New Insights into the Pathogenesis of Idiopathic Hypercalciuria

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Abstract

Idiopathic hypercalciuria (IH) is the commonest metabolic abnormality in patients with calcium kidney stones. It is characterized by normocalcemia, absence of diseases that cause increased urine calcium, and calcium excretion that is above 250 mg/day in women and 300 mg/day in men. Subjects with IH have a generalized increase in calcium turnover, which includes increased gut calcium absorption, decreased renal calcium reabsorption, and a tendency to lose calcium from bone. Despite the increase in intestinal calcium absorption, negative calcium balance is commonly seen in balance studies, especially on a low calcium diet. The mediator of decreased renal calcium reabsorption is not clear; it is not associated with either an increase in filtered load of calcium or altered PTH levels. There is an increased incidence of hypercalciuria in first-degree relatives of those with IH, but IH appears to be a complex polygenic trait with a large contribution from diet to expression of increased calcium excretion. Increased tissue vitamin D response may be responsible for the manifestations of IH in at least some patients.

Definition of Hypercalciuria

Calcium, the most abundant cation in human beings, is an important participant in many physiologic processes, including hormonal secretion, cardiac contraction, blood clotting, and neurotransmission. In addition, growth and repair of our skeleton demands an adequate supply of calcium, and careful maintenance of extracellular calcium concentrations. For this reason, prevailing levels of intracellular and extracellular calcium are tightly regulated, by a complex system of control mechanisms. These mechanisms control calcium absorption by gut and renal tubular epithelia, as well as fluxes of calcium on and off bone, during varying dietary calcium intakes. In healthy, non-pregnant adults, whose skeleton is no longer growing, net intestinal calcium absorption is matched by renal excretion, and provides sufficient calcium for skeletal maintenance; however, under pathologic conditions, some urine calcium may derive from bone loss.

Abnormalities of calcium homeostasis could result in a number of undesired consequences, including abnormally high or low serum calcium levels, or inadequate maintenance of bone mineral. Hypercalciuria might be defined as any level of urine calcium that exceeds net intestinal absorption, leading to net loss of calcium. However, in practice net intestinal absorption is seldom measured, and under the assumption that urine calcium is primarily derived from intestinal absorption, the working definition of hypercalciuria is urine calcium excretion that exceeds that found in the majority of healthy adults eating their usual diets. In practice, this is usually defined as a daily calcium excretion over 250 mg/day in women or 300

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mg/day in men [1], or 4 mg/kg body weight in either sex [2;3]; these excretions are higher than those in 80% of normal individuals in our experience.

One of the sequelae of increased daily urine calcium excretion is the potential for formation of insoluble calcium salts, calcium oxalate or calcium phosphate (as brushite or apatite), in the urinary tract, resulting in nephrolithiasis or nephrocalcinosis. High urine calcium concentrations, which may be due to increased calcium excretion, low urine volume, or both, lead to elevated urine supersaturations with respect to these minerals in the distal nephron and urine, where crystals may form. Elevated urinary calcium excretion has been recognized as a risk factor for kidney stone formation since Flocks [3] reported that calcium stone formers had higher daily calcium excretion than non-stone formers, whether they ate diets containing 7.5 or 62.5 mmol calcium/day. In most cases, the elevated urine calcium excretion was accompanied by normal serum calcium, normal or slightly low serum phosphorus, and no overt evidence of bone disease; known causes of hypercalciuria such as primary hyperparathyroidism, sarcoidosis, Cushing's syndrome, cancer, excess vitamin D intake, hyperthyroidism, glucocorticoid use, Paget's disease, or renal tubular acidosis were absent. The term idiopathic hypercalciuria (IH) was coined to describe this constellation of findings [4]. IH is the most common metabolic abnormality found in adult calcium stone formers, present in 30–60% of such patients; it is common among pediatric calcium stone formers, as well [5].

Mechanisms of IH

IH is the result of the interplay between genetic background and environment. Studies have shown an increased incidence of nephrolithiasis and hypercalciuria among first degree relatives of stone formers. Among families of nine patients with kidney stones and IH, hypercalciuria was found in 19 of 44 first-degree relatives, often in multiple generations, indicating that IH has a genetic basis [6]. The precise gene or genes that contribute to IH are still unknown; the trait is most likely polygenic in origin, with contributions from several genes which may differ from one individual with IH to another. In addition, there is a large effect of diet on expression of hypercalciuria in individuals with IH.

Calcium homeostasis involves the coordinated control of mineral handling by the intestine, kidney and bone, under the influence of parathyroid hormone (PTH) and $1,25(OH)_2D_3$. These hormones regulate the synthesis and activity of transporters responsible for calcium translocation in these sites. In addition, the calcium sensing receptor (CaSR) allows cells of the parathyroid, renal tubule, and potentially intestine and bone to monitor local calcium ion levels, and alter cell function in response to changes. Abnormalities of calcium regulation in these sites have been implicated in causing IH, however the underlying mechanisms are not completely understood and the relative contributions of these sites may vary from one individual to another.

