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Characteristic clinical and biochemical profile of recurrent
calcium-oxalate nephrolithiasis in patients with metabolic syndrome

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Abstract

Background. Metabolic syndrome is a risk factor for nephrolithiasis. This study was performed to evaluate the clinical and biochemical profile of calcium-oxalate nephrolithiasis in stone formers with metabolic syndrome.

Methods. A total of 526 recurrent stone formers, 184 of them with metabolic syndrome, and 214 controls were examined on a free diet and after a sodium-restricted diet (sodium intake <100 mmol/24 h).

Results. On free diet, stone formers with metabolic syndrome showed higher sodium excretion [mean (95% confidence interval), 196 (176–218) vs 160 (150–168) mmol/24 h; P < 0.01] and lower citrate excretion [2.23 (1.99–2.58) vs 2.84 (2.51–3.17) mmol/24 h; P < 0.01] compared to controls, whereas stone formers without metabolic syndrome showed higher calcium and oxalate excretion [5.43 (5.01–5.82) vs 3.58 (2.84–4.19) and 0.34 (0.32–0.36) vs 0.26 (0.20–0.31) mmol/24 h for calcium and oxalate, respectively; P < 0.01] and lower citrate excretion [2.18 (1.98–2.38) vs 2.84 (2.51–3.17) mmol/24 h; P < 0.01] compared to controls. The ion activity product of urinary calcium-oxalate salts was similar between stone formers with and without metabolic syndrome [1.41 (1.31–1.59) vs 1.40 (1.35–1.45); P > 0.05]. After the test diet, this index was lower in diet-compliant stone formers with metabolic syndrome compared to diet-compliant stone formers without metabolic syndrome [1.15 (1.01–1.21) vs 1.39 (1.31–1.45); P < 0.01].
Conclusions. The biochemical profiles and responses to the sodium-restricted diet were significantly different between stone formers with metabolic syndrome and those without. Dietary habits play a central role in the pathogenesis of nephrolithiasis in stone formers with metabolic syndrome.

Keywords: calcium-oxalate nephrolithiasis; ion activity product; metabolic syndrome; sodium intake; sodium-restricted diet

Introduction

Metabolic syndrome (MetS) is a constellation of highly interrelated risk factors carrying an increased risk of atherosclerotic cardiovascular disease, type 2 diabetes mellitus and all-cause mortality [1]. There is general consensus that the major components of MetS are obesity, hypertension and disorders of carbohydrate and lipid metabolism [2]. MetS has also been recognized as a risk factor for chronic kidney disease, including nephrolithiasis (NL) [3–6]. A relationship has also been demonstrated between constitutive traits of MetS (specifically, hypertension, obesity, diabetes and insulin resistance) and the occurrence of NL and/or the urinary excretion of biochemical risk factors for NL (e.g. calcium, oxalate, citrate and uric acid) [7–15]. The primary outcome of this study was a comparison of the clinical and biochemical profiles of recurrent calcium-oxalate stone formers with MetS to those of recurrent calcium-oxalate stone formers without MetS and to those of healthy controls. We also evaluated the changes in these profiles induced by a 7-day metabolic diet containing a normal amount of calcium and a reduced amount of sodium. The data are clinically relevant, considering that calcium-oxalate salts constitute the vast majority of all kidney stones passed or removed in the adult population worldwide [16] and that the proposed diet is currently recommended for the prevention of NL recurrence [17]. The study was conducted in southern Italy, a region featuring a high prevalence of NL compared with most other Italian and European regions [18].

Materials and methods

We examined 526 unrelated Caucasian patients with recurrent calcium-oxalate NL (male:female ratio, 266:260; mean age, 42.1 years (95% confidence interval 38.1–49.6); body mass index, 27.1 kg/m² (25.1–30.2)) who were referred to the Department of Clinical and Experimental Medicine of Federico II University, Naples, Italy, between 1 January 2002 and 31 December 2007. All patients reported the elimination or removal of two or more calcium-oxalate stones on different occasions over the preceding 4 years. Stones were analysed using Fourier transform infrared spectroscopy and high-resolution X-ray diffraction. Stones with a calcium oxalate content >70% and a calcium apatite content <5% were considered calcium-oxalate stones [19]. During the same period, 214 unrelated control subjects without any history of NL were enrolled. Patients and controls were born and lived in southern Italy and gave written informed consent before entering the study, which was conducted according to the Declaration of Helsinki. The study protocol received the approval of the local ethical committee.

