RELATIONS BETWEEN OXALIC ACID, CALCIUM, MAGNESIUM AND CREATININE EXCRETION IN NORMAL MEN AND MALE PATIENTS WITH CALCIUM OXALATE KIDNEY STONES

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SUMMARY

1. The daily excretion of oxalate, calcium, magnesium and creatinine was determined in fifty-two normal men and sixty-five male patients with calcium oxalate-containing renal stones.

2. Direct relationships were found between calcium and oxalate excretion, magnesium and oxalate excretion and calcium and magnesium excretion in both normal subjects and stone-formers. The significance of these relationships is discussed.

3. The mean excretion of calcium and oxalate was significantly higher in the stone-formers, compared with the controls, both calcium and oxalate excretion being raised by about 20%.

4. The effect of oral ingestion of glucose and casein on the rate of excretion of calcium, magnesium, oxalate and phosphate was examined. Glucose increased the rate of calcium and magnesium excretion but had no effect on oxalate excretion and suppressed phosphate excretion. Casein also increased calcium excretion but had little or no effect on magnesium or oxalate excretion, and it increased phosphate excretion.

5. The association of high calcium excretion with high oxalate excretion, in both normal subjects and stone-formers, results in a high degree of supersaturation of the urine with respect to calcium oxalate. The implication of these findings with respect to the cause and treatment of calcium oxalate stones is discussed.

Key words: urinary calculi, urine, oxalates, calcium, magnesium, creatine.

It is now widely accepted that calcium excretion is increased in a high proportion of patients with calcium oxalate-containing kidney stones but there is less agreement regarding the excretion of oxalate. Some workers have reported that oxalate excretion is within normal limits (Albuquerque & Tuma, 1962; Mayer, Markow & Karp, 1963; Takasaki & Shimano, 1967), but most workers have found raised values (Hodgkinson, 1958; Cottet & Vittu, 1966; Elliot, 1966).

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Although many studies have been made of the urinary excretion of calcium and its relationship to other variables, such as age, sex, body weight and creatinine excretion, few comparable studies have been made in relation to oxalate excretion, an exception being the study of Gibbs & Watts (1969) on the variation of urinary oxalate excretion with age. We drew attention in an earlier review (Hodgkinson & Zarembski, 1968) to a direct relationship which appeared to exist between the urinary excretion of oxalic acid and calcium in normal subjects and in most patients with renal calculi. This observation has now been confirmed in a detailed study in which oxalate excretion by normal subjects and stone-formers has been compared and related to age, body weight and the urinary excretion of calcium, magnesium and creatinine. Several statistically significant relationships were observed and some possible explanations for these are discussed.

SUBJECTS AND METHODS

Observations were made on fifty-two normal men who were members of the laboratory staff and whose ages ranged from 23 to 61 years, with a mean age of 34.6 years, and on sixty-five male patients with recurring idiopathic calcium oxalate-containing renal stones whose ages ranged from 24 to 71 years, with a mean value of 45.6 years. Patients with primary hyperoxaluria or ileal dysfunction were excluded. Twenty-two of the patients (34%) had stones consisting predominantly of calcium oxalate. The remaining patients had stones containing varying proportions of calcium oxalate and calcium phosphate. Patients with stones consisting predominantly of calcium phosphate were excluded.

Single, 24 h urine collections were made while the subjects were following their normal daily activity and eating a diet of their own choice. Urine was collected in polythene containers to which had been added 1 ml of 0.35 mol/l (20 g/100 ml) chlorhexidine hydrochloride (Hibitane). The volume of the urine sample was measured and after determining the pH, conc. HCl was added (1 ml/100 ml of urine) to dissolve any crystals of calcium salts that might be present. Urine collections for shorter periods were made without the addition of Hibitane but the samples were acidified with HCl as described above. The acidified samples were analysed immediately or stored at −18°C for 1–2 days before analysis.

Oxalic acid was determined colorimetrically with chromotropic acid after separation from urine by co-precipitation with calcium sulphate and reduction to glycollic acid with zinc (Hodgkinson & Williams, 1972). This method, which is specific for oxalic acid, gave values ranging from 0.19 to 0.48 mmol/24 h (17–43 mg/24 h) in twelve normal men on free diets.

