in nephrolithiasis: epidemiology, pathogenesis, and future directions☆,☆☆,★

Baris Afsar [a], Murat C. Kiremit [b], Alan A. Sag [c], Kayhan Tarim [d], Omer Acar [b], Tarik Esen [b], Yalcin Solak [e], Adrian Covic [f], Mehmet Kanbay [g,*]

[a] Division of Nephrology, Department of Medicine, Konya Numune State Hospital, Konya, Turkey
[b] Department of Urology, Koc University School of Medicine, Istanbul, Turkey
[c] Division of Interventional Radiology, Department of Radiology, Koc University School of Medicine, Istanbul, Turkey
[d] Division of Nephrology, Department of Medicine, Koc University School of Medicine, Istanbul, Turkey
[e] Department of Medicine, Koc University School of Medicine, Istanbul, Turkey
[f] Department of Nephrology, Sakarya Training and Research Hospital, Sakarya, Turkey
[g] Nephrology Clinic, Dialysis and Renal Transplant Center, 'C.I. PARHON' University Hospital, and 'Grigore T. Popa' University of Medicine, Iasi, Romania

ARTICLE INFO

Article history:
Received 29 April 2016
Received in revised form 20 June 2016
Accepted 1 July 2016
Available online xxxx

Keywords:
Diet
Diet therapy
Sodium, dietary
Nephrolithiasis
Primary prevention

ABSTRACT

The prevalence of nephrolithiasis has doubled over the last decade and the incidence in females now approaches that of males. Since dietary salt is lithogenic, a purported mechanism common to both genders is excess dietary sodium intake *vis-a-vis* processed and fast foods. Nephrolithiasis has far-reaching societal implications such as impact on gross domestic product due to days lost from work (stone disease commonly affects working adults), population-wide carcinogenic diagnostic and interventional radiation exposure (kidney stone disease is typically imaged with computed tomographic imaging and treated under imaging guidance and follow-up), and rising healthcare costs (surgical treatment will be indicated for a number of these patients). Therefore, primary prevention of kidney stone disease via dietary intervention is a low-cost public health initiative with massive societal implications. This primer aims to establish baseline epidemiologic and pathophysiologic principles to guide clinicians in sodium-directed primary prevention of kidney stone disease.

1. Introduction

The incidence of kidney stone disease is rising rapidly. Prevalence has doubled [1] in just the last decade, rising from approximately 6%–11% among men, and 4%–7% among women, respectively, between 1994 and 2012. Of note, the gender gap is also closing [2], with the male/female incidence ratio shrinking from 3.4 to 1.3.

Signs point to a dietary etiology. Increased body mass index (BMI) is inversely associated with acidic urine pH [3] in men and women and leads to increased excretion of urate, sodium, ammonium, and phosphate. Obese nephrolithiasis patients have higher percentages of urate, calcium oxalate, and calcium phosphate stones [4]. Curhan *et al* [5] analyzed the Nurses' Health Study ($n = 89,376$ women) and the Health Professionals Follow-up Study (HPFS) ($n = 51,529$ men), finding that calcium oxalate stone disease was associated directly with body mass index (BMI), with a higher age-adjusted prevalence odds ratio in younger women (the population of the Nurses' Health Study). Nowfar *et al* [6] confirmed these trends using the Nationwide Inpatient Sample database. In the same study, Curhan*et al* showed that dietary calcium, but not supplemental calcium, and dietary phytate, reduced kidney stone formation. Taylor *et al.* [7] showed no link to fatty acid intake. Taylor and Curhan [8] showed no link to dietary oxalate or vitamin C [9] (which can metabolize to form oxalate). Calcium and vitamin D [10] supplements increased kidney stones as did grapefruit juice [11] while caffeinated beverages and wine reduced kidney stone incidence.