In the general Italian population, the number of subjects affected by NL is almost 1 000 000, with a prevalence of 17.2/1000 [20]. Among such patients, the prevalence of recurrent calcium-oxalate stone formers ranges between 30 and 40% [20–22]. Based on these epidemiological data, we estimated using a sample size calculator (http://www.epicentro.iss.it/stumenti/SampleSize.asp) that the patients enrolled in our study were representative of recurrent calcium-oxalate stone formers living in Italy, with a margin of error of 5% and a confidence level of 95%.

Exclusion criteria for stone formers and controls included the following: uric acid and creatinine. Biochemical parameters were measured again after 3 days of adaptation so that urinary values reach constant levels [26]. We categorized patients as compliant or non-compliant with the sodium-restricted diet on the basis of a reduction in urinary sodium excretion and dietary sodium intake able to induce a significant reduction in the long-term risk of cardiovascular events according to the Trials of Hypertension Prevention I study [27] and/or urinary sodium excretion equal to or lower than the suggested dietary sodium intake. Thus, after the test diet, subjects showing a reduction in urinary sodium excretion ≥44 mmol/24 h, corresponding to a difference in sodium dietary intake ≥2.6 g/24 h, and/or those with urinary sodium excretion ≤100 mmol/24 h were defined as diet compliant. Patients showing no reduction in urinary sodium excretion ≤10 mmol/24 h were defined as non-diet compliant.

Upon enrolment, the height and weight of each enrolled subject were measured at 09:00, and the body mass index (BMI) was calculated. Blood pressure (BP) was measured three times while the subjects were seated, and the last two measurements were averaged for analysis. A fasting urine specimen was also collected 3 h after primary void, and its pH was determined using a commercial pH meter. Afterward, 24-h urine collections were obtained according to Tiselius and co-workers [28] and analysed for pH and calcium, magnesium, phosphate, sodium, potassium, chloride, citrate, creatinine, oxalate, urate and cystine contents. Fasting venous blood samples were taken for the measurement of serum glucose, triglycerides, HDL cholesterol, total calcium, magnesium, phosphate, chloride, sodium, potassium, intact parathormone (iPTH), 25(OH)D3, 1,25(OH)2D3, uric acid and creatinine. Biochemical parameters were measured again after the 7-day sodium-restricted diet. The determination of biochemical parameters was performed as previously described [29].

Diagnosis of MetS was made in subjects who fulfilled at least three of the following criteria: (i) waist circumference ≥102 cm in men or ≥88 cm in women; (ii) serum triglycerides ≥1.7 mmol/L or current drug treatment for hypertriglyceridaemia; (iii) serum HDL cholesterol ≤1.03 mmol/L in men or ≤1.3 mmol/L in women; (iv) untreated blood pressure ≥150/95 mmHg or treated blood pressure ≥140/90 mmHg; (v) current diuretic and/or β-blockers and/or thiazide diuretics and/or angiotensin-converting enzyme inhibitors, glucocorticoids or oestrogens. None of the stone formers or controls had been diagnosed with rickets during childhood, and none had abnormal height or bone deformity as an adult.

All enrolled subjects were examined (i) on a free diet and (ii) after a 100 mmol/day sodium-restricted diet containing 1000 mg/day calcium, 900 mg/day phosphorus, 300 g/day carbohydrates, 57 g/day fat and 70 g/day protein (a total of 2000 kcal/day) for 7 days. As previously described, a metabolic steady state is reached after 3 days of adaptation so that urinary values reach constant levels [26]. We categorized patients as compliant or non-compliant with the sodium-restricted diet on the basis of a reduction in urinary sodium excretion and dietary sodium intake able to induce a significant reduction in the long-term risk of cardiovascular events according to the Trials of Hypertension Prevention I study [27] and/or urinary sodium excretion equal to or lower than the suggested dietary sodium intake. Thus, after the test diet, subjects showing a reduction in urinary sodium excretion ≥44 mmol/24 h, corresponding to a difference in sodium dietary intake ≥2.6 g/24 h, and/or those with urinary sodium excretion ≤100 mmol/24 h were defined as diet compliant. Patients showing no reduction in urinary sodium excretion ≤10 mmol/24 h were defined as non-diet compliant.