Patients with IH have sometimes been categorized by the presumed site of the primary abnormality [7;8]. The major subtypes have included 1) 'absorptive' hypercalciuria in which a primary increase in intestinal calcium absorption may result in increased urine calcium; 2) 'resorptive' hypercalciuria, caused by an increase in bone turnover, leading to loss of bone calcium in the urine; and 3) 'renal leak' hypercalciuria, in which a primary defect in renal tubule calcium transport allows loss of calcium in the urine, with compensatory increase in calcium absorption from gut or mobilization from bone. Classification has rested on measurement of fasting and 24-hour urine calcium, and urinary calcium responses to low calcium diet (400 mg/day) and to a calcium load (1 gm). In particular, those patients with a low fasting calcium excretion, and normal or low PTH, have been categorized as 'absorptive'; their urine calcium may or may not fall into the normal range on low calcium diet. In contrast,

those patients with fasting hypercalciuria and a mildly elevated PTH (but normocalcemia) have been diagnosed with 'renal leak'. Resorptive-type hypercalciuria would manifest fasting hypercalciuria with a suppressed PTH. However, in many cases, classification into one of these groups has proved difficult. Most individuals with IH appear to have a more generalized acceleration of calcium transport, which affects all these processes, and the clinical value of classification appears modest, at best.

Intestinal Absorption of Calcium in IH

Increased gut absorption of calcium is a feature noted in essentially all patients with IH. Studies using radio-labeled calcium that have compared intestinal calcium absorption in patients with IH to that in normal subjects find consistently increased calcium uptake in IH (Figure 1, panel a) [9;10]. Although not measured in these studies, other work has shown that gut calcium secretion is not altered in subjects with IH, meaning that net absorption is also increased [11]. Absorption is higher in IH at all levels of calcium intake [12], and reflects an increase in active calcium transport by the intestine. One potential mechanism for increased absorption may be the higher levels of serum calcitriol found in patients with IH compared to normal subjects in many studies (Figure 1, panel b) [9;10]. Calcitriol upregulates expression of calcium transport proteins in the intestine, including the apical calcium channel, TRPV6 [13], and calcium absorption is directly related to calcitriol levels [14]. In some hypercalciuric subjects, however, intestinal calcium absorption appears to be increased out of proportion to the calcitriol level [14]. Patients with IH maintain normal fasting serum calcium levels, and PTH levels have generally been reported as normal or slightly low [15].

Urine calcium rises in normal subjects as net intestinal calcium absorption increases (Figure 2, solid lines). However, in patients with IH, urine calcium is higher than normal at any level of net calcium absorption (calculated as [diet calcium-fecal calcium]) (Figure 2) [9]. Thus, while a normal subject with net calcium absorption of 200 mg/day will excrete about 150 mg calcium in the urine, a patient with IH with the same absorption may have a calcium excretion of 250–400 mg/day, implicating abnormal renal calcium conservation in the production of hypercalciuria. The balance studies shown in Figure 2, using controlled diets, demonstrate that urine calcium is often higher than net absorption, meaning that some of the urine calcium must be derived from bone.

A critical prediction that arises from Figure 2 is that IH patients will lose bone mineral more readily than normal when challenged by an extremely low calcium diet. This was demonstrated in a study in which 27 subjects with IH were compared to 9 normal subjects on days 7–9 of an experimental diet containing very little calcium (2 mg/kg body weight/day) but otherwise composed of normal foods [16]. Patients with IH frequently excreted more calcium in the urine than was ingested (Figure 3), whereas normal subjects did not. The loss of calcium in the urine above that in the diet is definitive proof of abnormal bone mineral wasting in IH, and again suggests that alterations in renal calcium handling that limit calcium conservation may be a common feature of IH. It is notable that the IH patients did not drop their serum calcium (unlike the normal subjects) or increase their serum PTH while on low calcium diet compared to levels seen on a free choice diet; serum PTH levels were lower in IH than in the normal subjects on both diets. Overall, it appears that renal mineral conservation must be abnormal in IH, and bone mineral loss somehow facilitated so that despite the absence of diet calcium to balance renal losses, serum calcium can remain normal and serum PTH suppressed. This is further suggested by studies of calcium kinetics using ^{47}Ca which demonstrate a larger exchangeable calcium pool and higher calcium turnover, together with increased rates of both bone formation and resorption, in 9 subjects with IH compared to 3 normal subjects [11].

A possible mechanism that could explain bone mineral lability and abnormal renal tubule conservation of calcium, as well as increased gut absorption of calcium, would be altered tissue

vitamin D response. A direct test of this conjecture was carried out in normal men [17;18] who were fed diets containing varying amounts of calcium - normal calcium (22 mmol/day), low-normal (9.3 mmol/day) or very low calcium (4 mmol/day) - with or without calcitriol supplementation, comparing calcium balance after an equilibration period (Figure 4). On both the 22 and 9.3 mmol calcium diets, calcitriol increased both gut calcium absorption and urine calcium; calcium balance was not affected (Figure 4). However on the 4 mmol calcium diet, urine calcium rose far above calcium absorption, and calcium balance became decisively negative when subjects were given calcitriol. Subjects were not hypercalcemic while on calcitriol, suggesting that filtered loads of calcium did not differ between the two groups. These results support the idea that high tissue vitamin D response can produce all the manifestations of IH: increased gut calcium absorption, decreased renal reabsorption, and increased mobilization of calcium from bone. They leave uncertain what mechanisms account for increased tissue vitamin D response: serum calcitriol itself, the vitamin D receptor, or other factors.

