‘Bad dietary habits’ and recurrent calcium oxalate nephrolithiasis

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Case report

A 32-year-old truck driver had previously been treated with allopurinol because of hyperuricaemia and gouty arthritis. After having first formed a kidney stone at age 20, he had passed calculi annually for 8 years before he finally underwent ESWL for bilateral radio-opaque kidney stones. The patient, whose mother had suffered from renal stones, continued to live on a self-selected diet, but considerably increased fluid intake. Three years later, after he had passed another stone, bilateral radio-opaque stones (3 stones on the right, 1 on the left side) were found on plain X-rays of the abdomen, and the patient was referred for metabolic evaluation of severe recurrent calcium stone disease.

Physical examination revealed a 32-year-old man (173 cm, 86.4 kg, body-mass index 28.9 kg/m²) with moderate hypertension (150/95 mmHg), but otherwise normal clinical findings. Laboratory analyses were as follows: values for serum creatinine, sodium, potassium, chloride, phosphate, magnesium, albumin, and venous bicarbonate were normal, and uric acid was high-normal (399 µmol/l, upper normal limit 416). Ionized calcium was 1.25 mmol/l, intact PTH 19 pg/ml (normal range 10–65), and calcitriol 51 pg/ml (25–79). In a 2-h fasting urine, Ca-E was 0.043 mmol/l GF (normal ≤0.037), and pH 5.87; after 3 days of ammonium chloride loading, fasting urine pH dropped to 5.29, indicating normal urinary acidification [1]. Unfortunately, no stone analysis was available. Nevertheless, the diagnosis of recurrent calcium nephrolithiasis with idiopathic hypercalciuria, hyperoxaluria, and hypocitraturia was made, based on the presence of bilateral radio-opaque calculi and measurements of main urinary risk factors for stone disease [2,3] in two 24-h urines collected on free-choice diet (Table 1).

Excessive consumption of protein and salt, an aggravating factor for calcium nephrolithiasis [4], was identified based on measurements of urinary markers of protein and salt consumption (Table 1). Assuming steady-state conditions, daily protein consumption was calculated according to the formula

\[ U_{\text{Urea}} \times V (\text{mmol/day}) \times 0.18 ] + 13 = \text{Protein consumption (g/day)} \]

(adapted from [5]); it amounted to 108.1 g or 1.25 g/kg BW per day. The patient’s daily intake of calcium from dairy products, estimated by using a questionnaire based on tabulated data of the calcium content of dairy products typically consumed in Switzerland [6], was 1240 mg/day.

Treatment only consisted of dietary advice by a dietician who instructed the patient to reduce meat protein intake to 5–7 servings per week, to lower consumption of salt-rich foods (sausages, cheese) and not to add salt during meals. Furthermore, the patient was told to reduce intake of oxalate-rich foods and to keep fluid intake high. Within 6 months, he lost 15 kg of weight, and urine chemistries were significantly altered, as shown in Figure 1. Whereas excretion rates of oxalate, phosphate and urea were reduced by 40–50%, urinary citrate almost doubled.

Four months later, urine volume remained very high (5430 ml/day), but the patient admittedly had increased his protein consumption, which was now calculated to be 102 g/day; this was also reflected by a rise in U_Ox × V to 57.3 mmol/day. Whereas hypercalciuria (12.98 mmol/day) and hyperoxaluria (0.478 mmol/day) persisted, U_Cit × V had fallen into the low-normal range (1.94 mmol/day). The patient was told to lower meat protein intake more and to slightly reduce calcium intake from dairy products towards normal, i.e. 800 mg/day. Another 4 months later, the patient’s urine volume was still high (5800 ml/day), whereas U_Ca × V had normalized (8.76 mmol/day) as well as protein consumption, derived from U_Urea × V. It had dropped to 81 g/day; this was also reflected by a decrease in U_P × V to 46.2 mmol/day. On the other hand, U_Gly × V had increased to 2.56 mmol/day. Surprisingly, U_Ox × V was erratically high, i.e. 1.259 mmol/day. Since measurements of urinary glycollate [6] had recently become available in our hospital, glycollate excretion rate was determined in the same 24-h urine and found to be 0.371 mmol/day (normal ≤0.700 mmol/day). This pattern—low-normal urinary glycollate in the presence of