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A fixed-sequence questionnaire, previously validated and aimed at detecting personal and family histories of upper urinary tract stones, was administered to all participants [30]. For each enrolled subject, we also estimated the NL family history score, a continuous variable based on the comparison of the number of observed or reported NL events with the expected number of events [31,32]. The NL family history score for the jth family was calculated as follows: $T_j = (2E_{ij} \cdot \Sigma E_{ijk} - \Sigma F_{ijk})/\sqrt{[\Sigma F_{ijk} (1 - E_{ij})]}$, where $T_j$ is the family history score for family i, $O_{ij}$ is the observed NL status for the jth member of the family $i$ (0 or 1) and $E_{ij}$ is the expected risk for NL for the jth member of the family i. This risk was estimated as $E_{ij} = 1 - \exp[-2iD_{i,k} \Delta t / \mu_i]$, where $k$ is the age group, $D_{i,k}$ is the disease incidence in the $i$th age group and $\Delta t$ is the age interval. A negative NL family history score indicates that a family contains fewer members with NL than would be expected, whereas a positive value indicates that it contains more. We set the NL family history score of families with a negative value to zero [31,32].

The ion activity product of calcium-oxalate salts in urine (APCaOx index) was evaluated using the formula ($4 \times \text{calcium}^{2+} \times \text{oxalate}^{-2}$...
Serum parameters

SF with MetS | SF without MetS | Controls
---|---|---
Creatinine (mmol/L) | 85.8 (79.6–92.8) | 78.7 (78.9–81.3) | 81.3 (78.7–90.1)
Sodium (mmol/L) | 140.0 (139.2–140.3) | 139.8 (139.6–140.2) | 139.9 (139.6–140.2)
Potassium (mmol/L) | 4.38 (4.29–4.84) | 4.53 (4.15–4.91) | 4.45 (4.25–4.89)
Calcium (mmol/L) | 2.41 (2.35–2.46) | 2.38 (2.34–2.42) | 2.37 (2.30–2.42)
Phosphate (mmol/L) | 1.07 (1.03–1.12) | 1.09 (1.05–1.13) | 1.12 (1.07–1.17)
Magnesium (mmol/L) | 0.82 (0.78–0.85) | 0.81 (0.79–0.82) | 0.82 (0.78–0.85)
Intact PTH (pmol/L) | 4.69 (4.06–5.32) | 3.99 (3.59–4.43) | 3.89 (3.69–4.19)
1,25(OH)2D3 (nmol/L) | 72.5 (59.8–86.2) | 82.8 (69.6–95.8) | 89.3 (63.4–93.1)

 Urinary parameters

SF with MetS | SF without MetS | Controls
---|---|---
Volume (L/24 h) | 1.96 (1.76–2.16)* | 1.37 (1.20–1.62) | 1.51 (1.42–1.68)
Fasting pH | 5.6 (5.2–5.8) | 5.4 (5.2–5.7) | 5.3 (5.1–5.6)
24-h urinary pH | 5.5 (5.2–5.7) | 5.5 (5.3–5.7) | 5.5 (5.3–5.6)
Calcium (mmol/24 h) | 6.43 (5.35–7.51)* | 5.43 (5.01–5.82)** | 5.38 (2.84–4.19)
Magnesium (mmol/24 h) | 3.58 (2.35–3.90) | 3.61 (3.39–4.08) | 4.21 (3.51–5.09)
Phosphate (mmol/24 h) | 24.6 (22.2–27.0) | 23.1 (21.9–24.4) | 23.0 (15.2–30.8)
Citrate (mmol/24 h) | 2.23 (1.99–2.58)** | 2.18 (1.98–2.38)** | 2.84 (2.51–3.17)
Sodium (mmol/24 h) | 196 (176–218)* | 165 (155–174) | 160 (150–168)
Oxalate (mmol/24 h) | 0.43 (0.34–0.49)* | 0.34 (0.32–0.36)** | 0.26 (0.20–0.31)
Body mass index (kg/m2) | 32.4 (27.8–37.0) | 27.6 (26.1–29.1) | 27.6 (17.5–37.7)
APCaOx index | 1.41 (1.13–1.59)** | 1.40 (1.35–1.45)** | 1.63 (0.53–0.73)

