Article

Epidemiology of primary hypercalciuria

Alberto Trinchieri

U.O. Urologia, Ospedale A. Manzoni, Lecco, Italy

Alberto Trinchieri, M.D.
Urology Unit, Hospital A. Manzoni
Via dell'Eremo, 3/9
23900 Lecco, Italy
Ph. +39 0341 489118
Fax +39 0341 489328
E-mail: a.trinchieri@ospedale.lecco.it

Summary

Primary hypercalciuria is a biochemical syndrome consisting of an exaggerated urinary excretion of calcium without any defined clinical cause. The figure of prevalence of hypercalciuria in the population varies according to its definition and to some factors such as age, gender, race, and diet. Urinary excretion of calcium is usually expressed in mg/24 hour with commonly accepted upper normal limits of 300 mg for men and 250 mg for women. The calcium/body weight ratio is an effective alternative to daily urinary output, with an upper limit of 4 mg/kg body weight/24 hour for both sexes. Finally hypercalciuria can be defined by more than 0.15 mg calcium for mg of urinary creatinine in a 24-hour collection.
Our previously unpublished data from a population study involving healthy subjects from a village nearby Milan (Northern Italy) showed a prevalence of hypercalciuria, greater than 300 mg/24 h in men and 250 mg/24 h in women of 12.5% (12% in males and 14% in females). In the same population, considering a 0.15 urinary calcium to creatinine ratio as the upper limit of normal, the prevalence of hypercalciuria was 34% (26% in males and 42% in females), whereas, when the 4 mg/kg/day limit was considered, the rate was 18% (16% in males and 20% in females). The mean daily urinary calcium and the mean calcium/creatinine ratio were significantly higher in males than in females. The daily calcium output rose over the first two decades and remained constant during adult life in both males and females until the last two decades when it was significantly reduced in both sexes. On the contrary the highest values of calcium/creatinine ratio were observed in the first decade. The ratio felt over the second decade and it rose during the third and fourth decades remaining relatively constant until the last decades. There was no significant difference of the mean calcium/body weight ratio between males and females. The calcium/body weight ratio remained constant with age.
Urinary calcium excretion seems to be influenced by dietary intakes of calcium, sodium, potassium, protein, and carbohydrate, although this relationship was not confirmed in populations with a low intake of nutrients.

KEY WORDS: primary hypercalciuria, epidemiology, age and gender.

Introduction

Hypercalciuria is a biochemical syndrome consisting of an exaggerated urinary excretion of calcium exceeding the upper "normal" limits.

Several definite diseases may account for hypercalciuria such as hyperparathyroidism, sarcoidosis, malignant neoplasm, immobilization, vitamin D excess, lithium, etc.
Hypercalciuria without clinical cause is defined as idiopathic hypercalciuria. It was originally described in male stone formers but also occurs in women with kidney stones and, at a much lower frequency, in otherwise normal people.
The figure of prevalence of hypercalciuria in the population varies according to its definition and to some factors such as age, gender, race and diet.

Definition

Urinary excretion of calcium is usually expressed in mg/24 hour. Commonly accepted daily upper normal limits for calcium excretion are 300 mg for men and 250 mg for women. They derive from a large study by Hodgkinson and Pyrah (1), who found that calcium excretion exceeded these limits in more than 30% of male and female stone formers, but in less than 5% of otherwise normal people. However these limits are arbitrary and the choice of the value that best separates abnormal from normal urinary calcium output is difficult owing to the wide range of mean urinary calcium excretion values observed in different series. Hodgkinson and Pyrah observed in Leeds a mean calcium excretion of 178 mg/day by normal men and 140 mg/day by normal women. A subsequent survey, 12 years later, revealed values of urinary calcium output in normal male and female subjects appreciably higher of 219 and 186 mg/day, respectively. Similarly, different mean values for urinary calcium excretion were reported from different geographical areas and in different periods of time. These differences can be explained by differences in the selection of the population examined, in the modality of collection of urinary samples, in the laboratory methods, and in the changes of dietary habits over the years or related to the geographical area (Table I).
Other confounding factors are related to possible variations of the urinary calcium excretion during the day and between different days, because hypercalciuria is frequently intermittent presumably because of dietary variations. Some evaluation protocols involve multiple collections of 24 hour samples or separate sample collections for working days and week-ends. On the other hand the collection of samples under defined or restricted dietary conditions could introduce biases difficult to define, so the preferred approach should be to study subjects ingesting their customary diets, by collecting urine on out-patient basis together with a brief dietary history. Another bias related to the evaluation of daily calcium output is an incomplete collection of the urines. This implies that urinary volume should be controlled through the values of creatinine excretion. Nordin suggested to employ the urinary calcium to urinary creatinine ratio in order to express urinary calcium excretion in both random and 24 hour collections. Hypercalciuria is consequently defined by more than 0.15 mg calcium for mg of urinary creatinine in a 24-hour collection. The calcium/creatinine ratio of random samples allows the evaluation of calcium excretion under different physiological (i.e. fasting, after meals) and experimental (i.e. calcium load, acid load) conditions. In order to minimize

