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 (1.10–1.21) 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 diseases, 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 kidney stones passed or removed in the adult population with a margin of error of 5% and a confidence level of 95%.

Exclusion criteria for stone formers and controls included the following: urinary tract infections, primary or secondary hyperparathyroidism, cystinuria ≥70 μmol/24 h, renal tubular acidosis (defined as fasting urinary pH ≥6, hypokalaemia and positive urinary net charge [23]), hyperuricosuria, creatinine clearance ≤0.75 ml/min/1.73 m² for women or ≤0.85 ml/min/1.73 m² for men, chronic diarrhoea, gouty diathesis [24], dietary or medical treatment for NL [25] and intake of diuretics, 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 a reduction in urinary sodium excretion ≤10 mmol/24 h were defined as non-diet compliant.

Upon enrolment, the weight and height 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 parathyrophin (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 or drug treatment for low HDL cholesterol, (iv) systolic BP ≥130 mmHg and/or diastolic BP ≥85 mmHg or current antihypertensive drug treatment in a patient with a history of hypertension and (v) fasting serum glucose ≥5.6 mmol/L or drug treatment for elevated blood glucose [30].

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 i-th family was calculated as follows: \( T_i = \left( \frac{\text{NL}_i - \text{Ei}}{\text{Ei}} \right) \times \text{sqrt}(\text{2} \times \text{Ei}) \), where \( T_i \) is the family history score for family i, \( \text{O_i} \) is the observed NL status for the i-th member of the family i (0 for 0 or 1) and \( \text{E_i} \) is the expected risk for NL for the i-th member of the family i. This risk was estimated as \( \text{E_i} = 1 - \exp(-2 \times \text{ID}_i \times \Delta_i) \), where k is the age group, ID is the age density in the k-th age group and \( \Delta_i \) 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 \( (4 \times \text{calcium}^{2+} \times \text{oxalate}/\text{mol/L})^{1/2} \).
Table 1. Clinical characteristics of recurrent calcium-oxalate stone formers with or without metabolic syndrome and controls

<table>
<thead>
<tr>
<th>Parameter</th>
<th>SF with MetS</th>
<th>SF without MetS</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>184</td>
<td>342</td>
<td>214</td>
</tr>
<tr>
<td>Male/female ratio</td>
<td>81:103*</td>
<td>185:157</td>
<td>111:103</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>47.4 (43.6–50.2)**</td>
<td>39.3 (37.3–41.4)</td>
<td>40.7 (38.1–42.1)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>30.4 (29.1–31.6)**</td>
<td>25.2 (24.5–26.1)</td>
<td>26.1 (24.8–27.8)</td>
</tr>
<tr>
<td>Age at onset of NL (years)</td>
<td>37.1 (33.2–41.0)*</td>
<td>29.3 (27.5–31.2)</td>
<td></td>
</tr>
<tr>
<td>Number of NL episodes</td>
<td>7.7 (6.2–9.1)*</td>
<td>4.8 (4.1–5.5)</td>
<td></td>
</tr>
<tr>
<td>NL-FHS</td>
<td>0.97 (0.15–1.89)</td>
<td>1.87 (0.94–2.75)***</td>
<td>0.65 (0.15–1.05)</td>
</tr>
</tbody>
</table>

SF: recurrent calcium-oxalate stone formers. MetS: metabolic syndrome. MetS diagnosis was performed according to AHA/NHLBI criteria [2]. NL-FHS: nephrolithiasis family history score [31,32]. To estimate the daily intake of total calories, carbohydrates, fat and protein on a free diet, a food-frequency questionnaire was administered to all participants at enrolment (http://www.olivettiheartstudy.org/databankmaterials.asp). Data are expressed as means (95% confidence intervals). Analysis of variance was performed using the Statistical Package for Social Science (SPSS)-13 statistical package (SPSS Inc., Chicago, IL, USA).

