Idiopathic hypercalciuria and calcium renal stone disease: our cases

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Summary

Renal idiopathic stone disease affects about 8% of the Italian population. The most common form in western countries (70-80% of the cases) is calcium nephrolithiasis, with stones formed mainly by calcium oxalate and phosphate. One of the main metabolic anomalies that is often associated with calcium nephrolithiasis is hypercalciuria. Primary hypercalciuria is a metabolic defect characterized by an increased renal calcium excretion. This metabolic alteration is present in the general population with a frequency of 5-10%, but can reach 45-50% in subjects affected by nephrolithiasis. We studied 149 patients affected by idiopathic calcium nephrolithiasis.The aim of the present study was to evaluate the association between familiarity for nephrolithiasis and hypercalciuria in this population of patients.

KEY WORDS: nephrolithiasis, hypercalciuria, stone disease.

Introduction

Primary hypercalciuria is a metabolic defect characterized by an increased renal calcium excretion, with values higher than 4 mg/kg/die or higher than 250 mg/24 h in women and 300 mg/24 h in men (1, 2) (Tab. I). This metabolic alteration is present in the general population with a frequency of 5-10% (1), but can reach 45-50% in subjects affected by nephrolithiasis (3).

Background

Calcium in human biology

The total amount of calcium in the human body varies between 1000 and 1300 grams, 99% of which is in the bone tissue, while the remaining 1% is in the intra and extra-cellular spaces. In physiological conditions, serum calcium is maintained within a narrow concentration range (8.5-10.4 mg/dl or 2.1-2.6 mmol/l). About 50% is free ionized calcium, while 10% is bound to bicarbonates, citrates, lactates and phosphates. These two fractions represent the so called "ultrafiltrable calcium". The remaining 40% is bound to plasma proteins, mainly to albumin and, to a lesser extent (5-10%), to globulins. In physiological conditions, only a fraction of the calcium binding sites on albumin are saturated, therefore the increase or decrease of the fraction of calcium bound to plasma proteins is able to buffer the effects of a rapid increase or decrease of calcemia. The hematic pH represents the most important factor able to affect the calcium binding to plasma proteins: alkalosis increases the binding, while acidosis has the opposite effect (4, 5).
Intracellular calcium is an important cation for the activation of several biological processes such as the contraction of skeletal and cardiac muscle cells, cell secretion and neuronal excitation, the regulation of membrane ion transport and signal transduction mechanisms. It takes also part in the regulation of several enzymes activities, and in cellular growth and division processes.
Calcium found in bone tissue, in addition to its structural role, represents the main supply in the organism, and it would be enough to keep normal calcemia levels for months or years if the calcium dietary intake was inadequate (4-6).
In normal subjects food is the only source of calcium for the organism. A normal-calcium diet gives approximately 700-1000 mg of calcium per day. For every gram of calcium about 800 mg are excreted with the feces and 200 mg with the urine. The amount of calcium found in the feces is represented by food calcium that has not been absorbed, plus calcium present in intestinal secretions, which is relatively constant and independent of calcemia. An adult requires a minimum daily intake of calcium of 400 mg to maintain calcium balance. If the calcium dietary intake is progressively increased, intestinal absorption also increases reaching a plateau. The link between dietary calcium and intestinal absorption is explained by the presence of different absorption mechanisms. Calcium intestinal absorption occurs both by an active transcellular saturable mechanism, and passively via a paracellular electrochemical and osmotic gradient. When endoluminal calcium concentration is high, absorption occurs mainly by a passive mechanism, while the active mechanism is particularly effective for low concentrations of the cation. Many factors regulate quantitatively calcium absorption, such as the amount of calcium in the diet, the patient's age, as well as vitamin D3 and parathyroid hormone (PTH) circulating levels (7-9).
In men, the daily amount of calcium filtered by the kidney glomerules is about 10 grams, while the amount excreted with the urine in 24 hours varies between 100 and 300 mg. This means that 98-99% of the calcium filtered by the kidney is reabsorbed at tubular level and more precisely, 60% by the proximal tubule, 20-30% by the loop of Henle, 10% by the distal convoluted tubule and 5% by the collecting duct (10).
Calcium reabsorption by the proximal tubule, descending and ascending limb of the loop of Henle is not saturable, is isotonic, and is strictly linked to the sodium reabsorption, but it is independent of PTH plasma concentration. Conversely, calcium reabsorption by the distal tubule (10%) is partially saturable, independent of sodium, dependent on serum PTH concentrations (10).

As already described, in physiological conditions, serum calcium concentration is maintained strictly constant. This regulation occurs mainly thanks to two hormones, *parathyroid hormone* (PTH) and the active form of vitamin D, $1,25(OH)_2D3$, acting mainly on the skeleton, gut and kidney. A reduction in serum ionized calcium, causes an increase in parathyroid hormone plasma concentration that restore calcemia by increasing calcium tubular reabsorption by the kidney, by stimulating osteoclastic bone resorption, thereby transferring skeletal calcium in the plasma, and finally, by stimulating renal production of active vitamin D3 that acts synergically with PTH in stimulating bone resorption via osteoclast activity and in promoting intestinal calcium reabsorption.