Table I - Daily urinary calcium (mg/24 hour) in healthy subjects and calcium renal stone formers (RSF) from different geographical areas.

	Healthy subjects	Calcium RSF	Dietary intake
South Africa (blacks) (3)	51±33	146±80	
North-West India (4)	99±24	128±32	
Bulgaria (5)	125±56	171±104	
Brazil (6)	149±77	245±133	468 543
South Africa (whites) (3)	161±69	233±108	
Australia (7)	164 (median)	188 (median)	
Italy (8)	202±93	296±125	
Italy (9)	178±86	234±120	956 1148
U.K. (1958) (1)	178 (males) 140 (females)	260 (males) 186 (females)	800
U.K. (1970) (2)	219±10 (males) 186±7 (females)	338±10 (males) 241±11 (females)	1000
U.K. (1978) (10)	238±15	320±14	

the effects of glomerular filtration rate on calcium excretion, calcium output can be also expressed as mg/100 ml of glomerular filtrate. The calcium/body weight ratio is an effective alternative to daily urinary output, especially for nutritional studies and for assessment of urinary calcium in children. Commonly the accepted upper limit is of 4 mg/kg body weight/24 hour, for both sexes.

Prevalence

In a group of 201 healthy subjects (99 males and 102 females) from a village nearby Milan (unpublished data) the prevalence of hypercalciuria, greater than 300 mg/24 hour in men and 250 mg/24 hour in women, was 12.5% (12% in males and 14% in females). In the same population, considering a 0.15 urinary calcium to creatinine ratio as the upper limit of normal, the prevalence of hypercalciuria was 34% (26% in males and 42% in females), whereas, when the 4 mg/kg/24 hour limit was considered, the rate was 18% (16% in males and 20% in females). The rates of prevalence vary in relation to age and sex (Figg. 1-3), according to the age- and sex-related variations of urinary calcium excretion. In fact, the mean daily urinary calcium and the mean calcium/creatinine ratio were significantly higher in males than in females. The daily calcium output rose over the first two decades and remained constant during adult life in both males and females until the last two decades when it was significantly reduced in both sexes. On the contrary, the highest values of calcium/creatinine ratio were observed in the first decade. The ratio felt over the second decade and it rose again during the third and fourth decades remaining relatively constant until the last decades. The mean calcium/body weight ratio did not differ between males and females and it remained

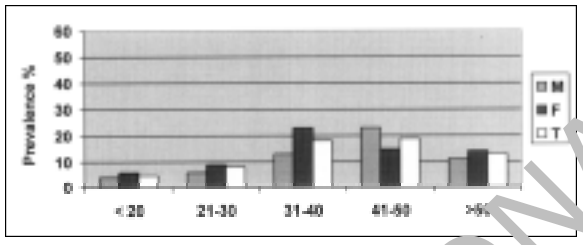

Figure 1 - Rate of hypercalciuria as mg/24 hour by gender and age.

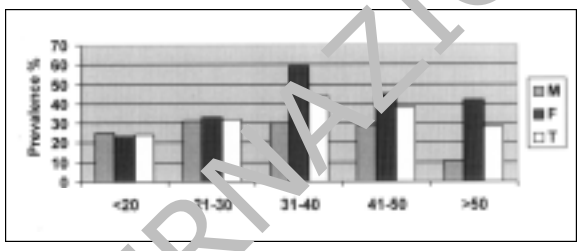

Figure 2 - Rate of hypercalciuria as Ca/Cr ratio by gender and age.

