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THE TALE OF PARATHYROID FUNCTION IN IDIOPATHIC HYPERCALCIURIA

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Abstract

At the origin, idiopathic hypercalciuria has been described as a syndrome consisting of normocalcemia, low plasma phosphate levels and abnormally high urinary calcium excretion. The cause of this syndrome was subject to many investigations throughout the years. Two main pathophysiologic hypotheses have been proposed: **a**) primary intestinal hyperabsorption of calcium, leading to depression of parathyroid hormone (PTH) secretion ("absorptive" hypercalciuria); and **b**) primary renal tubular leak of calcium which stimulates PTH secretion (secondary hyperparathyroidism). Most of the published studies indicate that intestinal hyperabsorption of calcium with subsequent relative hypoparathyroidism is the primary event causing idiopathic hypercalciuria, and that this occurs as a consequence of increased production of $1,25(OH)_2$-vitamin D_3 (calcitriol). Fasting hypercalciuria, originally taken as evidence for a "renal leak" of calcium, appears to be, at least in part, the consequence of relative hypoparathyroidism.

Key Words: Calcium renal stone disease, idiopathic hypercalciuria, absorptive/renal hypercalciuria, parathyroid hormone, calcitriol.

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Introduction

Hypercalciuria is defined as a daily urinary excretion of calcium of more than 4 mg/kg body weight (BW) ($>$ 0.1 mmol/kg BW) in either sex (11). It can be found in nearly 50% of patients with idiopathic calcium nephrolithiasis and in about 5% of normal people (11, 27). Hypercalciuria is a familial trait (8) with characteristics of autosomal dominant inheritance (24). Since hypercalciuric subjects produce urine which is abnormally supersaturated with respect to calcium oxalate (36), and since lowering urinary calcium concentration by thiazide diuretics reduces the activity of nephrolithiasis (10, 38), hypercalciuria can be considered as a risk factor for calcium oxalate crystallization and, subsequently, renal stone formation (11). It has to be noted, however, that for identical standard deviation increments in urinary calcium and oxalate concentrations above the normal means, the rise in urinary oxalate is much more critical for calcium oxalate stone formation than that in urinary calcium (33).

This article reviews **idiopathic hypercalciuria**, with special emphasis on assessment of parathyroid function as well as on the production of $1,25(OH)_2$-vitamin D_3 (calcitriol) in patients affected by this syndrome.

History of Idiopathic Hypercalciuria

In 1939, Flocks described 35 patients suffering from calcium stones in kidneys or ureters and from "slight infection" of the urinary tract (13). When these patients were administered a diet with high calcium content (2500 mg/d), they clearly separated into two groups: those (n = 12) whose urinary excretion of calcium remained normal or low ($<$ 300 mg/d), and those (n = 23) in whom it was elevated ($>$ 420 mg/d), two of them probably having hyperparathyroidism (13). In 1953, Albright *et al.* described a syndrome consisting of normocalcemia, low plasma phosphorus levels and hypercalciuria in 21 patients in whom the cause of hypercalciuria was considered to be "not as yet clear" (1), e.g., no hyperparathyroidism, hyperthyroidism, progressing osteoporosis, high calcium intake, metastatic malignancy, myeloma, sarcoidosis, renal tubular acidosis, or vitamin D

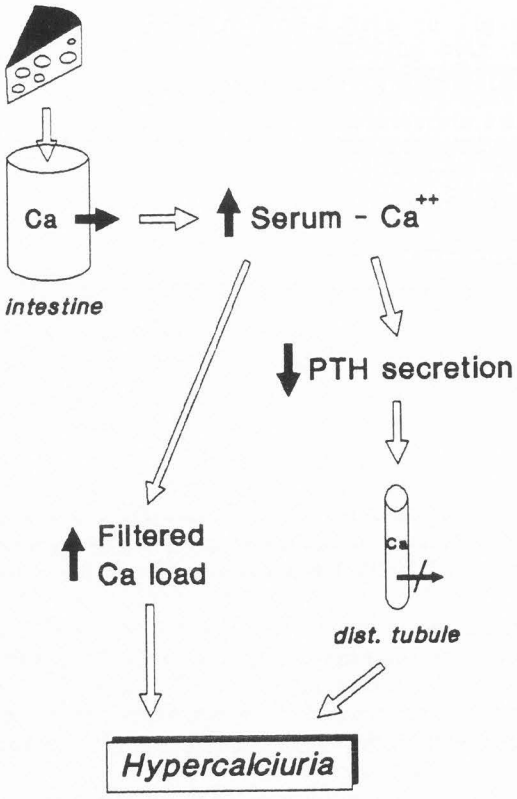

Figure 1. Pathophysiology of "absorptive" hypercalciuria. Ca = calcium; PTH = parathyroid hormone.