SF: recurrent calcium-oxalate stone formers. MetS: metabolic syndrome. MetS diagnosis was performed according to AHA/NHLBI criteria [2]. AP-CaOx index: ion activity product of calcium oxalate salts in urine [33]. Data are expressed as means (95% confidence intervals). Analysis of variance with the Bonferroni correction for multiple comparisons was used for inter-group comparisons.

*P < 0.05 vs SF without MetS and controls; **P < 0.05 vs SF without MetS; ***P <0.05 vs SF without MetS and controls; ****P <0.05 vs SF with MetS and controls.
Sodium intake, metabolic syndrome and nephrolithiasis

The biochemical profile of diet-compliant subjects is presented in Table 3. According to the criteria described above, after the 7-day test diet, 42 stone formers with MetS...
Table 3. Urinary parameters after the 7-day test diet in diet-compliant stone formers and controls

<table>
<thead>
<tr>
<th>Parameter</th>
<th>SF with MetS (42)</th>
<th>SF without MetS (57)</th>
<th>Controls (46)</th>
</tr>
</thead>
<tbody>
<tr>
<td>After test diet</td>
<td>Mean (95% CI)</td>
<td>Δ (95% CI)</td>
<td>Mean (95% CI)</td>
</tr>
<tr>
<td>Sodium (mmol/24 h)</td>
<td>142 (130–151)*</td>
<td>−56 (52–61)</td>
<td>115 (105–127)</td>
</tr>
<tr>
<td>Volume (L/24 h)</td>
<td>1.56 (1.49–1.62)*</td>
<td>−0.28 (0.25–0.31)*</td>
<td>1.29 (1.20–1.36)</td>
</tr>
<tr>
<td>Calcium (mmol/24 h)</td>
<td>5.38 (5.09–5.49)**</td>
<td>−1.11 (1.07–1.15)*</td>
<td>5.17 (5.01–5.38)**</td>
</tr>
<tr>
<td>Citrate (mmol/24 h)</td>
<td>2.16 (2.07–2.26)**</td>
<td>−0.03 (0.02–0.04)</td>
<td>2.11 (1.98–2.25)**</td>
</tr>
<tr>
<td>Oxalate (mmol/24 h)</td>
<td>0.32 (0.28–0.36)**</td>
<td>−0.09 (0.07–0.10)*</td>
<td>0.33 (0.29–0.36)**</td>
</tr>
<tr>
<td>Magnesium (mmol/24 h)</td>
<td>3.44 (3.06–3.99)</td>
<td>−0.07 (0.05–0.09)</td>
<td>3.61 (3.18–3.95)</td>
</tr>
<tr>
<td>Urate (mmol/24 h)</td>
<td>3.01 (2.82–3.20)*</td>
<td>−0.30 (0.24–0.34)*</td>
<td>2.51 (2.31–2.70)</td>
</tr>
<tr>
<td>APCAox index</td>
<td>1.15 (1.10–1.21)**</td>
<td>−0.29 (0.25–0.32)*</td>
<td>1.39 (1.31–1.45)**</td>
</tr>
</tbody>
</table>

Test diet composition: 100 mmol/day sodium, 1000 mg/day calcium, 900 mg/day phosphorus, 300 g/day carbohydrates, 57 g/day fat and 70 g/day protein (a total of 2000 kcal/day). Diet compliance was defined as a reduction in 24-h urinary sodium excretion of at least 44 mmol after the 7-day test diet and/or a sodium urinary excretion equal to or lower than the suggested sodium dietary intake. SF: recurrent calcium-oxalate stone formers. MetS: metabolic syndrome [2]. CI: confidence interval. APCAox index: ion activity product of calcium oxalate salts in urine [33]. Analysis of variance with the Bonferroni correction for multiple comparisons was used for inter-group comparisons.