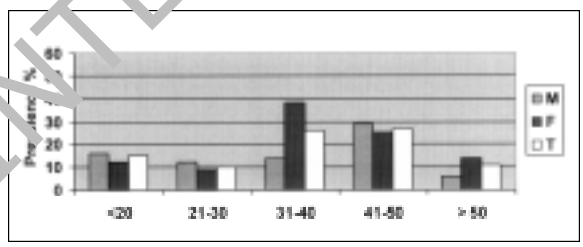

Figure 3 - Rate of hypercalciuria as mg/kg/24 hour by gender and age.

constant with age.

Age and gender

Bulusu et al (2) examined the relationships between age and sex and urinary calcium excretion, expressed in a variety of ways, in a large population of normal subjects (146 men and 190 women, aged 3-89 years).

The mean daily urinary calcium and the mean calcium/creatinine ratio were significantly higher in males than females.

The daily calcium output rose over the first two decades and remained constant during adult life in both males and females until the eight decade when it was significantly reduced in both sexes.

On the contrary the highest values of calcium/creatinine ratio were observed in the first decade. The ratio felt over the second decade and it remained relatively constant in men, whereas it rose during the fifth and sixth decades in women. Finally, there was a fall in calcium/creatinine ratio in both males and females.

The mean calcium/body weight ratio between males and females did not differ and the calcium/body weight ratio remained constant with age until the eighth decade when it felt. The different trend with age of the calcium/body weight ratio with respect to calcium/creatinine ratio could be explained by the concomitant variation with age of creatinine excretion and body weight. Urinary creatinine excretion increased steeply during the first two decades to a maximum value in the third decade,

followed by a gradual decrease with age. This trend reflects the changes in lean body mass during growth and ageing. Body weight also increased in the first two decades, remaining relatively constant thereafter. This could be due to the progressive loss of muscle mass with concomitant gain of fat tissue.

Children

In children urinary calcium/creatinine ratio on random urine samples is preferred for the screening of hypercalciuria, although reference values are not well established.
The ratio urinary calcium/body weight was extensively used for the evaluation of urinary excretion of children (11).
In newborns the ratio urinary calcium/creatinine is relatively low (12).

Elderly

The daily excretion of calcium tend to fall with age, probably as the consequence of reduced intestinal absorption considering that daily intake appears to be unchanged with age (13). A decreased intake of protein and sodium could concurrently decrease the urinary excretion of calcium.

Distribution of values

According to Robertson et al. (10,14) the distribution of values of urinary calcium excretion seems to be a continuous trait. However, calcium excretion rate values are skewed with a long tail of high values that represents a group of subjects with "abnormal" calcium excretion that should be classified as "hypercalciuric".
Holmes et al. (15) recognized in the distribution of urinary calcium excretion of healthy subjects a group with definitely high calcium excretion above 0.18 mg/mg creatinine. In their opinion the distribution of calcium excretion in the remaining population was broad and did not appear to fit a normal distribution. On this basis they suggested that the non-hypercalciuric group could more appropriately divided into two groups: one with low excretion (< 0.1 mg/mg creatinine) and the other with an intermediate calcium excretion (0.1-0.18 mg/mg creatinine). The identification of these two subpopulations depended on the collection of three urinary specimens and the subdivision of the calcium excretion into smaller intervals. These results could indicate that a pair of codominant alleles exert a major influence on urinary calcium excretion.

Genetics

Two familial studies have attributed hypercalciuria to the presence of an autosomal dominant gene (16,17). More recently mutations of the CLCN5 chloride channel gene and mutations affecting the calcium-sensing receptor have been identified in rare forms of hypercalciuria. Over-expression of the vitamin D receptor and deficiencies in renal tubule enzymes may be involved in idiopathic hypercalciuria.