The Genetic Hypercalciuric Rat

A rat model of hypercalciuria has been generated by breeding rats for increased urine calcium excretion, and has been called the genetic hypercalciuric stone-forming (GHS) rat [19]. These rats have now been bred for 70 generations, and consistently excrete 8–10 times as much calcium as control rats from the same background strain; they form kidney stones composed of calcium oxalate or calcium phosphate, depending on dietary components [20].

Like humans with IH, the GHS rats have increased gut absorption of calcium, decreased renal calcium reabsorption, and a tendency to bone demineralization; when placed on low-calcium diet, they excrete more calcium than is absorbed, indicating a loss of bone mineral [19]. Overall, they have a systemic abnormality in calcium homeostasis, which appears to be similar to that found in human stone formers with IH. Unlike many humans with IH, $1,25(OH)_2D_3$ levels are normal in the GHS rat. However, significantly higher levels of vitamin D receptors (VDR) have been found in bone, kidney and intestine, compared to normal rats, which would explain the increased sensitivity to $1,25(OH)_2D_3$ that was found in tissues taken from GHS rats [21]. In the gut, vitamin D-responsive genes are expressed at increased levels in response to small doses of $1,25(OH)_2D_3$ [22], with consequent increased expression of proteins related to calcium homeostasis, such as epithelial calcium channels (TRPV6 in gut), and calbindins. The calcium sensing receptor (CaSR) is another $1,25(OH)_2D_3$-responsive gene, and increased levels of CaSR protein and mRNA have also been found in the kidneys of GHS rats compared to control rats fed the same diet [23].

Altered $1,25(OH)_2D_3$ Activity in IH

As shown previously, humans with IH frequently have high $1,25(OH)_2D_3$ levels, and administration of calcitriol to normal men can replicate much of the picture seen in IH [17]. The importance of $1,25(OH)_2D_3$ was further demonstrated by a study of 19 hypercalciuric subjects treated with the P450 inhibitor ketoconazole, which suppresses $1,25(OH)_2D_3$ levels by 30–40% [24]. Twelve subjects had significant decreases in intestinal ^{47}Ca absorption (76 ± 8 vs 62 ± 8%, p < 0.03) and urine calcium excretion (7.6 ± 1.4 vs 5.7 ± 1.1 mmol/day, p < 0.03) during the ketoconazole treatment, suggesting that these abnormalities were at least in part secondary to $1,25(OH)_2D_3$; however, 9 subjects had minimal or no change in gut and renal calcium handling, despite similar drops in $1,25(OH)_2D_3$ levels, suggesting that in their cases, these abnormalities were independent of $1,25(OH)_2D_3$. In addition, of the 12 subjects who responded to ketoconazole, nine had $1,25(OH)_2D_3$ levels that were not elevated, leading to the possibility that increased sensitivity to $1,25(OH)_2D_3$ rather than frankly elevated vitamin D levels caused the alterations. This would be consistent with the abnormalities seen in the GHS rat.

Whether VDR levels are increased in some patients with IH is unsettled. One study has looked at VDR in peripheral blood monocytes from 10 male stone formers with IH, compared with age matched normal controls [25]. The VDR levels were twice as high in the patients with IH (49 ± 21 vs 20 ± 15 fmol/mg protein, $p < 0.008$), while $1,25(OH)_2D_3$ levels did not differ. Increased levels of VDR could lead to an increased tissue effect of $1,25(OH)_2D_3$, despite comparable serum levels of the hormone. However, whether monocyte VDR expression reflects tissue levels of VDR is not known.

Renal Mineral Handling in IH

It is evident that renal calcium handling in most patients with IH differs from normal. As shown in Figure 3, when patients with IH are placed on a very low calcium diet, most are unable to reabsorb calcium with the same efficiency as normal subjects. Even on diets that provide normal or increased amounts of calcium, many subjects excrete calcium in excess of absorption, as shown in Figure 2. Studies have shown that patients with IH have an increased fasting fractional excretion of calcium, and many have fasting hypercalciuria, suggesting a role for decreased tubule calcium reabsorption [26]. Alternatively, the increased absorption of calcium with meals in IH could lead to a post-absorptive rise in blood calcium that increases the filtered load; this has been seen in studies using single high calcium foods or calcium alone [27]. Speculatively, PTH could be suppressed as well, which would decrease tubule calcium reabsorption. In order to better understand the mechanism of increased urine calcium excretion in IH, we studied ten stone formers with IH (5 female) and seven normal subjects (4 female) during a 3-meal day, while on diets composed of whole foods containing equivalent amounts of daily calcium (1160 mg), phosphorus (1240 mg), sodium (2141 mg) and potassium (2427 mg) [28]. Urine was collected hourly, and blood samples taken every 30–60 minutes, during both fasting and fed periods; iothalamate was used as a filtration marker. As shown in Figure 5, neither ultrafiltrable calcium nor filtered load of calcium differed between the normal subjects and those with IH, either while fasting or after meals. However, urine calcium excretion was significantly higher after meals in subjects with IH, and fractional reabsorption was lower both during the fasting and the post-absorptive periods. Therefore, the increased calcium absorbed with meals in IH is removed into the urine mainly via decreased tubule reabsorption. This occurred despite the fact that PTH levels did not differ between normal subjects and those with IH, either fasting or with meals (Figure 6). Although PTH levels fell with eating in both groups, PTH levels overlapped in the two groups, and at any given level of PTH calcium reabsorption was significantly lower in subjects with IH. Urine sodium excretion did not differ between the two groups, as would be expected on this controlled diet.