Urinary calculi were analysed by quantitative chemical analysis (Hodgkinson, 1971). Calcium and creatinine were determined by automatic colorimetry (Technicon AutoAnalyzer Methods N-3b and N-11b respectively). Magnesium was determined by atomic absorption spectrophotometry with a model SP90 atomic absorption spectrophotometer (Pye Unicam Ltd, Cambridge, U.K.).

RESULTS

Urinary excretion of oxalic acid by normal men and male patients with calcium oxalate-containing renal stones

The distribution of daily urine oxalate values for the fifty-two normal men is shown in Fig.
Urine oxalic acid

The distribution of urine oxalate values appeared to be Gaussian and this was confirmed by probit analysis. When the cumulative percentage frequency distribution was plotted on an arithmetical probability scale the curve was linear over most of its range (Fig. 2a). However, there was a slight deviation at higher values, indicating an excess of subjects with high urine oxalates. The probit curve for the patients was similar, but less steep, and was displaced to the right, indicating that excretion by the patients tended to be higher and more variable than that of the controls. The difference in mean oxalate excretion between normal subjects and stone-formers was highly significant (see Table 2), and this difference persisted if the two patients with exceptionally high oxalate values were omitted (\(P<0.001\)).

Relationships between oxalate excretion and various other parameters

No significant relationship was found between oxalate excretion and the age of the subject, either in normal men or patients with stones (Table 1). A relationship which was just significant (\(P<0.05\)) was observed between oxalate excretion and body weight in the normal subjects but not in the patients. There was, however, a highly significant relationship (\(P<0.001\)) between oxalate and creatinine excretion in both the normal subjects and the patients. There was no
significant relationship between the creatinine excretion and the age of the subjects in either normal individuals or stone-formers but there was a highly significant relationship \((P < 0.001)\) between creatinine excretion and body weight.

The relationship between oxalate and calcium excretion was of particular interest in the present context, a direct correlation being found which was significant for both the normal men \((P < 0.01)\) and the patients \((P < 0.05)\) (Fig. 3). The possibility that this was a spurious relationship caused by incomplete urine collections or by differences in body weight or creatinine was tested by relating the ratios oxalate/creatinine to calcium/creatinine; this resulted in a still closer relationship \((P < 0.001)\). A similar direct relationship was observed between oxalate and magnesium, the correlation being significant both in the normal subjects \((P < 0.01)\) and in the patients \((P < 0.001)\). In this case, however, the degree of correlation was slightly reduced when the values were expressed in terms of creatinine, though the relationships were still significant in both the normal subjects \((P < 0.02)\) and stone-formers \((P < 0.001)\).

Magnesium excretion showed a significant inverse relationship to age in the normal subjects \((P < 0.02)\) but there was no significant relationship in the patients, and the correlation observed in the normal subjects was abolished when magnesium was expressed as a ratio to creatinine. There was no significant relationship between magnesium excretion and body weight in either group nor between magnesium excretion and creatinine, except in the patients, where there

![Cumulative percentage frequency distribution of urine oxalate values plotted against arithmetical probability.](image) Fig. 2. Cumulative percentage frequency distribution of urine oxalate values plotted against arithmetical probability. ○, Control subjects; ■, stone-formers.
appeared to be a direct correlation \((P<0.01)\). Magnesium and calcium excretion appeared to be significantly correlated, both in the normal men \((P<0.05)\) and in the patients \((P<0.001)\).

There was no significant relationship between calcium excretion and age or body weight. Similarly there was no significant relationship between calcium and creatinine excretion except in the patients, where there appeared to be a direct relationship which was significant at the 2% level. Creatinine excretion was not related to age in either group but there was a close correlation between creatinine excretion and body weight in both groups \((P<0.001)\).