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Table 1. Urinary volume and excretion rates of urinary risk factors as well as of markers of protein and salt consumption (means of two 24-h urine collections)

<table>
<thead>
<tr>
<th>Volume (ml/day)</th>
<th>$U_{Ca} \times V$ (mmol/day)</th>
<th>$U_{Ox} \times V$ (mmol/day)</th>
<th>$U_{Cit} \times V$ (mmol/day)</th>
<th>$U_{Mg} \times V$ (mmol/day)</th>
<th>$U_{UA} \times V$ (mmol/day)</th>
<th>$U_{P} \times V$ (mmol/day)</th>
<th>$U_{Crea} \times V$ (mmol/day)</th>
<th>$U_{Na} \times V$ (mmol/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
<td>2543</td>
<td>12.69</td>
<td>0.530</td>
<td>1.41</td>
<td>5.57</td>
<td>4.495</td>
<td>64.09</td>
<td>528.4</td>
</tr>
<tr>
<td>Normal men</td>
<td>$&gt;1200$</td>
<td>$\leq9.00$</td>
<td>$\leq0.440$</td>
<td>$\geq1.70$</td>
<td>$\geq3.00$</td>
<td>$\leq5.00$</td>
<td>(Strongly diet-dependent)</td>
<td></td>
</tr>
<tr>
<td>Normal women</td>
<td>$&gt;1200$</td>
<td>$\leq8.00$</td>
<td>$\leq0.440$</td>
<td>$\geq1.90$</td>
<td>$\geq2.20$</td>
<td>$\leq4.00$</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Ca, calcium; Ox, oxalate; Cit, citrate; Mg, magnesium; UA, uric acid; P, phosphate; Crea, creatinine; Na, sodium. Normal values are based on 24-h urine collections in 103 male and 73 female healthy volunteers on free-choice diet [3].
rather severe hyperoxaluria—was consistent with hyperoxaluria of non-metabolic origin [7]. Indeed, diet history revealed that, in order to keep urine volume high during the hot summer season, the patient had inadvertently ingested up to 2.5 litres/day of ice-tea, which consists mainly of black tea, a well-known source of oxalate [8]. Shortly thereafter, the patient passed another stone, and a plain X-ray film of the abdomen revealed that one of the three calculi previously demonstrated in the right kidney had vanished. The patient once more was seen by the dietician.

In a patient with highly active stone disease and positive family history for kidney stones, other factors such as abnormal macromolecular modifiers of crystal aggregation have to be considered [9]. Therefore, Tamm–Horsfall glycoprotein (THP), a major modifier of crystal aggregation in urine [10], was isolated from the patient’s 24-h urine [11]. Compared with control conditions in vitro (no THP, 5 mM calcium, 200 mM sodium chloride and pH 5.7) which signify zero percent inhibition of crystal aggregation, THP from eight healthy male controls at 40 mg/l inhibited aggregation of calcium oxalate crystals by 26.5±9.1% (mean±SE) [11]; the patient’s THP, however, inhibited by −18.8%, indicating promotion of crystal aggregation [11]. At the same physicochemical conditions, intrinsic viscosity of healthy controls was 123±33 ml/g (mean±SE) [11]; the patient’s THP, however, had a viscosity of 209 ml/g, indicating structural alterations of THP molecules [10,11].

The patient adheres to a high fluid intake and reduced consumption of meat protein and salt, while trying to avoid oxalate-rich foods and consuming sufficient calcium from dairy products. He has been stone-free for almost 6 years.

