Bone disease in hypercalciuria: a new form of osteodystrophy?

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Key words: bone mineral density; hypercalciuria; osteoporosis; renal stone disease; urolithiasis

Introduction

Nephrolithiasis is a common clinical disorder affecting 1–5% of the general population, with an annual incidence of 0.1–0.3% [1]. Excessive calcium excretion represents the major pathophysiological cause of kidney stones. Most of the series have shown that almost half of the patients with renal stones had idiopathic hypercalciuria as the primary metabolic alteration [2].

The excessive urinary calcium excretion, the fact that some of these patients have excessive intestinal calcium absorption and the knowledge that the majority of the stones are composed of different forms of calcium crystals, have led to a customary dietary calcium restriction. This nutritional indication has been suggested by the majority of physicians, independently of the cause of the kidney stones. However, this calcium restriction has not prevented kidney stone recurrence; on the contrary, it might have increased their incidence [3]. At the same time, calcium restriction can induce a situation of persistent negative calcium balance, with potential damage to another organ: the bone.

Bone mineral in hypercalciuria

Decreased bone mineral density has been reported in different series of patients with nephrolithiasis using different techniques, such as single or dual photon, X-ray and computerized tomography absorptiometry, radiological evaluation or in vivo neutron activation analysis. Bone histomorphometric studies in hypercalciuric patients have yielded controversial results. Some have reported increased osteoclastic resorption accompanied by decreased osteoblastic surfaces, while others, have reported reduced bone formation, increased bone resorption and a severe mineralization defect [4].

In a recent retrospective analysis of bone mineral density by dual X-ray absorptiometry, we compared a group of post-menopausal women with a previous history of kidney stones with age- and post-menopausal time-matched normal controls [5]. The women with previous kidney stones had significantly less bone mineral density at both cortical and trabecular sites.

To assess whether diminished bone mass would already be present during early stages of the disease, we analysed the bone mineral density of hypercalciuric children and normal controls, matched for gender, age and height. The hypercalciuric children demonstrated lower trabecular bone mineral density than controls [6]. The potential impact of these findings on final peak bone mass, a major determinant of adult bone mass, needs to be evaluated further prospectively.

Hypercalciuria, cause or consequence?

At this point, a question remains to be answered: is hypercalciuria the result of a primary disorder of bone metabolism, or is the decrease in bone mineralization a consequence of the negative calcium balance induced by hypercalciuria?

Studies by Pacifici et al. demonstrated that monocytes from patients with fasting hypercalciuria had an increased production of interleukin-1 (IL-1), a potent in vivo and in vitro stimulator of bone resorption [7]. These findings were not present in patients with absorptive hypercalciuria. These observations led us to examine further whether a specific fraction of the IL-1 (α or β) or other cytokines involved in bone resorption, such as IL-6 or tumour necrosis factor-α (TNF-α), may play a role in the bone resorption of hypercalciuria [8]. We examined a group of patients with recurrent renal stones with and without hypercalciuria, and normal controls matched for age, height and weight. The hypercalciuric subjects showed statistically significant lower trabecular (lumbar spine) bone mineral density than the normocalciuric or control subjects (Figure 1). It is important to mention that no difference was found in bone mineral density between
Role of the diet and the acid load

Another factor to be considered, potentially leading to increased bone turnover, consists of subtle metabolic acidosis, as a result of high dietary protein intake. This condition could lead to the release of calcium salts from bone, as calcium carbonate acts as a buffer [9]. The oral administration of potassium bicarbonate, at a dose sufficient to neutralize endogenous acid, improves calcium and phosphorus balance and reduced bone resorption in post-menopausal women [10]. The efficacy of this therapeutic manoeuvre in patients with hypercalciuria remains to be evaluated.

Genetics

We already know that idiopathic hypercalciuria can be genetically determined, and there is a known increase in intestinal vitamin D receptor number in hypercalciuric rats. Recently, Morrison et al. suggested that bone mass, a main determinant of osteoporotic fracture, has a genetic component ascribed largely to a simple allelic change in the vitamin D receptor gene [11]. These authors demonstrated that monozygotic twins show less variation in bone mass than dizygotic twins, and that the main mechanism responsible for this genetic effect is linked to polymorphism of the vitamin D receptor gene. The heredity of hypercalciuria as related to the metabolic bone alterations should also be addressed. In preliminary studies we have demonstrated that asymptomatic mothers of children with idiopathic hypercalciuria and low bone mass also have decreased bone mineral density at trabecular and cortical sites.

Effect of drugs that inhibit bone resorption

In a recent study, we examined the effect of alendronate, a bisphosphonate that inhibits bone turnover, upon calcium excretion, bone resorption markers and bone mass. Bisphosphonates are pyrophosphate analogues that bind strongly to the bone mineral, hydroxyapatite. However, the reduced osteoclastic resorption is mainly the result of inhibition of osteoclastic recruitment and osteoclastic activity on the bone surface, and by shortening the osteoclast life span [12].