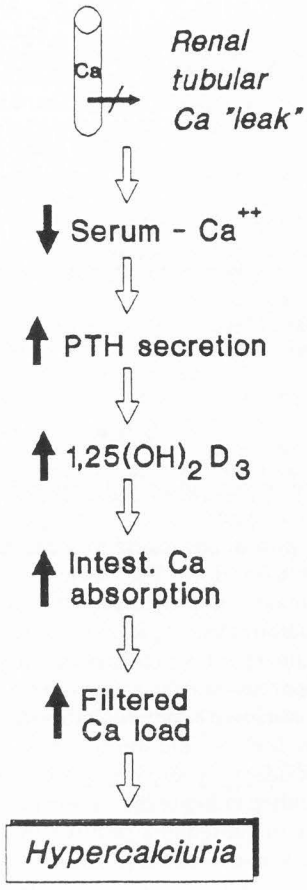

Figure 2. Pathophysiology of "renal" hypercalciuria. For abbreviations, see Fig. 1. $1,25(OH)_2D_3$ = calcitriol.

poisoning were present; the term "idiopathic hypercalciuria" (IH) was thus coined (1).

Five years later, Henneman *et al.* (16) essentially described the same syndrome in 35 patients (including the 21 cases originally studied by Albright *et al.*), in comparison with 14 patients with "mild" hyperparathyroidism. Although an assessment of parathyroid function at this time was impossible "unless one has explored the neck" (16), the following sequence of events leading to IH was postulated: a tubular damage by (staphylococcal) pyelonephritis would result in decreased reabsorption of calcium, and thus, in hypercalciuria; subsequently, a tendency towards hypocalcemia would be followed by compensatory hyperparathyroidism with consecutive hyperphosphaturia and hypophosphatemia (1, 16). The concept of "**primary renal tubular hypercalciuria**" was thus born (16).

However, balance studies in four of Henneman's patients with IH revealed an abnormally low fecal calcium excretion (about half the normal value) which only could be explained by **increased intestinal calcium absorption**, possibly due to "excessive vitamin D activity" (16). Actually, studies performed in the sixties did demonstrate elevated intestinal absorption of calcium in patients with IH, compared with normal controls (3, 12, 23). Based on their calcium kinetic studies, Liberman *et al.* concluded "that the primary disturbance in idiopathic hypercalciuria is neither intestinal hyperabsorption nor urinary hyperexcretion of calcium, but **both** these..." (23), which perfectly anticipated forthcoming studies on the pathophysiology of IH.

"Absorptive" versus "Renal" Hypercalciuria

In the early seventies, serum parathyroid hormone (PTH) immunoassays became available. In 1973, Coe *et al.* (7) reported that serum PTH levels, measured by a radioimmunoassay which detected carboxy- as well as amino-terminal PTH fragments, were elevated in 26 out of 40 patients with IH; thus, a **primary renal leak of calcium** with secondary hyperparathyroidism in the majority of cases with IH appeared as a reasonable hypothesis (7). The latter was further supported by studies in 4 normal volunteers to whom furosemide had been administered for 9 days: urinary calcium excretion had risen, e.g., hypercalciuria had developed, and serum PTH had increased to levels equivalent to those observed in patients with IH (7).

The dogma of a primary renal leak of calcium in IH was challenged one year later (30): based on measurements of PTH (using an antiserum mainly recognizing the amino-terminal portion of the PTH molecule) and of urinary cAMP as well as fractional absorption of calcium from the intestinal tract (orally administered ^{47}Ca) in patients with calcium nephrolithiasis on a low calcium diet (400 mg/d), Pak *et al.* (30) demonstrated that **primary intestinal hyperabsorption of calcium** was the backbone of the IH syndrome in 22 out of 30 stone formers; they thought, however, that both "absorptive" and "renal" hypercalciuria might be found as distinct entities in patients with IH and calcium renal stones.