**Discussion**

It is generally agreed that elaborate metabolic evaluation should be recommended in patients with recurrent calcium nephrolithiasis, such as in the present case [12]. In order to obtain an adequate metabolic profile in an ambulatory setting, it appears that three 24-h urine collections under original conditions of stone formation, i.e. on free-choice diet, provide more diagnostic accuracy than one or two, and that the diagnostic yield is highest 4–6 months after a stone event [3]. Among the acknowledged urinary risk factors for recurrent idiopathic calcium nephrolithiasis, hypercalciuria (39% of cases) is the most frequent one, followed by hyperoxaluria and low urine volume (32% each), hypocitraturia (29%), hyperuricosuria (23%) and hypomagnesuria (19%) [3].

The question arises whether or not these urinary abnormalities directly cause calcium stone disease. It has been known for many years that the volume of calcium oxalate crystals in freshly voided urines from stone formers as well as the severity of stone disease do not correlate with urinary calcium excretion, but strongly depend on urinary oxalate [13]. Indeed, for physicochemical reasons outlined elsewhere [14], small increases in urinary oxalate concentration are much more important than relatively large increases in calcium for raising the level of urine supersaturation with calcium oxalate and therefore the risk of calcium stone formation.

**Hypercalciuria**

Even after several decades of studies on idiopathic hypercalciuria (IHC) and renal stone formation, a recent review only stated that ‘hypercalciuria could cause or contribute to calcium stone formation’ [15]. Many studies have addressed the issue of the pathogenesis of IHC itself, and evidence has been gathered for increased intestinal absorption of calcium, due to inadequately elevated serum levels of 1,25(OH)2 vitamin D3 (calcitriol), as the primary cause of IHC (reviewed in [16]). Thus, a low-calcium diet appeared to be a straightforward strategy. However, no prospective trial has ever established the efficacy of such a regimen with respect to stone recurrence [17], and evidence has been presented that a low-calcium diet prescribed for years predisposes to osteopenia [18,19].

As in our patient, overconsumption of meat protein as well as high salt intake are often associated with IHC [4]. Whereas excess sodium intake directly lowers renal tubular calcium reabsorption [20], the link between high meat protein intake and IHC as well as the fact that calcium renal stone formers appear to be hypersensitive to the hypercalciuric action of increased protein intake [21] are not entirely clear. It has been suggested that excess meat protein consumption induces an increased endogenous acid production and thus raises urinary net acid excretion; the latter might then inhibit calcium reabsorption along the distal nephron and subsequently stimulate bone resorption and intestinal calcium absorption [4]. We did not, however, find evidence for increased bone turnover in renal stone formers with IHC on free-choice diet [19]. On the other hand, chronic overconsumption of meat protein might increase renal mass and thereby the number of 1α-hydroxylase-producing cells, which might additionally upregulate calcitriol production. Indeed, it has been demonstrated that renal mass was increased in male hypercalciuric calcium stone formers in comparison with normocalciuric stone formers whose protein intake was lower, and that serum calcitriol was positively related to renal mass [22].

The observed rise in calcitriol activity in patients with IHC might diminish renal tubular reabsorption of calcium by direct suppression of PTH production [23]. Indeed, at equal levels of blood ionized calcium, 30 male calcium stone formers with IHC had lower levels of intact PTH (25.3±1.8 pg/ml) than their 31 normocalciuric counterparts (31.4±1.8 pg/ml, P=0.017) whose calcitriol levels tended to be lower (47.3±2.9 pg/ml vs 52.8±3.2 pg/ml in IHC, NS) [19]; the calcitriol/PTH ratio as an index of calcitriol upregulation was 2.53±0.29 in stone formers with IHC,
higher than in normocalciurics (1.66 ± 0.15, \(P=0.001\) vs IHC) [19]. Our present patient fitted exactly into this pattern of relative hypoparathyroidism [19]: whereas intact PTH level was low-normal (19 pg/ml), serum calcitriol concentration amounted to 51 pg/ml, and calcitriol/PTH ratio was high (2.68).