It is not clear what tubule segment is responsible for abnormal calcium absorption. Prior work has shown that hypercalciuric subjects respond with abnormally large increments in urinary sodium, magnesium and calcium excretion to acute hydrochlorothiazide administration; conversely, acetazolamide raises urine sodium in hypercalciuric patients less than normal [29]. These observations point to an underlying defect in proximal tubule reabsorption of sodium and calcium. As acute thiazide administration acts on the distal tubule to increase both sodium and calcium excretion, the greater increment in calcium excretion in IH may stem from either increased distal delivery due to a decrease in proximal reabsorption or abnormal sensitivity to the drug. By the same token, a pre-existing proximal tubule defect in absorption would lead to a smaller increment in sodium excretion from the effect of acetazolamide, a proximal-acting diuretic, in IH.

Both our work [28] and that of others [7] provides evidence for a defect in renal phosphate reabsorption in some patients with IH. Despite levels of PTH that are not different from normal, fractional reabsorption of phosphate after eating was decreased compared to controls in our study [28]. The ability to conserve phosphorus on a low-phosphorus diet may be compromised

[30], and IH patients have a trend toward negative phosphorus balance, even on normal intakes [12]. Many patients with IH have slightly decreased serum phosphate levels, and perhaps 15–20% are frankly low [7]. It has been suggested that some patients with IH have a defect in phosphate metabolism, which may lead to elevated $1,25(OH)_2D_3$ levels, and increased calcium absorption. To pursue this question, Prie et.al. [31] studied 207 calcium stone formers with normal PTH levels and compared them to 105 normal subjects of similar age (although there was a higher percentage of females among the normals, 53% vs. 31% of the stone formers). The stone formers of both sexes had a significantly decreased renal phosphate threshold (TmPi) compared to normal subjects; values were normally distributed, but shifted to lower values among the stone formers. Among the stone formers, 19% had a TmPi below 0.63 mmol/liter, while only 5% of normals did so. The stone formers with low TmPi had lower serum phosphate levels and higher urine calcium excretion than stone formers with TmPi > 0.63 mmol/liter, but their $1,25(OH)_2D_3$ levels did not differ, although $1,25(OH)_2D_3$ levels of both groups exceeded that in the normal subjects. It may be that abnormal phosphate excretion is part of a more general defect in proximal tubule function, but this defect may not explain raised $1,25(OH)_2D_3$ levels in many patients with IH.

Effect of Dietary Components on Calcium Excretion

Diet is known to have an effect on urine calcium excretion, in both normal subjects and those with IH, and the increasing incidence of stones that has been noted in the Western world over the past several decades surely has more to do with diet than heredity. Several common components of the Western diet can increase urine calcium excretion.

Sodium—Increasing sodium intake is accompanied by increased urine calcium excretion; in healthy subjects the urine calcium increases about 0.6 mmol/day for each 100 mmol/day increment in sodium excretion [30]. Patients with IH have higher calcium excretion at any given sodium excretion, compared to normals [32]; lowering salt intake will decrease calcium excretion, but high sodium intake is seldom the sole cause of IH.

Protein—Increased dietary protein intake will also raise urine calcium excretion, by about 0.04 mmol/gram protein intake in healthy men and women [30]. Metabolism of ingested protein creates an acid load, due to the oxidation of organic sulfur in amino acids to sulfate, leading to increased excretion of net acid and calcium. Administration of alkali reduces both net acid and calcium excretion [12]. The increase in net acid production inhibits renal tubular reabsorption of calcium. Studies in mice have shown that induction of acidosis leads to decreased renal tubular expression of the distal tubular apical calcium channel, TRPV5; mice in which the TRPV5 gene was inactivated did not have an increase in calcium excretion with acidosis [33]. Decreasing protein intake (together with a lower salt intake) has been shown to decrease urine calcium excretion and recurrence of calcium stones [34]. However, urine calcium is higher in patients with IH than among normals at comparable levels of acid excretion suggesting that high protein intake worsens but does not usually cause IH.

Glucose, sucrose, and ethanol—Several rapidly metabolized nutrients cause increased excretion of urine calcium due to diminished tubular calcium and magnesium reabsorption [35], and patients with IH appear to have an exaggerated calciuric response to a carbohydrate load [36]. This effect is not accompanied by augmented sodium excretion; in fact, urine sodium excretion falls significantly with carbohydrate load, in most studies. Urine phosphate excretion may be increased at the same time [37]. The increase in calcium excretion seen with glucose ingestion is additive to that caused by acidosis, suggesting a different site of action [38]. Since the studies looking at this phenomenon used glucose ingestion in the absence of calcium intake, increased gut calcium absorption is not the source of the elevated urine calcium. Insulin may mediate changes in renal tubular calcium reabsorption [39], and some studies suggest an

exaggerated insulin response to carbohydrates in patients with IH [40]. Both calcium stone formers and their relatives have an exaggerated calciuric response to a glucose load compared to normal subjects, suggesting a disturbance in renal tubular function that may be genetic in origin [36].