Ethnicity

In a population-based study of South-African adults (3), black healthy controls showed a significantly lower excretion of calcium than white healthy controls. The lower urinary calcium output in blacks probably reflects a lower calcium, sodium and protein intake (Table II). In an another study (20), after adjustment for counfounders including age and gender, 24 hour urinary calcium was significantly and independentely associated with ethnic origin: mean 24 hour urinary calcium (mmol) was 4.62±0.11 in whites, 3.33±0.12 in Asians and 3.16±0.13 in blacks ($p<0.001$). These differences may reflect ethnic differences in renal tubular handling as they are present also after an overnight fast.
Worldwide variations of the urine calcium/creatinine ratio were reported also in children (21). Two recent studies were undertaken to set normal values of random non-fasting U Ca/Cr by age and race in the pediatric population of Hat-Yai (Thailand) and Kansas City (United States).
The 95th percentile for U Ca/Cr by age are shown in Table III. The data showed a strong inverse correlation between urinary Ca/Cr and age; urinary Ca/Cr of Caucasian and Thai children exceeded the corresponding value in African-Americans. Urinary Na/K ratio was correlated with urinary Ca/Cr in Thai children, whereas no significant correlation was observed in Caucasian and Afro-American children.
It has been, therefore, concluded that the child's age, ethnicity and geographic location should be taken into consideration when assessing U Ca/Cr ratio.

Table II - Urinary excretion of calcium (mmol/24 hour) related to dietary nutrients in white and black healthy subjects (HS) and renal stone formers (RSF).

Table	Black HS	White HS	Black RSF	White RSF
CaU	1.27±0.84	4.03±1.73	3.65±2.01	5.83±2.70
Cadiet	635±341		644±397	854±460
Nadiet	3809±1718		3183±1337	4437±2144
Protdiet	ND		99±28	113±39

Table III - Age dependent 95th percentile of urinary Ca/Cr values for Caucasian, Afro-American and Thai children.

	Thai	Caucasian	Afro-American
< 6 months	0.75	0.70	0.38
6-12 months	0.64	0.50	
1-2 years	0.40		
2-5 years	0.38	0.28	0.24
5-10 years	0.29	0.20	
10-15 years	0.26		

Diet

Urinary calcium excretion seems to be influenced by dietary intakes of calcium, sodium, potassium, protein, and carbohydrates. However, this relationship was not demonstrated in populations with a low intake of nutrients (3,6).

Calcium

Calcium-load studies conducted by Marshall et al. (23) and Le-

mann et al. (24) have demonstrated a linear relation between oral assumption and urinary excretion of calcium up to calcium-intake values of 20 mmol/day. Further increases in the intake of calcium involve smaller increases in urinary calcium excretion, which become nil with values above 50 mmol/day. In healthy subjects direct measurement showed absorption of a larger fraction of dietary calcium on a low calcium diet (400 mg) than on an high calcium diet (1700 mg) (50 vs 31%) (25). Recently Robertson et al. showed that urinary calcium is dependent on the logarithm of the calcium intake (26). Urinary calcium seem to be abnormally dependant upon dietary calcium intake in patients with idiopathic hypercalciuria.
Intake by calcium supplements should be considered separately from intake by calcium containing foods and beverages because of the different timing of ingestion and the different pattern of use.
In healthy subjects on a standard diet calcium excretion increased from 5.44 to 6.42 mmol/day after ingestion of calcium-rich mineral water (339 mg/day calcium) and from 5.60 to 6.91 mmol/day after calcium carbonate supplementation (800 mg/calcium).

Sodium

Dietary sodium intake can affect markedly the urinary excretion of calcium: an increase of 25 mmol/24 hours in urinary sodium causes an increase of approximately 0.6 mmol/24 hours in urinary calcium. Calciuria and natriuria are, indeed, correlated, even though proximal tubular sodium reabsorption does not correlate with calcium reabsorption (28-31).

Potassium

In healthy human subjects dietary habits with a normal intake of NaCl dietary potassium deprivation is associated to an increase in urinary calcium excretion togheter with and for weight gain (32).This effect seems to be mediated by sodium and chloride retention and expansion of extracellular volume. In fact, dietary NaCl intake prevents the calciuria of potassium deprivation.