Primary Hypercalciuria

The link between increased calcium urinary excretion and nephrolithiasis was first described in the thirties; however, the concept of hypercalciuria was introduced only twenty years later. Hogkinson and Pyrah fixed calciuria normal values at up to 250 mg/day for women and 300 mg/day for men, or up to 4 mg/kg of body weight independently of sex and age. According to this rule, still the most used today, about 50% of the patients affected by calcium nephrolithiasis are also suffering from hypercalciuria, versus 2-5% of the healthy population (1).
According to the Pak's classification, done in the eighties, hypercalciuria syndromes are traditionally divided in three main types: *absorptive hypercalciuria*, when the elevated calcium excretion can be normalized with an hypocalcic diet or with the administration of chelants such as cellulose phosphate; *renal hypercalciuria*, characterized by high fasting calcium excretion, with the tendency to hypocalcaemia and secondary hyperparathyroidism; *resorptive hypercalciuria*, that Pack identified with the clinical picture of primary hyperparathyroidism, characterized by fasting hypercalciuria, increased bone turnover and reduced bone mineral density (11).
It later emerged that an increase in PTH production was rarely found in subjects with increased fasting calcium urinary excretion that were diagnosed with renal hypercalciuria (11). The term *fasting hypercalciuria*, or diet-independent, instead of *renal hypercalciuria* was then introduced (12).
More recently, bone densitometry studies have reported a reduction in hypercalciuric subjects bone density, with a higher prevalence of osteopenia in subjects with fasting hypercalciuria compared to subjects with normocalciuria or absorptive hypercalciuria (13, 14).
It is now well established that bone can be a primary source of hypercalciuria, not necessarily caused by primary hyperparathyroidism, although bone calcium cannot account entirely for the total urinary calcium that hypercalciuric patients eliminate in excess compared to healthy subjects.
Primary hypercalciuria syndromes are considered today as a whole of complex clinical pictures characterized by the prevalence of one metabolic alteration (absorption, renal or resorption), rather than a group of different pathologies clearly distinguishable from one another.
Therefore, primary hypercalciuria is currently classified as follows: diet-dependent or diet-independent according to fasting calcium excretion values (15) (Table I).

Hypercalciuria and nephrolithiasis

Renal idiopathic stone disease affects about 8% of the Italian population. About 35% of the patients have positive familiarity for renal lithiasis. The most common form in western countries (70-80% of the cases) is calcium nephrolithiasis, with stones formed mainly by calcium oxalate and phosphate. The causes of calcium nephrolithiasis remain largely unknown. Research shows that it is a disease with multifactorial pathogenesis, with several genetic and dietary predisposing factors (16).
The main metabolic anomalies that are often associated with calcium nephrolithiasis are: hypercalciuria, hyperoxaluria, and hypocitraturia. The causative role of these anomalies is suggested by the fact that they increase the risk of calculosis as well as being more frequent in patients with calculosis (17).
The increased calcium urinary excretion increases the risk of lithiasis via at least two known mechanisms: by increasing the saturation state of the urinary calcium salts (calcium oxalate, calcium phosphate), and by chemical bound with inhibitors (citrates) with consequent reduction in their activity (18).

Table I - Hypercalciuria: diagnostic definition.

Free diet reference values:	> 300 mg/24h ♂ > 250 mg/24h ♀ > 4 mg/kg/24h (both sexes)
Diete-independent hypercalciuria	> 0.11 mg Ca/mg Creatinine Fast urine sample
Diet-dependent hypercalciuria	< 0.11 mg Ca/mg Ceatinine Fast urine sample

Our cases

The high degree of familiarity in patients affected by nephrolithiasis highlights the importance of genetic background that has also emerged from several studies in men and animals, although validated genetic markers are not available yet, and the pathogenetical mechanisms through which the genetic alteration affect the susceptibility to the disease are not known.
The aim of the present study was to evaluate the association between familiarity for nephrolithiasis and hypercalciuria in a population of patients affected by idiopathic calcium nephrolithiasis.
We studied 149 patients affected by idiopathic calcium nephrolithiasis, 79 women and 70 men, aged between 20 and 82, that had been attending our clinic in the last 14 months and underwent metabolic screening for the disease.
Based on the results obtained, hypercalciuria was present in 43 patients (34%). The hypercalciuric patients have been divided in the following groups: a) patient with isolated hypercalciuria b) patients with hypercalciuria combined with other metabolic alterations.
We have then evaluated the prevalence of familiarity (defined as presence of the disease in at least one first degree relative) in the totality of patients affected by idiopathic calcium nephrolithiasis and in the groups of hypercalciuric patients. Results are reported in Table II, III.
The prevalence of familiarity in the whole population examined resulted to be 42.9%. This, in agreement with the literature, strengthens the hypothesis that genetic factors interact with environmental conditions in causing lithiasis. From our study it is also emerging that familial prevalence of nephrolithiasis does not change significantly between the whole population of idiopathic calcium nephrolithiasic patients and the normocalciuric and hypercalciuric subgroups of patients.
Our finding, although needs to be confirmed in a larger number of patients (currently in progress), is a further evidence of the

Table II - Familiarity prevalence in nephrolithiasic patients.

	Familiality presence	Familiality absence	Total number of patients	Familiality prevalence
Total number of patients	67	82	149	42,90%
Hypercalciuric patients	16	27	43	34,70%
Hypercalciuric patients without others metabolic defects	10	19	29	34,70%
Hypercalciuric patients with others metabolic defects	6	8	14	42,80%

Table III - Statistical report of familiarity prevalence in hypercalciuric subgroups of patients.

		Familiarity		
		Yes	No	
Hypercalciuria in total number of nephrolithiasic patients (149)	Yes	6	8	14
	No	10	19	29
p-value (X^2)= 0,23 (α=5%)		16	27	43
Metabolic defects in hypercalciuric patients (43)	Yes	16	27	43
	No	51	55	106
p-value (X^2)= 0,59 (α=5%)		67	82	149

difficulty to identify specific phenotypes for genetic investigations of nephrolithiasis.

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