Sodium, not yet mentioned, is a wild card in the equation. For example, the BMI–nephrolithiasis link breaks down in pediatric patients; Kim *et al.* [12] found no association between BMI and pediatric kidney stones, while Kieran *et al.* [13] showed the highest prevalence of pediatric kidney stones is in the normal-BMI category. If so, then how do we explain the striking increase in pediatric nephrolithiasis [14], especially since this age group develops mainly calcium-based (not urate) stones [15] compared to adults. Dietary sodium directly increases urinary calcium excretion while BMI does not [16] and the average dietary intake of sodium increased from 200 to 3000 mg between 1970 and 2000 for this age group [17]. The pediatric patient population

☆ Authors have no conflict of interest.
☆☆ All authors approved the final version of manuscript.
★ Financial support: None.

* Corresponding author at: Koc University School of Medicine, Sariyer, Istanbul, Turkey. Tel.: +90 2122508250; fax: +90 2123454545.
E-mail addresses: mkanbay@ku.edu.tr, drkanbay@yahoo.com (M. Kanbay).

http://dx.doi.org/10.1016/j.ejim.2016.07.001
0953-6205/

studies are specific to calcium-based stones, exactly the type of stones that may be most receptive to dietary sodium intervention in adults.

Sodium is easily targeted in dietary intervention. The aforementioned examples are meant to show how wide and deep the dietary intervention literature has spanned. However, this review will serve as an in-depth primer regarding rationale for dietary sodium intervention in adult patients.

2. How does dietary sodium cause nephrolithiasis?

Crystallization of calcium-based kidney stones (calcium oxalate or calcium phosphate) occurs in supersaturated urine depleted of crystallization inhibitors. Dietary salt may lead to hypercalciuria and hypocitraturia, which are risk factors for calcium stones. Below, we summarized the effect of salt intake on urinary calcium and citrate excretion.

3. The effect of salt intake on urinary calcium and citrate excretion

Kleeman *et al*. showed that increasing dietary sodium from 19 to 419 mEq/day increased calciuria by 82% [18]. This is synergistic when combining high salt and high protein [19]. The mechanism is that high sodium intake creates a perceived hypervolemic state by the kidneys, which respond by reducing proximal tubular sodium reabsorption due to glomerulotubular balance (which is coupled to calcium reabsorption passively). The distal nephron is not able to reabsorb this high amount of calcium since in the distal sections of nephron calcium reabsorption is unrelated to volume status [20] and this may be active aggravator of calcium excretion [21]. Apart from this, modest sodium increases, including cooking salt (salt added to foods by individuals), also increase calciuria in healthy subjects [22–24]; for example, increasing dietary salt by 3.5 g (60 mEq/day) is associated with a 1.63-fold increased relative risk of hypercalciuria [25]. Patients with idiopathic kidney stones showed increased hypercalciuria (possibly genetic [26])with increased dietary salt [27,28] regardless of dietary calcium and nephrolithiasis history [28]. Patients with kidney stones have exaggerated calciuria for the same dietary salt intake [29], and fortunately, moderately low-salt diet corrects this hypercalciuria [24] and even normalizes mild oxaliuria [30]. In a slight deviation from the expected findings, Eisner *et al.* [31] showed that increased urine sodium was associated with increases in urine calcium and urine volume, but confusingly, that urine calcium oxalate was *less* supersaturated at the same time, possibly because these patients consume more fluids out of thirst. Stoller and colleagues had similar findings [32].

Urinary citrate inhibits stone formation. Moe *et al*. demonstrated that high sodium intake is associated with low urinary citrate excretion [33]. Specifically, a 5 g dietary salt increase may increase urine calcium concentration by 40 mg/day and reduce the urine citrate concentration by 50 mg/day [34]. In addition, a diet high in salt or protein content impairs citrate excretion by inducing a subclinical intracellular and extracellular acidosis [35].

Eisner *et al*. [36] showed that among stone-forming patients, high BMI was associated with increased sodium excretion despite dietary counseling to limit oral sodium intake 1 month before the 24-h urine collection. This suggests that even with counseling, overweight patients will still excrete greater amounts of sodium than non-overweight patients. Other studies also purport a link between high BMI and high urine sodium [37,38]. Fig. 1 outlines the purported relationship between salt intake and calcium output.