Table 2. Biochemical parameters of recurrent calcium-oxalate stone formers with or without metabolic syndrome and controls on a free diet

<table>
<thead>
<tr>
<th>Parameter</th>
<th>SF with MetS</th>
<th>SF without MetS</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum parameters</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine (mmol/L)</td>
<td>85.8 (79.6–92.8)</td>
<td>78.7 (78.9–81.3)</td>
<td>81.3 (78.7–90.1)</td>
</tr>
<tr>
<td>Sodium (mmol/L)</td>
<td>140.0 (139.2–140.3)</td>
<td>139.8 (139.6–140.2)</td>
<td>139.9 (139.6–140.2)</td>
</tr>
<tr>
<td>Potassium (mmol/L)</td>
<td>4.38 (4.29–4.84)</td>
<td>4.53 (4.15–4.91)</td>
<td>4.45 (4.25–4.89)</td>
</tr>
<tr>
<td>Calcium (mmol/L)</td>
<td>2.41 (2.35–2.46)</td>
<td>2.38 (2.34–2.42)</td>
<td>2.37 (2.30–2.42)</td>
</tr>
<tr>
<td>Phosphate (mmol/L)</td>
<td>1.07 (1.03–1.12)</td>
<td>1.09 (1.05–1.13)</td>
<td>1.12 (1.07–1.17)</td>
</tr>
<tr>
<td>Magnesium (mmol/L)</td>
<td>0.82 (0.78–0.85)</td>
<td>0.81 (0.79–0.82)</td>
<td>0.82 (0.78–0.85)</td>
</tr>
<tr>
<td>Intact PTH (pmol/L)</td>
<td>4.69 (4.06–5.32)</td>
<td>3.99 (3.59–4.43)</td>
<td>3.89 (3.69–5.10)</td>
</tr>
<tr>
<td>25(OH)D3 (nmol/L)</td>
<td>72.5 (59.8–86.2)</td>
<td>82.8 (69.6–95.8)</td>
<td>89.3 (63.4–93.1)</td>
</tr>
<tr>
<td>1,25(OH)2D3 (pmol/L)</td>
<td>89.8 (75.4–104.4)</td>
<td>99.8 (82.1–113.1)</td>
<td>97.9 (82.8–112.6)</td>
</tr>
</tbody>
</table>

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.

Results

Characteristics of study population at enrolment

One hundred and eighty-four stone formers (35%) were diagnosed with MetS, whereas none of the controls received this diagnosis. As shown in Table 1, stone formers with MetS were older and heavier than stone formers without MetS.
Sodium intake, metabolic syndrome and nephrolithiasis

Fig. 1. Comparison of clinical and biochemical parameters significantly related to the occurrence of calcium-oxalate nephrolithiasis in recurrent stone formers with MetS (open triangles) and in those without MetS (open diamonds). Two separate models of logistic regression analysis were used to compare stone formers with MetS and controls (first model) and stone formers without MetS and controls (second model).

Only biochemical and clinical parameters found to be significantly different by univariate analysis of stone formers with MetS and controls and stone formers without MetS and controls were considered in the first and second model, respectively. Data are expressed as odds ratios (95% confidence intervals). Variables listed in bold were significantly associated with the occurrence of calcium-oxalate nephrolithiasis in recurrent stone formers with MetS and/or in those without MetS.

without MetS and controls (P < 0.01 for each). The female sex was significantly overrepresented in stone formers with MetS compared to those without MetS (P < 0.02). Stone formers with MetS had a higher age at onset of NL (P < 0.01); however, they suffered a greater number of NL episodes than stone formers without MetS (P < 0.01). These results were confirmed after adjustment for age, BMI and gender (P < 0.01). On the other hand, stone formers without MetS had a higher NL family history score compared to both stone formers with MetS and controls (P < 0.01). Using food-frequency questionnaires, stone formers with MetS reported a daily dietary intake of total calories moderately higher than that reported by stone formers without MetS and controls. The self-reported daily intakes of carbohydrate, fat and protein, expressed as percentage values, were not different between study groups and were similar to those found in the metabolic test diet proposed for longitudinal evaluation of enrolled subjects.

