Consensus statement on diagnosis of primary hypercalciuria

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Background

The first intuitions on the existence of a link between increased urinary calcium excretion and nephrolithiasis date back to the nineteen-thirties, but the concept of hypercalciuria was defined only twenty years later. Hodgkinson and Pirah defined, as normal, urinary calcium levels of up to 250 mg/day for females and 300 mg/day for males, or levels of up to 4 mg/kg body weight, regardless of sex and age. According to this criterion, the one most followed even today, approximately 50% of patients with idiopathic calcium nephrolithiasis show hypercalciuria, as opposed to 2-5% of the healthy population (1). Excess in urinary calcium excretion was originally attributed to increased intestinal cation absorption (2).
When PTH assay became available, from low to frankly elevated PTH levels were reported in hypercalciuric stone formers. The hypothesis that a primitive renal calcium leak could be responsible for the secondary hyperparathyroidism observed in some cases, lead to the definition of *renal hypercalciuria,* alongside the previously described *absorptive hypercalciuria* (3). The hypocalciuric and hypercalcemic effects of thiazide diuretics were described in 1966 and it later became widely accepted that the reduction of urinary calcium excretion induced by thiazides could have been associated to an increased calcium deposition in bone (4,5). Furthermore, epidemiological studies demonstrated a reduction of fracture risk in hypertensive patients who were taking these drugs (6).
In the first half of the 1980's, the possibility of assaying serum calcitriol confirmed most of the pathophysiologic hypotheses on hypercalciuria until so far suggested (7). Hypercalciuric syndromes were thus classified in three main categories according to Pak's classic description: (a) *hyperabsorptive hypercalciuria* when the high calcium excretion lowered to normal values while on a low-calcium diet or on a supplementation with calcium-chelating agents such as cellulose phosphate; (b) *renal hypercalciuria* characterized by elevated fasting calcium excretion, with tendency toward hypocalcemia and secondary hyperparathyroidism; and (c) *resorptive hypercalciuria* consequent to primitive parathyroid hypersecretion and characterized by fasting hypercalciuria, increased bone turnover and reduced bone mineral density (3).
In the following years however, it became evident that in patients with the so-called *renal hypercalciuria*, that is fasting hypercalciuria with normal serum calcium levels, a secondary hyperparathyroidism was rare (3). Thus, the term *fasting hypercalciuria* was suggested by some authors in place of renal hypercalciuria (8). In fact, a hypercalciuria due to primitive renal loss remains, nonetheless, a confirmed physiopathological entity, both at experimental level in mice as well as in some hereditary forms in man (9,11). This changed attitude in regard to renal hypercalciuria resolved essentially in the drastic reappraisal of its attributed role within the scope of idiopathic hypercalciuria (8).
During these same years, studies in man confirmed previous hypotheses according to which patients affected by idiopathic hypercalciuria showed, without exception, an increased intestinal absorption of calcium. However, these studies revealed that intestinal hyperabsorption of calcium per se was unable to justify hypercalciuria, because more than half of the cases studied showed a urinary calcium excretion greater than the amount absorbed (12).
Investigations performed by means of X-ray absorptiometry reported, albeit with significant controversies, reduced levels of bone mass in hypercalciuric subjects, with greater prevalence of osteopenia in subjects with fasting hypercalciuria, as opposed to subjects with normal urinary calcium or those with absorptive hypercalciuria (13,14).
On the basis of such clinical and experimental evidences in the last two decades a radical rethinking has occurred on the role of bone metabolism alterations in idiopathic hypercalciuria. It is now widely accepted that bone can be a primitive source of hypercalciuria not caused by primitive parathyroid stimulation, even if the amount of calcium originating directly from bone can not entirely account for the total quantity of urinary calcium that hypercalciuric subjects eliminate in excess compared to normal individuals.
Numerous studies in the last twenty years showed that patterns of calcium excretion are distributed according to a continuum both in normal and stone forming subjects. That does not allow a clearcut differentiation of the causal mechanisms.

Currently it seems more appropriate to consider primary hypercalciuria as an aggregate of complex clinical features, due to the varying contribution of different pathophysiologic mechanisms, namely intestinal hyperabsorption, renal leak and bone reabsorption.
Therefore, it appears that hypercalciuria should not be viewed as an organ-related disease any more. Rather, it must be considered as an expression of complex mineral metabolism alterations encompassing nephrology, endocrinology, and osteology specialities.
On the basis of these observations a heterogeneous group of specialists collaborated in promoting a true interdisciplinary approach to primitive hypercalciuria, through a critical re-examination of the main diagnostic criteria and procedures*. This could make possible to reach a consensus on a first-level clinical approach in patients with primitive hypercalciuria, on the basis of which it might be easier to build-up a protocol for the subsequent clinical investigations.
In this first temptative some significant points of agreement in regard to previous reports on primitive hypercalciuria emerged (1). These latter may constitute a worthwhile opportunity for thought and subsequent investigations by the international scientific community.