4. How should dietary sodium intake be measured in the clinic?

As legendary business management guru Peter Drucker once said, "If you can't measure it, you can't manage it." Unfortunately, the literature currently reflects multiple systems of dietary sodium measurement [39]. Recall bias will play a role for most patient-driven tools and the clinician should prepare for under-reporting especially since casual/discretionary salt use is almost never counted. Dietary diaries are not objective and can be difficult to employ [40] even though Rhodes *et al.* did validate diary accuracy compared to dietary recall and food-frequency questionnaires (FFQs) [41]. FFQs assess sodium intake over a longer period (thus arching over the issue of day-to-day sodium variability) [42].

However, urine collection is still the gold standard. Direct urine sodium excretion measurement reflects 90% of the ingested sodium amount [39] but has been criticized for potentially underestimating salt intake by up to 40% [43–45] and has also been criticized for potentially overestimating salt intake by up to 30% [46,47]. Patients are less likely to participate in urine collection [48] than surveys. A single spot urinalysis [49] is more practical for population-based measurement and can be used [50] to estimate 24 h urinary sodium excretion at the expense of accuracy with known diurnal variations even within the same patient [39].

We suggest that 24 h urine collection may be used as gold standard to evaluate sodium intake until there are more reliable data regarding single spot urine analysis.

5. Population-based rationale for sodium restriction

Curhan *et al* showed dietary sodium increased kidney stone risk in >90,000 healthy women (specifically, maximum RR 1.30 for a salt intake >10.3 g/day (176 mEq/day)) [51]. Sorensen *et al.* confirmed this trend in a secondary analysis of 78,293 women from the prospective WHIOS (Women's Health Initiative Observational Study) [52]. However, other large prospective have also failed to connect dietary sodium and kidney stones [19,53,54], probably due to the long observation period over which dietary salt intake was likely to change surreptitiously (for example in younger patients), and due to the use of food-frequency questionnaires, which may not always be sufficiently precise for estimating the actual salt intake [55].

Few high-quality sodium-directed dietary intervention studies exist regarding nephrolithiasis:

- Hills *et al.* (in 1959) raised the flag on dietary salt restriction epidemiology, showing that it reduced calcium excretion [56].
- Nordin *et al* [57] showed that in postmenopausal women increasing salt intake to 150 mmol raised urine calcium to 4.4 mmol, and reducing salt intake to 90 mmol reduced urine calcium to 3.1 mmol/day.

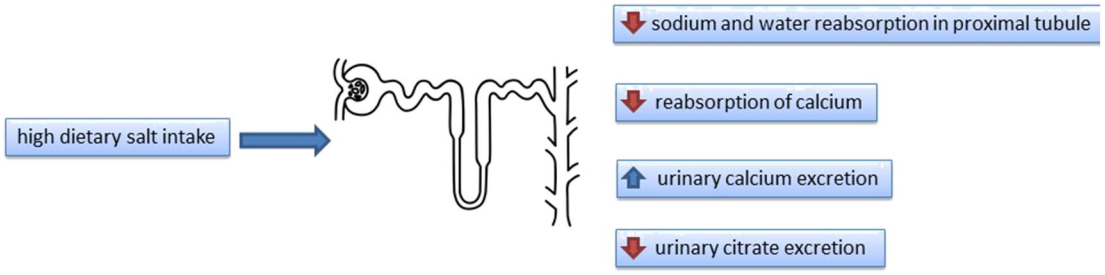

Fig. 1. The changes that occur in the nephron after excessive dietary salt intake.

Please cite this article as: Afsar B, et al, The role of sodium intake in nephrolithiasis: epidemiology, pathogenesis, and future directions, Eur J Intern Med (2016), http://dx.doi.org/10.1016/j.ejim.2016.07.001