**Hyperoxaluria**

Normally, only 10–15% of urinary oxalate is derived directly from the diet, the remainder coming from endogeneous production [7]. On the one hand, ascorbic acid is metabolized to oxalate; this is probably not of clinical significance, since recent studies suggest that daily amounts of up to 4 g of ascorbic acid may be ingested without significantly increasing urinary oxalate [7]. On the other hand, Robertson [4] has emphasized that overconsumption of meat protein increases metabolic production of oxalate from precursors such as hydroxyproline and tryptophan. Indeed, positive correlations between oxalate as well as glycollate, a metabolic precursor of oxalate, with urinary markers of protein intake have been described [7]. Excess meat protein consumption in certain patients could therefore be responsible for what has been named ‘mild metabolic hyperoxaluria’ [24]: in a subset of recurrent calcium stone formers, urinary excretion rates of oxalate as well as of glycollate are moderately increased; in some of these patients, remission may be obtained by pyridoxine therapy [24]. It remains to be seen whether or not ‘mild metabolic hyperoxaluria’ represents an incomplete form of primary hyperoxaluria [7]. Unfortunately measurements of urinary glycollate initially were not available in our patient; nevertheless the 50% reduction in \(U_{\text{Ox}} \times V\) upon lowering protein intake (Figure 1) strongly suggests that excess meat protein may have been a causative factor for hyperoxaluria.

Incidentally, our patient also illustrates the second possibility whereby hyperoxaluria may occur, i.e. increased intestinal absorption of oxalate leading to non-metabolic hyperoxaluria. In our case, the latter occurred several months after oxaluria had normalized upon reducing meat protein intake and was due to excess consumption of oxalate-rich black tea (ice-tea). The non-metabolic origin of hyperoxaluria was emphasized by the fact that urinary glycollate excretion rate was low-normal in the presence of severe hyperoxaluria.

Excess oxalate consumption, however, is certainly not the only cause of hyperoxaluria of non-metabolic origin. More often, patients who have been advised a low-calcium diet exhibit non-metabolic hyperoxaluria, since intestinal oxalate absorption increases as a consequence of insufficient oxalate binding by the reduced amount of calcium available in the intestinal lumen [8]. This mechanism probably accounts for the fact that secondary increases in urinary oxalate excretion on a low-calcium diet have been observed by several authors (reviewed in [7]) and that a large prospective trial recently demonstrated increasing rates of \(de novo\) stone formation with decreasing daily calcium consumption [25]. Further evidence that increasing calcium intake reduces urinary oxalate comes from a preliminary study in healthy male controls, where we demonstrated that daily ingestion of 2220 mg of oxalate (about 20-fold normal) together with 1200 mg of calcium (normal) induced severe hyperoxaluria, whereas subjects remained normo-oxaluric when challenged with the large amount of 3840 mg of calcium together with the otherwise unchanged diet [26].

Finally, one always has to look for secondary hyperoxaluria in stone patients with intestinal malabsorption due to inflammatory bowel disease (with or without bowel resection) and after jejunoileal bypass surgery (reviewed in [7]).

**Hypocitraturia**

Citrate retards rates of crystallization by two means [27]: on the one hand, by complexing calcium, it reduces concentration of ionized calcium and thus urinary supersaturation of calcium oxalate and calcium phosphate; on the other hand, citrate binds to surfaces of calcium-containing crystals, thereby inhibiting crystal growth and aggregation.

Urinary citrate excretion is largely affected by variations in acid–base status [1,27]. Metabolic alkalosis increases the rate of urinary citrate excretion, whereas metabolic acidosis lowers urinary citrate, because cytosolic acidification increases citrate uptake by proximal tubular cells [1]. Thus, intracellular rather than systemic acid–base variations are the denominators of urinary citrate excretion.

As demonstrated by our patient, the amount of dietary acid may greatly modulate urinary citrate excretion rate. After considerably reducing meat protein intake, the patient’s citraturia doubled (Figure 1).
Indeed, by the acid load that it conveys, excess meat protein intake significantly lowers urinary citrate excretion, thereby contributing to reduced inhibition of aggregation of calcium oxalate crystals [28]. On the other hand, citraturia positively relates to net gastrointestinal absorption of alkali [27] and to the intake of a main source of alkali, i.e. vegetable fibres [1]. Usually, low alkali consumption and/or excess intake of meat protein only induce severe hypocitraturia if they are superimposed on a state of relative acid retention such as incomplete renal tubular acidosis. Indeed, the latter was significantly more frequent in a series of calcium renal stone formers with low-normal citruria or hypocitruria (91%) than in those with normocitruria (26%) [1]. After a 3-day loading with ammonium chloride (0.95 mEq/kg/day, divided into three doses taken 20 min. before meals), fasting urine pH normally falls below 5.32, while venous bicarbonate remains at > 20.5 mmol/l [1]; these criteria were marginally fulfilled by the present patient (urine pH lowered to 5.29).