Question #1
Is it advisable to redefine the normal levels of calciuria, referred to different phases of life (i.e. childhood, adulthood, elderly, pregnancy and menopause)?

The current upper limits of normality, for calcium excretion (300 mg/24 h in males and 250 mg/24 h in females; 4 mg/kg body weight or 0.20 mg/24 h per mg of urinary creatinine in both sexes) have been defined in a healthy adult population, in a particular geographic context, and have not been corrected for dietetic intake (1).
This fact reduces the reliability of these limits, especially in certain age segments, such as in infancy and senility. In fact, the different indexes of calcium excretion, determined in a sample essentially made up of healthy adult individuals, are less applicable in other age segments characterized by relevant differences in the main body parameters (i.e. body surface area, adipose tissue and lean mass).
Thus it would be worthwhile to reconsider these parameters of normality through epidemiological studies on healthy populations of different age. This could make possible to obtain information beyond the entity of calcium excretion also on the general style of diet, with particular reference to the intake of calcium, sodium and animal proteins.
It would be important to integrate these data with information on the coexistent nutritional and calciotropic hormonal status.

Question #2
Advantages and limitations of calcium excretion measurements. Which indices are deemed most appropriate for a diagnosis of hypercalciuria (i.e. 24 hour calcium excretion, 24 hour and fasting calcium to creatinine ratio and 24 hour urine calcium/kg body weight)?

In general terms, it is advisable to assess all the above parameters in each patient and, when one of these indices is above threshold level, define the subject as having hypercalciuria. For further categorization of hypercalciuria (renal, reabsorptive, hyperabsorptive, etc.), the above parameters must be integrated with additional metabolic indicators (ionized serum calcium, bone alkaline phosphatase, PTH, urine pyridinoline to creatinine ratio, $TmPO_4$, vitamin D metabolites).

Question #3
Standardization of urine collection for the assessment of calcium excretion.

For reliable determination of calcium in urine collections, the precipitation of slightly soluble calcium salts must be avoided. This can be obtained by means of preliminary acidification of the sample, aimed at obtaining pH values around 3. If urine has also to be assayed for oxalate, further reduction of pH until 2 is advisable.
For this purpose, 24 hour urine can be collected in plastic containers previously filled with concentrated HCl solution (for example, 10 mL HCl at 37%, or 20 mL at 10%).
Conversely, if acidification is carried out at the end of the 24 hour collection, an adequate solubilization of the oxalate calcium salts requires both acidification to pH 1 and heating of the sample.
For pediatric urinary collection, the employment of high concentration and condensed volume HCl is recommended to avoid dilutional effect on the sample.
If the urinary collection is aimed to the study of supersaturation with stone forming salts, it is necessary to avoid the interference of the preliminary acidification on some urinary components (i.e. pH, chloride and uric acid). For this purpose, each sample should be exposed to two different conditions (i.e. 10-20 mL of HCl and 5 mL of a neutral preservative, such as chlorexidine).

Question #4
Which exams should be performed when a syndrome of hypercalciuria has been identified?

In other words, the problem is to define whether bone metabolism must somehow be investigated in hypercalciuric patients with nephrolithiasis and, conversely, whether nephrologic assessment must be performed in patients in which the diagnosis of hypercalciuria has come about during an osteometabolic evaluation.
An abnormal urinary excretion of calcium is a metabolic feature that is not shared by the major part of the population. Thus, it must be considered a biological marker that deserves clinical observation.
The prevailing opinion is that patients with fasting hypercalciuria, beside accurate investigation on the main nephrologic and osteometabolic risk factors, should be further evaluated by means of bone densitometry, renal echography and first-level biochemical assessment of mineral metabolism, as urea and creatinine clearances; serum and urinary sodium, potassium, calcium and phosphate; serum ionized calcium; serum protein electrophoresis; bone alkaline-phosphatase; and fasting urine, calcium, creatinine and pyridinoline.

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* This Consensus document is from the First Florentine Seminar on Mineral Metabolism held December 14, 2001 in Florence, Italy. It also includes components from subsequent discussions.

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