*P < 0.05 vs SF without MetS and controls; **P<0.05 vs SF with MetS and controls; ***P < 0.05 vs controls. Data in bold were significantly different compared to baseline parameters on a free diet by Student’s t-test for paired variables; a P-value <0.05 was considered statistically significant.

![Graph](https://example.com/graph.png)

**Fig. 3.** Ion activity product of calcium oxalate salts in urine (APCaOx index) before and after the 7-day test diet in stone formers with metabolic syndrome (MetS), divided according to diet compliance. Stone formers with MetS were considered diet compliant when they showed a reduction in urinary sodium excretion of at least 44 mmol/24 h and/or a sodium urinary excretion equal to or lower than the suggested sodium dietary intake after the test diet (squares) and non-compliant when they showed a urinary sodium excretion lower than 10 mmol/24 h after the test diet (circles). The two subgroups of stone formers with MetS were age-, sex-, and BMI-matched and had similar APCAox indices on a free diet. Test diet composition: 100 mmol/day sodium, 1000 mg/day calcium, 900 mg/day phosphorus, 300 g/day carbohydrates, 57 g/day fat and 70 g/day protein (a total of 2000 kcal/day).
variance with what was observed on a free diet [APCaOx index on a free diet, 1.45 (1.36–1.62) vs 1.45 (1.37–1.60) for stone formers with and without MetS, respectively; P = 0.97]. The between-group difference in APCaOx index after the test diet remained upon logistic regression analysis after correction for age, gender and BMI (P = 0.01). No significant differences were observed after the 7-day diet in the other biochemical parameters measured but not reported in Table 3.

Comparison of the effects of the test diet in compliant and non-compliant stone formers with MetS (Figure 3)

We further compared the APCaOx index in 15 diet-compliant stone formers with MetS and 15 age-, gender- and BMI-matched non-diet-compliant stone formers with MetS. On a free diet, the two subgroups showed the same APCaOx indices [1.44 (1.39–1.49) vs 1.44 (1.39–1.49); P = 0.89]. After the test diet, the diet-compliant patients showed an APCaOx index significantly lower than that of their non-diet-compliant counterparts [1.37 (1.32–1.43) vs 1.14 (1.10–1.19); P < 0.01].

Discussion

MetS and NL are common disorders determined by the interaction of genetic, environmental and hormonal factors. Both are highly prevalent in the adult population of economically developed countries and are characterized by high morbidity rates if not adequately identified and treated [1–4,34,35]. In the last few years, epidemiological and clinical studies have unravelled the pathophysiological links between these two clinical conditions [3–6]. In the present study, we analysed the clinical and biochemical profile of NL in recurrent calcium-oxalate stone formers with MetS and compared this profile to those observed in recurrent calcium-oxalate stone formers without MetS and in controls without NL history.

Stone formers with MetS were older and showed a lower NL family history score compared to stone formers without MetS. Despite their higher mean age at the time of the first manifestation of NL, they suffered a greater number of NL episodes. Moreover, as depicted in Figure 1, the biochemical profiles of the two groups of stone formers on a free diet displayed important differences: stone formers with MetS showed levels of 24-h urinary excretion of sodium and citrate that were significantly different from controls, whereas stone formers without MetS showed significant differences in 24-h urinary excretion of calcium, citrate and oxalate, as compared to controls. These data suggest a different balance between genetic susceptibility and acquired metabolic and nutritional factors in the pathogenesis of NL in the two groups of patients. In particular, the elevated urinary sodium excretion characterizing subjects with MetS appears to play a major role in the pathogenesis of calcium-oxalate NL in this setting. This contention is supported by the different correlation between APCaOx index and urinary sodium excretion occurring in stone formers with or without MetS and by the biochemical response observed in the two stone former groups after the low-sodium test diet. In fact, a direct correlation between APCaOx index and urinary sodium excretion was evident in both stone former groups. Moreover, the data depicted in Figure 2 clearly demonstrate that stone formers with MetS had lower APCaOx indices than stone formers without MetS for each level of 24-h urinary sodium excretion. The similar APCaOx indices measured on a free diet in the two stone former groups could thus be explained by the higher sodium excretion characterizing stone formers with MetS. According to this consideration, after the low-sodium test diet, the APCaOx index decreased in both stone former groups, but this reduction was significantly higher in diet-compliant stone formers with MetS. In particular, the reduced sodium intake caused a significant reduction in calcium and oxalate urinary excretions in diet-compliant stone formers with MetS, which manifested in an APCaOx index significantly lower than that of stone formers without MetS after the low-sodium test diet. Further confirmation of our hypothesis was obtained when the effect of the test diet on APCaOx index was evaluated in two subgroups of patients with MetS (i.e. diet-compliant and non-diet-compliant patients) matched for age, gender and BMI (Figure 3).