### Idiopathic calcium nephrolithiasis—simply due to ‘bad eating habits’?

‘Bad eating habits’ with meat protein overconsumption, may induce hypercalciuria, hyperoxaluria, hypocitraturia, and hyperuricosuria [4], but do not always lead to calcium renal stone formation and are very often found in people who never form stones [29]. Therefore, other factors such as abnormal macromolecular modifiers of crystal aggregation [9] have to be considered in cases with extremely high disease activity and positive family history for kidney stones, as in the patient under discussion. In an important study almost 20 years ago, Robertson et al. [30] demonstrated that under identical conditions of oral oxalate loading, urines of patients with accelerated calcium nephrolithiasis contained larger calcium oxalate crystals than healthy controls, and that crystals were often fused into large polycrystalline aggregates. Whereas numerous tiny microcrystals normally form in human urine, the occurrence of large polycrystalline aggregates is the most important feature which distinguishes recurrent calcium renal stone formers from healthy people [9]. Since urinary macromolecules appear to be major modifiers of crystal aggregation in human urine [9], the question arises whether structural and functional abnormalities of macromolecules in recurrent stone formers might be responsible for exaggerated crystal aggregation and subsequent stone formation.

Among the various macromolecules present in human urine [31], Tamm–Horsfall glycoprotein (THP) has gained attention for the following reasons: (1) it is the most abundant protein normally excreted in human urine [10]; (2) THP molecules exhibit peculiar properties, allowing for inhibition or promotion of crystallization processes, depending on physicochemical solution conditions [10]; and (3) studies by at least three groups [11,32,33] have provided evidence that recurrent calcium renal stone formers may excrete structurally abnormal THP molecules.

Available studies indicate a structure–function relationship, i.e. the specific properties of THP directly affect its function as a modifier of calcium oxalate crystallization processes [10]. It appears that—when studied at the very same physicochemical conditions as normal THP—abnormal stone former THP molecules have an increased tendency to self-aggregate into viscous, gel-like fibres which act like a glue and allow for crystals to aggregate; this abnormality is likely to be inherited [10]. In vitro studies indicate that hypercalciuria as well as hypocitraturia might directly affect structure and function of THP molecules with respect to aggregation of calcium oxalate crystals [11]. With rising calcium concentrations, THPs from severely recurrent calcium renal stone formers exhibit marked increases in intrinsic viscosities and start to promote crystal aggregation, whereas normal THPs have lower viscosities and act as aggregation inhibitors [11]. When the concentration of ionized calcium drops due to
chelation formation with citrate, however, viscosities of these abnormal stone former THPs return to normal, and the proteins inhibit crystal aggregation as much as normal THPs do [11]. Figure 2 (unpublished data) depicts calcium oxalate crystals produced from a highly supersaturated solution (calcium 5 mM, oxalate 0.5 mM) in the presence of 30 mg/l of stone former THP alone, where crystals are more aggregated with longer diameters (Figure 2a) than in presence of the same THP together with 3.5 mM of citrate (Figure 2b).

Altogether, the present case illustrates that environmental factors such as ‘bad eating habits’ are most unlikely to account fully for recurrent calcium nephrolithiasis. Highly active renal stone formation only occurs by the interplay of pre-existing (acquired or inherited) abnormalities of urinary macromolecules with alterations of the chemical composition of urine (such as hypercalciuria or hypocitraturia). Since the latter, however, are strongly influenced by dietary habits, the advice of a ‘common-sense diet’ (Table 2) remains a cornerstone in the treatment of patients with idiopathic calcium nephrolithiasis.

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References