Bone Mineral in IH

When urine calcium exceeds gut absorption, some of the calcium in urine must be derived from bone. Recent studies have confirmed that bone mineral density is often mildly decreased in patients with IH [41]. Bone seems to participate in the accelerated calcium turnover in IH, but the mediators of this tendency to lose mineral are still unclear. A chapter in this seminar details bone mineral regulation in IH in more detail. (see article by J. Zerwekh).

Genetic Associations of IH and Hypercalciuria

A number of rare monogenic disorders are associated with hypercalciuria, with or without renal calcification, as part of their phenotype [42], however, most of these are unlikely to be confused with IH. Perhaps the best-studied of these disorders is Dent's disease, which is caused by a mutation in a voltage-gated chloride channel, leading to defects in reabsorption in the proximal tubule. The disease is characterized by kidney stones, renal failure, and low molecular weight proteinuria; screening of a group of male patients with typical IH suggests that mutations of this gene are rarely the underlying cause [43].

IH is a complex trait, and is likely to be the result of contributions of several genes, which may differ from individual to individual. Studies searching for such genes have utilized various approaches. A genome-wide linkage study of three kindreds with IH and low bone density identified a locus that encodes a gene for the human soluble adenylyl cyclase [44]. Several sequence variations in the gene tracked with IH in an unrelated group of 80 hypercalciuric patients with kidney stones, compared with a group of non-stone formers [45]. The protein is found in kidney and in bone, and may function as a bicarbonate sensor [46]. Its link to hypercalciuria is still unclear.

Several candidate genes have been screened for possible association with IH; some examples include:

Vitamin D receptor—Polymorphisms of the Vitamin D receptor gene that segregate with hypercalciuria have been detected in some [47], but not all, studies [48]. A study of a cohort of 54 French Canadian sibships found evidence for linkage to nephrolithiasis of a gene in the region of the VDR [49].

TRPV5—The gene for the renal epithelial calcium channel was screened for mutations in 9 families with IH, but none were found [50].

Calcium sensing receptor—A polymorphism has been identified in the gene encoding the calcium sensing receptor which produces a gain-of-function of the receptor when transfected into HEK-293 cells [51]. In a study from Italy, the relative risk of hypercalciuria was increased in individuals carrying this haplotype, both among stone formers [52] and non-stone formers [51], but it explained only 4.1% of the total variance in urinary calcium excretion, and was not felt to be a major gene determining IH.

Sodium-phosphate co-transporter (NPT2a)—A study of 20 subjects with osteoporosis or stones found 2 with *NPT2a* variants, associated with renal phosphate leak [53]. However, a later study of a cohort of 98 French-Canadian families of hypercalciuric stone formers did

not find an association between *NPT2a* gene variations and phosphate leak associated with hypercalciuria and stones [54].

Recently Described Regulators of Urine Calcium and Phosphate Handling

The last few years have given us a clearer picture of renal and intestinal calcium and phosphorus transporters. Regulated renal calcium transport involves a calcium channel, TRPV5, found in the distal nephron; it is closely related to the analogous channel, TRPV6, found in the gut [13]. Proximal tubule phosphate transport is primarily conducted by a sodium-phosphate co-transporter, NPT-2a, a member of the type 2 family of phosphate transport proteins [55]. Both of these transporters are controlled by the PTH - vitamin D axis, but in the last few years, new transport regulators have been identified.

Klotho, a gene product that co-localizes in distal convoluted tubule with TRPV5, appears critically important to calcium reabsorption; klotho-deficient mice exhibit reduced TRPV5 expression and renal calcium reabsorption [56]. The effect of klotho appears to involve its ability to cleave a carbohydrate residue from the calcium channel, which increases TRPV5 activity by trapping it in the plasma membrane [57]. Knockout mice over-express the 25(OH) D-1α-hydroxylase, and have high serum $1,25(OH)_2D_3$ levels with consequent hypercalcemia and hypercalciuria. Subtle variations in klotho could possibly cause a syndrome like IH if $1,25(OH)_2D_3$ increase were not so high as to cause hypercalcemia.

FGF-23, a bone derived hormone, reduces tubule phosphate reabsorption and $1,25(OH)_2D_3$ synthesis. Klotho is required for FGF-23 to mediate its effects via its receptor [58]. Variations in the klotho-FGF23 axis could mediate alterations in calcium and phosphate handling by the kidney, and play a role in IH.

Leptin, an important regulator of nutrient uptake, suppresses formation of $1,25(OH)_2D_3$ [59]. Mice lacking leptin or the leptin receptor manifest high serum $1,25(OH)_2D_3$ levels, hypercalcemia and hypercalciuria. Therefore, variations of leptin expression or receptor could also lead to a syndrome resembling IH.

Data is lacking at present about the role that these interconnected mediators play in IH, if any, but future research may shed some light on this question.