Protein

The first observations on the effects of a protein diet on calcium excretion date back to the twenties, when Sherman et al. (33) observed that an addition of meat to the diet generated an increase in calcium excretion without increasing the absorption of dietary calcium. An increase in urinary calcium excretion after an acute and chronic load of protein was subsequently confirmed by several Authors (34-37).
An explanation for this phenomenon is the endogenous acid load that follows the oxidation of sulphated proteins (methionine, cysteine) with consequent reduction in tubular calcium reabsorption and a state of chronic acidosis, that causes mobilization of calcium from the bone. In parallel, intestinal absorption of calcium could be enhanced by methionine and lysine load.

Carbohydrates

The classic observations made by Lemann et al. (38) have shown that an acute load of refined carbohydrates, glucose or saccharose, can cause increased urinary calcium excretion both in lithiasic patients and in healthy controls.
Subsequently, Blacklock et al. (39-41) produced a considerable body of evidence on this subject, confirming the acute and chronic calciuretic effect of glucose and demonstrating that there is a subpopulation of patients with renal calculosis in which the administration of refined carbohydrates leads to a distorted calciuric response, probably linked with an abnormal insulin response.
Hypercalciuria following an acute load of glucose in patients with kidney hypercalciuria has also been confirmed by Pak et al. (42).
The calciuric effect of an oral load of sugar was initially explained by a mechanism of reduced reabsorption of calcium at the level of the distal tubule (38). More recent studies (43,44) have shown how glucose can, in dose-dependent mode, enhance the intestinal absorption of calcium by means of a mechanism that has not yet been fully defined. Other Authors (45-47) indicated insulin as the stimulatory mechanism of intestinal calcium absorption.

Climate and seasonal variations

In hot climates the increase in daily urinary excretion of calcium in non-acclimatised subjects was explained by the action of ultraviolet rays that stimulate the production of vitamin D_3 with consequent increased intestinal absorption of calcium (48).
In regions with temperate climates, seasonal variations in calcium excretion were also recorded during the summer months and corresponded with increased plasma levels of vitamin D_3 (49).
Conversely, it has been observed that levels of circulating vitamin D_3 in the Saudi Arabian population are normal (50). One must therefore suggest mechanisms for adaptation in regions constantly exposed to solar radiation.

Idiopathic calcium renal stone disease

Mean urinary calcium has been found to be higher in patients with idiopathic calcium renal stone disease compared with controls. This relation has been showed in men and women, in children and adults, and in different countries (Table I).
Furthermore, it has been demonstrated that, after adjusting for other urinary risk factors, daily urinary calcium output is an independent risk factor for calcium kidney stone formation. The risk for stone formation in men with daily urinary calcium output greater than 300 mg is four-fold higher than in men excreting less than 150 mg/day, whereas for the same values the risk in women is twice higher (51). According to the commonly accepted criteria, about 50% of patients with calcium oxalate stones are hypercalciuric. However, comparison of renal stone formers with recurrences and those with no further stone episodes showed that recurrence was not significantly influenced by an increased value of urinary calcium (52).

Hypertension

Hypertension is often associated with increased urinary calcium excretion. Borghi et al. (8) demonstrated that daily urinary calcium output was significantly higher in healthy controls (202±93 mg/24 hour) than in essential hypertensive subjects (275±112 mg/24 hour)). Urinary calcium excretion remained higher in hypertensive subjects even if corrected for body mass index. A 20 mmHg higher systolic blood pressure predicts a 0.28 mmol higher urinary calcium.

Obesity

Some Authors (52,53) have pointed out that body mass index

is significantly correlated with urinary calcium excretion. A retrospective review (54) of a large data base on urinary stones was recently performed in order to determine the effect of obesity on stone recurrence. Obese patients represented 3.8% of the males and 12.6% of the females. Obesity alone increased slightly the risk of recurrence in male obese (>120 kg) patients, but not in obese (>100 kg) females. Obese subjects had increased urinary excretion of urinary calcium (togheter with sodium, magnesium, citrate, sulfate, phosphate, oxalate, and urate), but they had also increased urinary volumes. In extremely obese women with an android phenotype, urinary excretion of calcium is elevated with an increase of bone remodelling markers (55).

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