**Effect of oral glucose and casein on the urinary excretion of calcium, magnesium and oxalate**

The possibility that the positive correlation between calcium, magnesium and oxalate excretion might be due, in part, to the ingestion of carbohydrate or protein was investigated. The effect of carbohydrate was examined by administering \(0.56 \text{ mol} (100 \text{ g})\) of glucose orally to a normal male subject who had fasted from 6 p.m. on the day before the test. The ingestion of

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**Table 1. Degree of correlation between oxalate and calcium excretion and other variables. n.s. = not significant.**

<table>
<thead>
<tr>
<th>Description of variables</th>
<th>Normal subjects</th>
<th>Stone-formers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>(r)</td>
</tr>
<tr>
<td>Oxalate (mmol/24 h): age (years)</td>
<td>52</td>
<td>0.04</td>
</tr>
<tr>
<td>Oxalate (mmol/24 h): body wt. (kg)</td>
<td>52</td>
<td>0.31</td>
</tr>
<tr>
<td>Oxalate (mmol/24 h): creatinine (mmol/24 h)</td>
<td>52</td>
<td>0.48</td>
</tr>
<tr>
<td>Oxalate (mmol/24 h): calcium (mmol/24 h)</td>
<td>52</td>
<td>0.44</td>
</tr>
<tr>
<td>Creatinine (mmol/24 h): calcium (mmol/24 h)</td>
<td>52</td>
<td>0.45</td>
</tr>
<tr>
<td>Creatinine (mmol/24 h): creatinine (mmol/24 h)</td>
<td>28</td>
<td>0.49</td>
</tr>
<tr>
<td>Creatinine (mmol/24 h): magnesium (mmol/24 h)</td>
<td>28</td>
<td>0.43</td>
</tr>
<tr>
<td>Calcium (mmol/24 h): age (years)</td>
<td>28</td>
<td>-0.45</td>
</tr>
<tr>
<td>Calcium (mmol/24 h): body wt. (kg)</td>
<td>28</td>
<td>-0.28</td>
</tr>
<tr>
<td>Calcium (mmol/24 h): creatinine (mmol/24 h)</td>
<td>28</td>
<td>0.06</td>
</tr>
<tr>
<td>Calcium (mmol/24 h): magnesium (mmol/24 h)</td>
<td>28</td>
<td>0.19</td>
</tr>
<tr>
<td>Calcium (mmol/24 h): creatinine (mmol/24 h)</td>
<td>28</td>
<td>0.40</td>
</tr>
<tr>
<td>Creatinine (mmol/24 h): calcium (mmol/24 h)</td>
<td>28</td>
<td>0.41</td>
</tr>
<tr>
<td>Creatinine (mmol/24 h): creatinine (mmol/24 h)</td>
<td>52</td>
<td>0.02</td>
</tr>
<tr>
<td>Creatinine (mmol/24 h): body wt. (kg)</td>
<td>52</td>
<td>0.22</td>
</tr>
<tr>
<td>Creatinine (mmol/24 h): magnesium (mmol/24 h)</td>
<td>52</td>
<td>0.14</td>
</tr>
</tbody>
</table>

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*Urine oxalic acid*
FIG. 3. Relation between daily excretion of calcium and oxalate. (a) Control subjects; (b) stone-formers.

FIG. 4. Effect of ingesting 0.55 mmol (100 g) of glucose on the rates of urinary excretion of calcium, magnesium, oxalate and phosphate. ■, Control (fasting) values; ●, experimental values. Arrows denote time of dose.
Urine oxalic acid

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glucose resulted in a rapid increase in the rate of excretion of calcium and magnesium (Fig. 4) but there was no detectable effect upon the rate of excretion of oxalate when compared with a control day when the subject fasted for the whole period of the experiment. It may be noted that phosphate excretion appeared to be suppressed by the ingestion of glucose.

The effect of an isocaloric quantity of casein (100 g) was examined in the same subject and showed a comparable increase in the rate of excretion of calcium but little or no effect on the rates of excretion of magnesium and oxalate. In contrast, the excretion of phosphate increased about five times after an initial delay (Fig. 5).