Summary

Perhaps the most important thing to keep in mind about IH is that it is not so much a disease as it is the physiology of people who occupy one extreme of a continuous spectrum of urine calcium excretion rates. Apart from stones and possibly bone disease, IH is simply a benign trait. When we speak of the pathogenesis of IH, we are in all likelihood describing the normal regulation of systemic calcium traffic as viewed at one of its extreme end-points, and comparing that view, usually, to the same regulation at a middle zone of human behavior. Because it is not a disease, we are likely at all times to encounter the extreme complexity of a normal homeostatic regulation. Studies of genes will almost certainly reveal subtle allelic variations as opposed to mutations. The IH rat is instructive in this regard, because it represents simply the in-breeding for a single trait. Understanding the physiology of IH improves our understanding of mineral homeostasis overall, and allows us to provide optimal treatment for our patients who manifest kidney stones.

Acknowledgements

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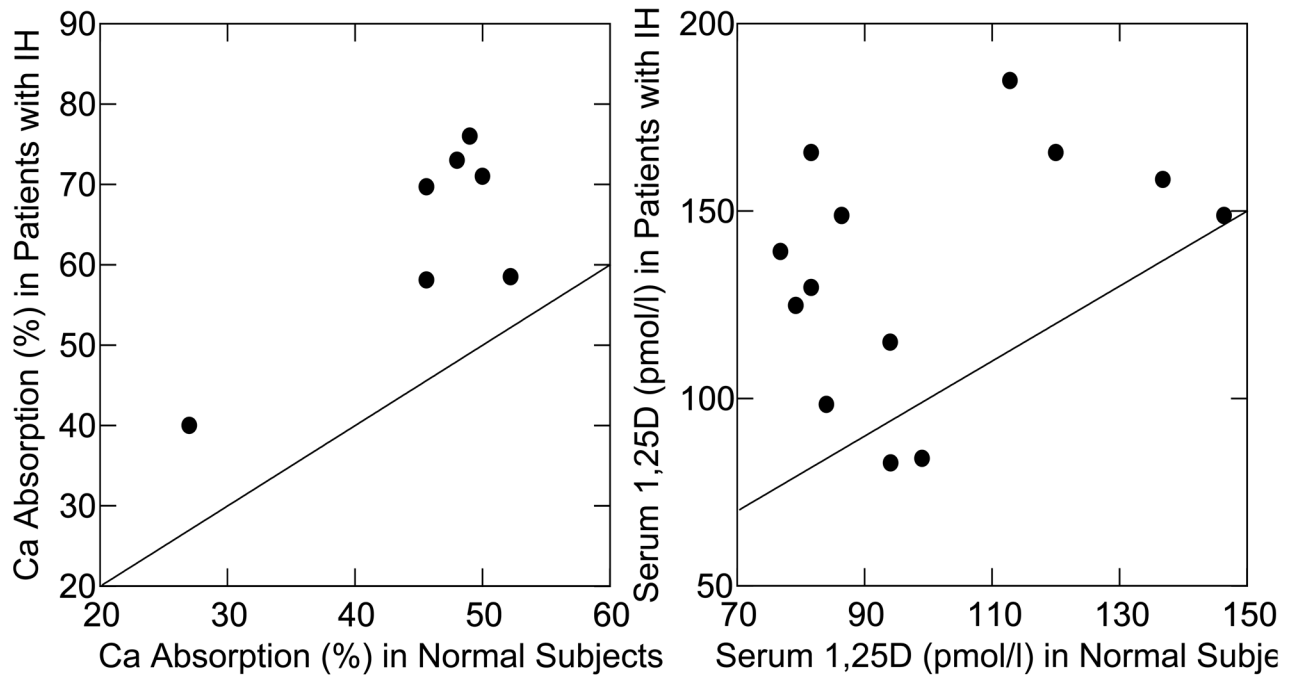
Figure 1. Intestinal Calcium Absorption and Serum 1,25(OH)$_2$D$_3$ Levels in IH and Normals
Fractional absorption of radio-labeled calcium by patients with IH (y-axis, left panel) exceeds that of normal subjects (x-axis, left panel) in 7 studies as shown by the displacements of points about the diagonal line of identity. Each point compares mean values for IH vs. normal within a single study. The same was true for serum 1,25(OH)$_2$D$_3$ levels: those of IH patients (y-axis, right panel) exceeded normals (x-axis, right panel) in 11 of 13 studies. (From reference [10]).