Dietary habits of patients are the major environmental risk factor for both NL and MetS and play a central role in causing the high urinary sodium excretion that characterizes subjects with MetS [36–45]. The self-reported dietary intake of total calories, carbohydrates, lipids and protein, reported in Table 1, was similar to those reported in previous studies regarding subjects with and without MetS from Italy [46]. One intriguing hypothesis is that the unfavourable effects of high dietary sodium intake on susceptibility to renal stone formation may be amplified in presence of MetS. This observation is in accord with previous reports describing alterations in renal tubular sodium handling associated with abdominal adiposity, insulin resistance and high blood pressure, potentially leading to hypercalciuria [13,47–53]. The difference in the slopes of the equations that describe the relationship between 24-h urinary sodium excretion and APCaOx index in the two cohorts of stone formers (with and without MetS) may support this hypothesis, but additional experimental studies are needed.

Experimental and clinical data indicate that the intestinal absorption and the renal excretion of calcium and oxalate, two major determinants of the APCaOx index, are significantly influenced by dietary intake and tubular handling of sodium. A higher amount of sodium in the diet could favour the formation of easily absorbable sodium oxalate in the gut, thus increasing the filtered load of oxalate to the kidney; in parallel, the greater filtered load of sodium tends to decrease tubular calcium reabsorption, thus increasing the supersaturation of calcium oxalate in the urine [54–61]. The clinical observation that a diet with lower sodium content was highly effective in the prevention of kidney stone recurrence is in keeping with these concepts [17,62].

Two further pieces of data should be emphasized. Reduced urinary citrate excretion is the only metabolic risk factor related to NL in both stone former groups, confirming its primary role in NL pathogenesis [16,20,45].
male-to-female ratio in our study cohort is also in agreement with the increased prevalence of NL in women observed in more recent epidemiological surveys [63,64].

Moreover, there was no difference in either fasting or 24-h urine pH between our study populations. These data contradict those reported by Maalouf and colleagues who observed a lower pH in obese stone formers, with a direct linear correlation between urine pH and weight [65]. However, it is necessary to highlight that our study populations were enrolled base on inclusion and exclusion criteria which were different to those reported by Maalouf and colleagues [65], as previously extensively detailed. In addition, all patients enrolled lived in southern Italy and had different dietary habits from the population of stone formers examined by Maalouf and colleagues, who reported a significant impact of dietary habits on their results [65].

The strengths of our study include the relatively large sample size and the recruitment of selected patients with recurrent calcium-oxalate NL living in a restricted geographical area and similar origins and lifestyles. The evaluation of all the major serum and urinary biochemical factors relevant to kidney stone formation in the same patients on a free diet and after a 7-day test diet allows us to rule out the influence of anthropometric parameters on the observed results. One limitation of this study is the limited follow-up of the enrolled subjects, which did not allow us to evaluate the long-term effect of the test diet on the examined biochemical parameters.

In summary, the novel findings of the present study include the following: (i) the demonstration that recurrent calcium-oxalate stone formers with MetS have clinical and biochemical NL features significantly different from those observed in calcium-oxalate stone formers without MetS, (ii) urinary supersaturation of calcium-oxalate salts appears to be dependent on the elevated dietary sodium intake in patients with MetS and (iii) in these patients, a reduction in sodium intake is associated with a substantial reduction in the APcAox index. These results may have a large clinical impact and practical relevance, given both the high prevalence of MetS and calcium-oxalate NL in economically developed countries and excessive sodium intake worldwide.

Conflict of interest statement. None declared.

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Sodium intake, metabolic syndrome and nephrolithiasis 2263


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