![Graphs showing the effect of ingesting 100 g of casein on the rates of urinary excretion of calcium, magnesium, oxalate and phosphate.](image)

**Fig. 5.** Effect of ingesting 100 g of casein on the rates of urinary excretion of calcium, magnesium, oxalate and phosphate. ■, Control (fasting) values; ○, experimental values. Arrows denote time of dose.

Comparison of oxalic acid, creatinine, calcium and magnesium excretion by normal subjects and patients with renal calculus

As mentioned earlier, the mean daily excretion of oxalic acid by normal men was 0.35 mmol (31.7 mg), significantly less than the mean value of 0.42 mmol (38.1 mg) in the patients with renal calculus. There was also a highly significant difference in oxalate excretion when this was expressed in relation to creatinine, the value of \( t \) being increased from 4.43 to 6.46. This
increase may be due to the mean creatinine excretion being slightly lower in the stone-formers than in the controls though this difference was not statistically significant.

The mean excretion of calcium was likewise significantly higher in the stone-formers compared with the controls and this difference was further emphasized by expressing calcium excretion in relation to creatinine, the $t$ value being increased from 3.72 to 4.88 (Table 2). The

TABLE 2. Comparison of oxalate excretion and other variables between normal subjects and stone-formers.

<table>
<thead>
<tr>
<th></th>
<th>Normal subjects</th>
<th>Stone-formers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>Mean</td>
</tr>
<tr>
<td>Oxalic acid (mmol/24 h)</td>
<td>52</td>
<td>0.35</td>
</tr>
<tr>
<td>(31.7)</td>
<td></td>
<td>(8.26)</td>
</tr>
<tr>
<td>Oxalic acid (mmol/24 h)</td>
<td>52</td>
<td>0.017</td>
</tr>
<tr>
<td>Creatinine (mmol/24 h)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium (mmol/24 h)</td>
<td>52</td>
<td>6.32</td>
</tr>
<tr>
<td>(253)</td>
<td></td>
<td>(103)</td>
</tr>
<tr>
<td>Calcium (mmol/24 h)</td>
<td>52</td>
<td>0.141</td>
</tr>
<tr>
<td>Creatinine (mmol/24 h)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Magnesium (mmol/24 h)</td>
<td>28</td>
<td>5.59</td>
</tr>
<tr>
<td>(136)</td>
<td></td>
<td>(45.8)</td>
</tr>
<tr>
<td>Magnesium (mmol/24 h)</td>
<td>28</td>
<td>0.076</td>
</tr>
<tr>
<td>Creatinine (mmol/24 h)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body wt. (kg)</td>
<td>52</td>
<td>74.2</td>
</tr>
<tr>
<td>Urine volume (ml)</td>
<td>52</td>
<td>1824</td>
</tr>
<tr>
<td>Creatinine (mmol/24 h)</td>
<td>52</td>
<td>16.12</td>
</tr>
<tr>
<td>(182)</td>
<td></td>
<td>(316)</td>
</tr>
</tbody>
</table>

mean daily excretion of oxalate by the stone-formers was 20.2% higher than the mean value for the control subjects, and the mean daily calcium excretion was 22.5% higher in the patients compared with the controls.

In contrast, magnesium excretion was lower in the stone-formers than in the control subjects ($P<0.01$), the mean value for the normal subjects being 5.6 mmol (136 mg)/24 h, compared with 4.6 mmol (111 mg)/24 h in the stone-formers. This difference persisted when magnesium excretion was expressed as a ratio to creatinine but the value of $t$ was slightly reduced.

DISCUSSION

The almost linear form of the cumulative percentage frequency distribution of urinary oxalate, when plotted on a probability scale (Fig. 2), suggests that the distribution of urine oxalate values for normal adult men on a free diet is Gaussian but with a small excess of high values. Robertson & Morgan (1972) reported similar results for calcium excretion, except that the
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probit transformation showed a distortion at the lower end of the frequency distribution, implying a deficiency of low values rather than an excess of high values. The reason for this apparent difference between calcium and oxalate is not clear.