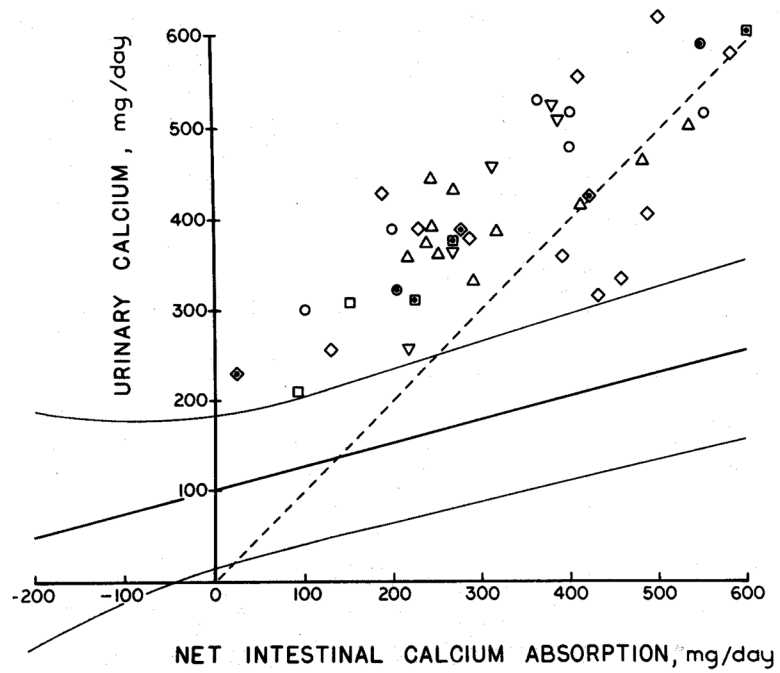
Figure 2. Balance Studies of IH
In each of 42 metabolic balance studies of subjects with IH (individual laboratories reporting data are denoted by differing symbols) IH subjects excreted more calcium (y-axis) for any given level of net calcium absorption (x-axis) than did 203 normal subjects represented by the curving 95% confidence limits. Moreover, in all but 7 subjects, calcium excretion exceeded or equaled net calcium absorption as indicated by points lying above the diagonal dashed line of identity. (From reference [9]).
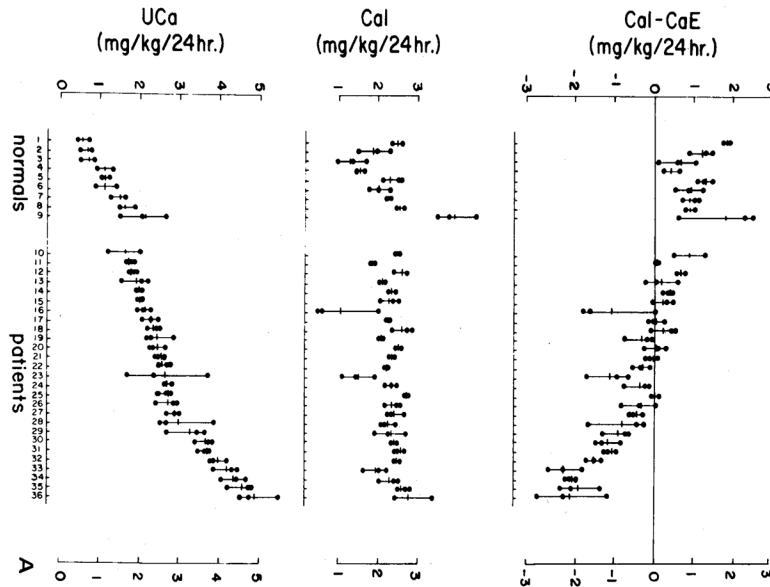
Figure 3. Response of IH and Normal Subjects to very Low Calcium Diet
Nine normal people and 27 people with IH ate a diet containing 2 mg/kg/day of calcium (middle
panel) for 9 days; the actual amounts of calcium ingested during days 7–9 (middle panel) by
normal and IH overlapped. Urine calcium excretion of IH subjects (lower panel) matched or
exceeded the highest values for the normals, as did the difference between ingested and
excreted calcium (upper panel, CaI – CaE). Many IH subjects excreted more calcium than they
ingested, whereas no normal did so; the loss of calcium above diet content can only mean loss
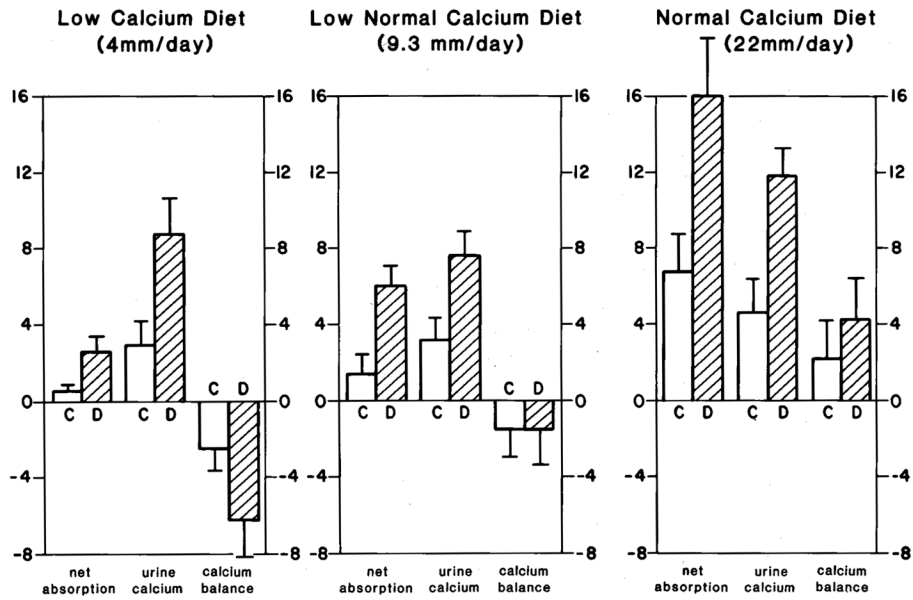of bone mineral into urine. (From reference [16])