The biochemical profiles obtained on a free diet for the three study groups are reported in Table 2. By univariate analysis, stone formers with MetS showed higher 24-h urinary volumes as well as higher 24-h urinary excretion of calcium, sodium, oxalate and urate compared to both stone formers without MetS and controls; they also showed lower urinary citrate excretion than controls. The urinary excretion of calcium and oxalate by stone formers without MetS fell between that of stone formers with MetS and that of controls. As expected, both groups of stone formers showed higher APCaOx indices than controls (P < 0.01 for each).

A model of logistic regression analysis restricted to stone formers with MetS and controls indicated that age [1.05 (1.02–1.09)] and 24-h urinary excretion of sodium [1.21 (1.10–1.30)] and citrate [0.64 (0.22–0.81)] were each independently associated with the occurrence of NL, accounting for gender, BMI, 24-h urinary volume and 24-h urinary excretion of calcium, oxalate and urate. A similar analysis restricted to stone formers without MetS and controls indicated 24-h urinary excretion of calcium [1.24 (1.08–1.52)], citrate [0.65 (0.23–0.84)] and oxalate [1.25 (1.10–1.48)] as factors significantly associated with the occurrence of NL in stone formers without MetS, again accounting for age, BMI, gender, 24-h urinary volume and 24-h urinary excretion of sodium and urate. A comparison between these two models of logistic regression analysis is depicted in Figure 1.

In all study populations, we observed a direct relationship between 24-h urinary sodium excretion and ion activity product of calcium-oxalate salts in urine (APCaOx index) in recurrent calcium-oxalate stone formers with metabolic syndrome (MetS) (triangle; fit line: solid line; linear regression equation: y = 76.375x + 87.708), recurrent calcium-oxalate stone formers without MetS (rhombus; fit line: dotted line; linear regression equation: y = 53.668x + 104.27) and controls (star; fit line: dot-dashed line; linear regression equation: y = 14.421x + 133.83).

Biochemical parameters in diet-compliant subjects

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.

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-diet 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). [22.8%; 17 males; mean age, 45.9 years (44.6–47.2); BMI, 30.7 kg/m² (29.7–31.7)], 57 stone formers without MetS [16.6%; 30 males; mean age, 40.5 years (38.8–41.9); BMI, 26.2 kg/m² (25.6–27.5)] and 46 controls [21.5%; mean age, 41.5 years (38.9–42.7); BMI, 26.4 kg/m² (25.2–27.6)] were considered ‘diet compliant’. On a free diet, these three subgroups had clinical and biochemical profiles similar to those observed in the respective groups of origin. On the test diet, 24-h urinary sodium excretion was reduced to a similar extent in each of the three subgroups. The reduction in 24-h urinary sodium excretion was associated with a significant decrease in 24-h urinary volume and 24-h calcium excretion in all subgroups (P < 0.01 vs baseline in all cases). The absolute reductions in 24-h urinary volume and 24-h calcium excretion were significantly higher in stone formers with MetS compared to the other two subgroups (P < 0.01 for each). As a consequence, after the test diet, the two stone former subgroups showed similar 24-h calcium excretion levels, in contrast with what was observed on a free diet [urinary calcium excretion on free diet, 6.49 (5.39–7.44) vs 5.49 (5.10–5.89)mmol/24 h for stone formers with MetS and those without MetS, respectively, P < 0.01].

Furthermore, the test diet caused a significant reduction in 24-h urinary oxalate excretion compared to baseline values only in stone formers with MetS (P < 0.02), filling again the gap with stone formers without MetS. After the test diet, the APCaOx index was significantly reduced in both stone former subgroups (P < 0.02 vs baseline), but the absolute reduction in APCaOx index was significantly higher in stone formers with MetS compared to that observed in stone formers without MetS (P < 0.01). As a consequence, after the test diet, the mean APCaOx value in stone formers with MetS was significantly lower compared to that of stone formers without MetS, again at
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 formers 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]. The
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 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 permits 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


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