Based on the observed correlation between fractional intestinal calcium absorption and calciuric response after oral calcium loading (1 g of calcium), Pak *et al.* subsequently developed a simple test for ambulatory evaluation of the causes of hypercalciuria (31); patients with normocalcemia, normal fasting and high urinary calcium after calcium loading were called "absorptive" hypercalciurics, whereas those with normocalcemia, high fasting urinary calcium and high fasting urinary cAMP were called "renal" hypercalciurics. In the latter group, however, a poor correlation was found between fractional intestinal absorption of calcium and calciuric response after oral calcium loading (40). Furthermore, when routinely applied to the clinical evaluation of patients with IH and calcium nephrolithiasis, the oral calcium loading test appeared to be of limited value, since either more than 50% of the patients could not be classified as "absorptive" or "renal" hypercalciurics (20), or the values largely overlapped in IH and in normals (22).

When carefully considering the regulatory feedback mechanisms (11) that occur as a consequence of either a primary intestinal hyperabsorption of calcium ("absorptive" hypercalciuria, Figure 1) or a primary renal leak of calcium ("renal" hypercalciuria, Figure 2), one realizes that, once steady-state conditions have been reached, both sequences of events predict increased intestinal absorption and decreased renal tubular reabsorption of calcium (11).

Intestinal Absorption of Calcium in Patients with IH

Since elevated intestinal absorption of calcium appears to occur in "absorptive" as well as in "renal" hypercalciuria (Figures 1 and 2), it is not surprising that comparative studies carried out in patients with IH and in normal controls unequivocally found such increased fractional intestinal absorption of calcium in IH (3, 12, 19, 23, 29, 30, 34, 37), irrespective whether (19, 29, 30) or not (3, 12, 23, 34, 37) patients were subdivided into "absorptive" and "renal" hypercalciurics.

From a theoretical standpoint, at that time, intestinal hyperabsorption of calcium could have been envisioned as **calcitriol-dependent** or calcitriol-independent. Over the years, however, refinement of calcitriol assays allowed to obtain substantial evidence in favor of the former. Indeed, as summarized in Table 1, numerous studies have clearly demonstrated increased or high-normal, but neither decreased nor low-normal serum levels of calcitriol in IH, irrespective of its "absorptive" or "renal" origin (2, 5, 15, 19, 34, 39); in other studies, serum calcitriol was at least up-regulated in the face of the status of its modulators, namely blood ionized calcium (9), phosphate (2) and PTH (9) concentrations. This points to a **disturbed control of calcitriol synthesis** (2, 11, 18) in patients with IH, with subsequent depression of PTH synthesis. Alternatively, one may envision **increased sensitivity** of the intestine and/or the parathyroid glands to calcitriol. Indeed, Silver *et al.* (35) have demonstrated that calcitriol decreases the transcription of the PTH gene and, subsequently, lowers PTH synthesis.

Parathyroid Function in Patients with IH

As postulated by Coe and Bushinsky (11), a primary increase in calcitriol synthesis would lead to low or low-normal PTH values in steady-state measurements, whereas a primary renal leak of calcium would tend to raise serum PTH values (secondary hyperparathyroidism). However, with exception of the original article by Coe *et al.* (7), as well as in part of the reports by Pak *et al.* (30), Bordier *et al.* (4) and Pak and Galosy (32), none of the published studies (2, 5, 6, 9, 15, 25, 28) ever confirmed the existence of secondary hyperparathyroidism in patients with IH. On the contrary, the vast majority of published data indicates normal (2, 6, 28) or even decreased (5, 9, 15, 25, 34) fasting blood levels of PTH levels in patients with IH, compared with healthy controls (Table 2). Recently, using a sensitive immunoradiometric assay to detect the intact PTH molecule, we confirmed the occurrence of **relative hypoparathyroidism** in male hypercalciurics with recurrent idiopathic calcium nephrolithiasis in comparison with normocalciuric calcium renal stone formers; furthermore, urinary excretion rates of urea and sulfate, markers of protein consumption, were significantly higher in hypercalciuric stone formers (17). It remains to be seen to what extent increased protein consumption, a known dietary risk factor for idiopathic hypercalciuria (14), may be related to the up-regulation of calcitriol and the subsequent relative hypoparathyroidism that can be observed in hypercalciuric calcium renal stone formers (17).