There appeared to be no significant variation of oxalate excretion with age in our adult subjects (Table I), a result which agrees with the findings of Gibbs & Watts (1969). There was also no close relationship between oxalate excretion and body weight but oxalate and creatinine excretion were closely correlated. However, the significance of this relationship is not yet clear.

The direct relationship between oxalate and calcium excretion does not appear to be due to incomplete urine collections or to differences in body weight since the degree of correlation between these two variables was increased when the data were expressed in terms of creatinine excretion. These observations apply also to the direct relationships between the ratios oxalate/magnesium and calcium/magnesium excretion (Table I). Other factors which might contribute to these relationships are variations in the diet, which was not controlled, and individual variations in the intestinal absorption or renal tubular reabsorption of calcium, magnesium and oxalate.

We have shown repeatedly that oxalate excretion is inversely related to the dietary intake of calcium (Hodgkinson, 1958; Zarembski & Hodgkinson, 1969; Marshall, Cochran & Hodgkinson, 1972a). Under normal conditions, however, variations in dietary calcium are accompanied by parallel changes in other food constituents, including oxalate, and under these circumstances calcium and oxalate excretion are directly related (Marshall et al., 1972a). However, individual variations in calcium excretion are only partly accounted for by variations in dietary calcium (Knapp, 1947; Hodgkinson & Pyrah, 1958; Davis, Morgan & Rivlin, 1970) and the available evidence suggests that differences in oxalate excretion are likewise only partially accounted for by changes in dietary oxalate (see, for example, Marshall et al., 1972a).

Other dietary constituents, notably sugar and protein, are known to increase the urinary excretion of calcium and magnesium (Thomas, Thomas, Rabussier & Desgrez, 1959; McIntosh, Carruthers & Copp, 1962; Hodgkinson & Heaton, 1965; Lindeman, Adler, Yiengst & Beard, 1967). These observations and the results illustrated in Figs. 4 and 5 suggest that variations in carbohydrate and protein intake may contribute to the direct relationship observed between calcium and magnesium excretion but there is no evidence that variations in these dietary constituents account for the direct relationships between calcium and oxalate or magnesium and oxalate excretion.

Intestinal absorption may also contribute to the positive correlations between calcium, magnesium and oxalate excretion. It is well established that the absorption of calcium is increased in subjects with idiopathic hypercalciuria (Henneman, Benedict, Forbes & Dudley, 1958; Peacock, Hodgkinson & Nordin, 1967), and the possibility that these subjects may also absorb an increased proportion of their dietary magnesium and oxalate is currently being investigated.

A third possible factor is the effect of an increased calcium load, resulting from increased intestinal absorption of calcium, on the renal tubular reabsorption of magnesium and oxalate. Thus the intravenous infusion of calcium salts results in an increased excretion of magnesium (Mendel & Benedict, 1909; Barker, Elkinton & Clark, 1959) and oxalate (Hodgkinson & Zarembski, 1968).

The observation that magnesium excretion was significantly lower in the stone-formers compared with the controls is in agreement with an earlier report by Evans, Forbes, Sutton &
Watson (1967), who found a mean daily excretion of 4.8 mmol (117 mg)/24 h in fifty-four stone-formers compared with 5.3 mmol (130 mg)/24 h in eighty-three normal subjects. The magnesium/creatinine ratio was also significantly lower in the stone-formers compared with the controls (Table 2). This difference may be due in part to differences in the mean ages of the two groups (normal subjects = 35 years; stone-formers = 45 years) since magnesium excretion appears to fall significantly with age (Dr W. G. Robertson, unpublished results). However, it is not yet clear whether this age difference accounts entirely for the observed difference in magnesium excretion between the two groups.

The tendency of calcium stone-formers to excrete increased quantities of calcium in their urine is now well recognized, but the importance of oxalate excretion is less well appreciated, probably because of the difficulties encountered in the accurate routine determination of urine oxalate. In the present study the mean calcium excretion was 22.5% higher in the stone-formers than in the control subjects, whereas oxalate excretion was 20.2% higher. These results suggest that increased oxalate excretion may be as important as increased calcium excretion in the aetiology of calcium oxalate stones.

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REFERENCES


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