A group of patients with idiopathic hypercalciuria and recurrent calcium stone formation and age- and gender-matched normocalciuric stone formers received 10 mg per day of alendronate for 1 year. Clinical characteristics, as well as gender and age distribution, were similar in both groups of patients.

It was found that in hypercalciuric subjects, urinary calcium decreased significantly at the end of the first month after alendronate, and remained lower thereafter, without reaching normal values (Table 1). Simultaneously, urinary hydroxyproline also decreased significantly after alendronate administration. Serum calcium, glomerular filtration rate and urinary sodium

Fig. 1. Bone mineral density determined at trabecular bone (lumbar spine), in normal subjects and renal stone formers with and without hypercalciuria. Bone mineral density is expressed as g/cm².

Fig. 2. Gel electrophoresis of IL-1α cDNA amplified by RT-PCR. Total RNA was extracted from unstimulated monocytes obtained from normal controls and hypercalciuric stone formers. Lane 1, IL-1α positive control; lanes 2 and 3, control subjects; lanes 4 and 5, normocalciuric subjects; and lanes 6 and 7 hypercalciuric patients.
did not change. We also found in the hypercalciuric patients that, after alendronate administration, lumbar spine bone mineral density increased significantly after 1 year without changes in femoral neck bone mineral density. On the contrary, normocalciuric subjects showed no significant changes in urinary calcium, hydroxyproline excretion or bone mineral density at trabecular or cortical sites.

Since alendronate significantly reduced calcium excretion in hypercalciuric subjects but not in normocalciurics, we can infer that bone has some relevance in the pathophysiology of the hypercalciuria. The fact that hypercalciuria did not disappear completely after alendronate treatment probably means that other factors beside bone are involved in the pathophysiology of the disease.

**Therapeutic implications**

Whether the decrease in bone mineral mass constitutes the primary event responsible for the hypercalciuria or its consequence, dietary calcium restriction in patients with hypercalciuria could have deleterious effects on bone metabolism. Dietary restriction of calcium not only fails to decrease the incidence of subsequent calcium oxalate stones, but possibly further aggravates bone mineral loss. The latter seems particularly of concern when treating children with active bone mineral accretion, and women who eventually will face menopause.

A rational approach to the treatment of patients with hypercalciuria and nephrolithiasis should include dietary restriction of sodium and protein, the use of potassium citrate as an inhibitor of calcium oxalate crystallization, and the eventual administration of thiazides or chlorothalidone for persistent hypercalciuria.

In summary, bone status has to be evaluated and followed in patients with hypercalciuria, and dietary calcium restriction in most of these subjects should be contraindicated, since this could introduce a new form of iatrogenic renal osteodystrophy.

**References**


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**Table 1. Urinary calcium excretion in hypercalciuric (n = 18) and normocalciuric (n = 8) calcium stone formers, before (month 0) and after alendronate treatment**

<table>
<thead>
<tr>
<th>Month</th>
<th>Hypercalciuria</th>
<th>Normocalciuria</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>277 ± 28</td>
<td>108 ± 9</td>
</tr>
<tr>
<td>1</td>
<td>235 ± 30*</td>
<td>129 ± 19</td>
</tr>
<tr>
<td>2</td>
<td>189 ± 23*</td>
<td>139 ± 37</td>
</tr>
<tr>
<td>3</td>
<td>210 ± 23*</td>
<td>121 ± 17</td>
</tr>
<tr>
<td>4</td>
<td>193 ± 20*</td>
<td>132 ± 49</td>
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<tr>
<td>5</td>
<td>194 ± 22*</td>
<td>139 ± 9</td>
</tr>
<tr>
<td>6</td>
<td>200 ± 17*</td>
<td>145 ± 16</td>
</tr>
<tr>
<td>7</td>
<td>210 ± 37**</td>
<td>134 ± 19</td>
</tr>
<tr>
<td>8</td>
<td>261 ± 31*</td>
<td>127 ± 28</td>
</tr>
<tr>
<td>9</td>
<td>195 ± 24*</td>
<td>146 ± 39</td>
</tr>
<tr>
<td>10</td>
<td>221 ± 47</td>
<td>144 ± 6</td>
</tr>
<tr>
<td>11</td>
<td>205 ± 36*</td>
<td>134 ± 12</td>
</tr>
<tr>
<td>12</td>
<td>202 ± 26*</td>
<td>110 ± 10</td>
</tr>
</tbody>
</table>

Urinary calcium is expressed as mg/g creatinine/day. Values shown are means ± SEM.

*P < 0.01 vs month 0; **P < 0.05 vs month 0.