Fasting Hypercalciuria

Fasting hypercalciuria has been thought to indicate a primary renal tubular leak of calcium (31). However, it could equally well be the consequence of relative hypoparathyroidism in IH. As demonstrated by Broadus *et al.* (5), there is a significant negative correlation between fasting urinary calcium excretion and parathyroid function, based on measurements of urinary cyclic AMP, a phenomenon that the intact PTH assay helped us to confirm (17). Thus, the ever-observed renal leak of calcium in some patients with IH could just have an hormonal basis (5).

Table 1. Plasma calcitriol in patients with hypercalciuria (HC) and calcium nephrolithiasis.

Type of HC	n	Mean plasma calcitriol†	Ref.No.
IH	26	+ 72	15
IH	15	+ 59	34
"AH"	21	+ 32	19
"RH"	3	+ 103	
"AH"	11	+ 113	9
"RH"	10	+ 53	
IH	24	+ 18	9
"AH"	50	+ 64	5
IH	42	+ 38	2

IH = idiopathic hypercalciuria;
"AH" = absorptive hypercalciuria;
"RH" = renal hypercalciuria.
n = number of patients;
† = % deviation from mean of controls
Ref. No. = Reference number.

In addition, dietary NaCl intake appears to be a determinant not only of daily, but also of fasting hypercalciuria. Indeed, an increase in dietary NaCl consumption lowers calcium reabsorption along the renal tubule (14), thus inducing with some time lag fasting hypercalciuria (21, 26). Since not all patients with recurrent calcium nephrolithiasis seem to consume NaCl in excess (14), undue sensitivity to the calciuric stimulus of NaCl has been postulated in these patients (14, 21).

Summary

Altogether, available data strongly suggest that the syndrome of IH includes features of both intestinal hyperabsorption and reduced renal tubular reabsorption of calcium (9, 23). There seems to be convincing evidence, however, for a primary increase in calcitriol production in patients with IH; alternatively, increased sensitivity of the intestine and/or the parathyroid glands to normal calcitriol levels might be present in some patients with IH. Both will depress PTH synthesis and induce relative hypoparathyroidism. The latter directly contributes to hypercalciuria, i.e., the lower PTH secretion, the higher urinary calcium excretion (Figure 3). A substantial body of evidence supports the view that "absorptive" and "renal" hypercalciuria are not distinctive entities, but rather two extremes of a continuum behavior (9): "absorptive" hypercalciuria will be found in patients in whom a night of fast suffices to finalize calcium absorption and elimination and to return PTH secretion to normal, whereas "renal" hypercalciuria will be found in those patients whose PTH suppression and ensuing renal

Table 2. Serum PTH in patients with hypercalciuria (HC) and calcium nephrolithiasis.

Type of HC	n	Mean plasma calcitriol†	Ref.No.
IH	40	+ 55*	7
"AH"	22	- 33	30
"RH"	2	+ 198	
"RH"	9	+ 30*	4
IH	26	- 3	15
IH	15	- 33	34
"AH"	51	- 47	32
"RH"	20	+ 172	
IH	41	- 41	25
IH	24	- 28	9
"AH"	15	- 60*	28
"RH"	21	- 54*	
IH	42	- 16	2

For abbreviation definitions, see Table 1.
* = % deviation from indicated upper limit of normal range of PTH values (no healthy controls studied).

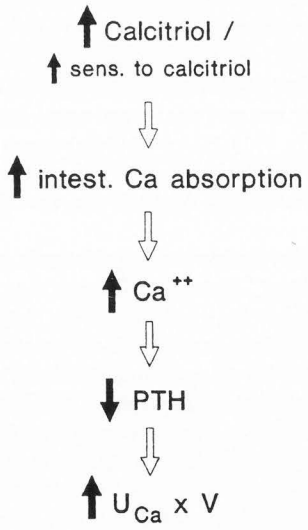

Figure 3. Sequence of events leading to hypercalciuria. U_{Ca} x V = 24-hour urine excretion of calcium. For other abbreviations, see Fig. 1.

leakage of calcium last longer. Whether a particular patient is an "absorptive" or "renal" (fasting) hypercalciuric probably depends, at least in part, also on dietary factors, such as NaCl consumption.

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Editor's Note: All of the reviewer's concerns were appropriately addressed by text changes, hence there is no Discussion with Reviewers.