Figure 4. Response of Normal Men Given 1,25(OH)$_2$D$_3$ Supplements
On a low calcium diet (left panel) vitamin D (hatched bars) increased net calcium absorption
and urine calcium excretion compared to control periods (clear bars), but because diet calcium
was limiting urine calcium rose more than calcium absorption could and bone mineral balance
became more negative than during the control periods. With 9.3 and 22 mM/day calcium diets
(middle and right panels) calcium balance became neutral (middle panel) and positive (right
panels) respectively. (From Coe FL, Parks JH: Nephrolithiasis: Pathogenesis and Treatment,
2nd ed. Chicago, Year Book Medical Publishers, 1988, p. 113. By permission.)
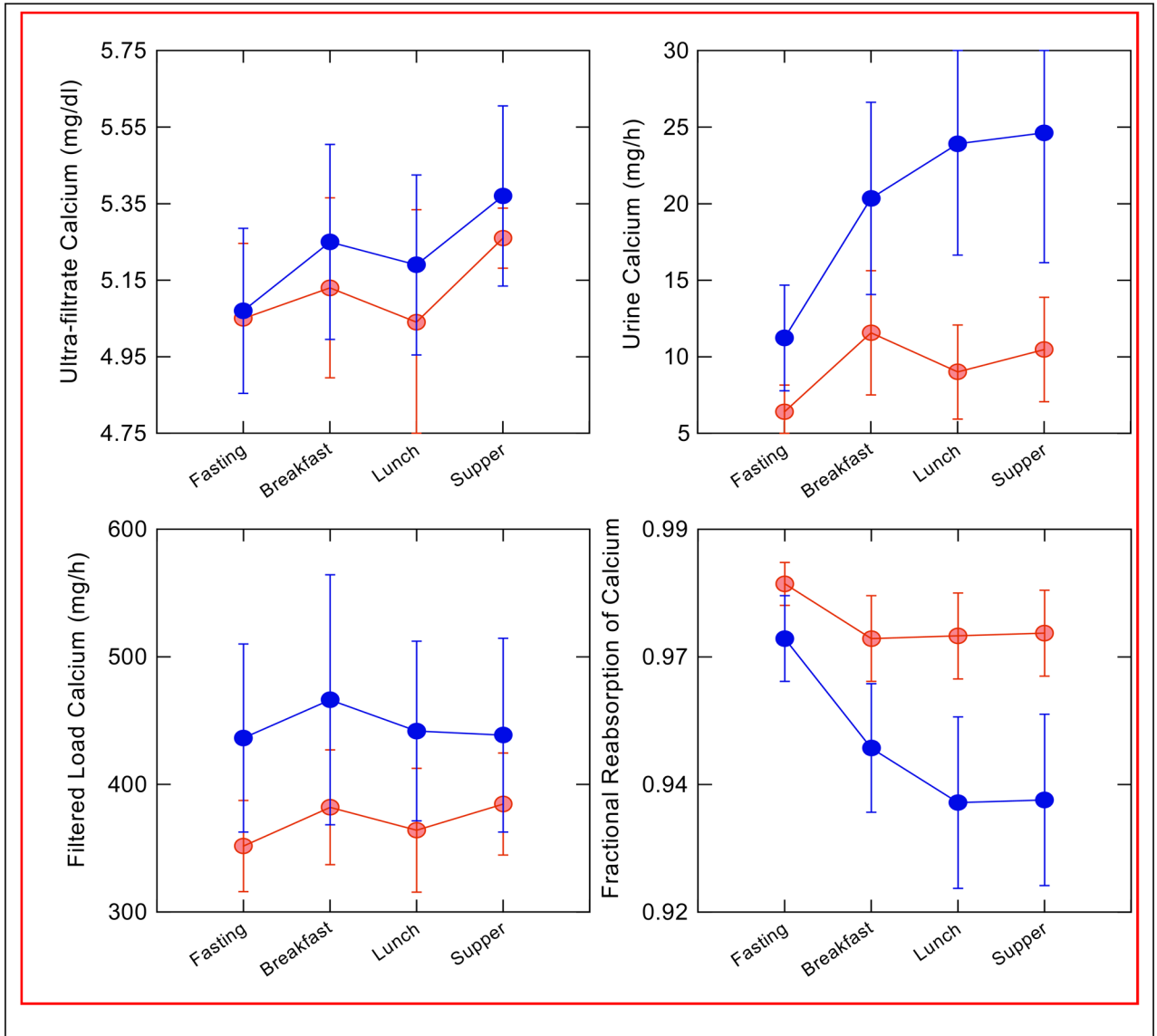
Figure 5. Response of IH Patients (Black circles) and Normals (Grey circles) to a Three Meal Day
Serum ultra-filtratable calcium rose with meals (upper left panel) but values did not differ
between IH and normal, nor did filtered load of calcium (lower left panel). Urine calcium of
IH rose far above normals, and fractional calcium reabsorption of IH was below normals.
Therefore, response of IH to feeding was an abnormally marked fall in tubule calcium
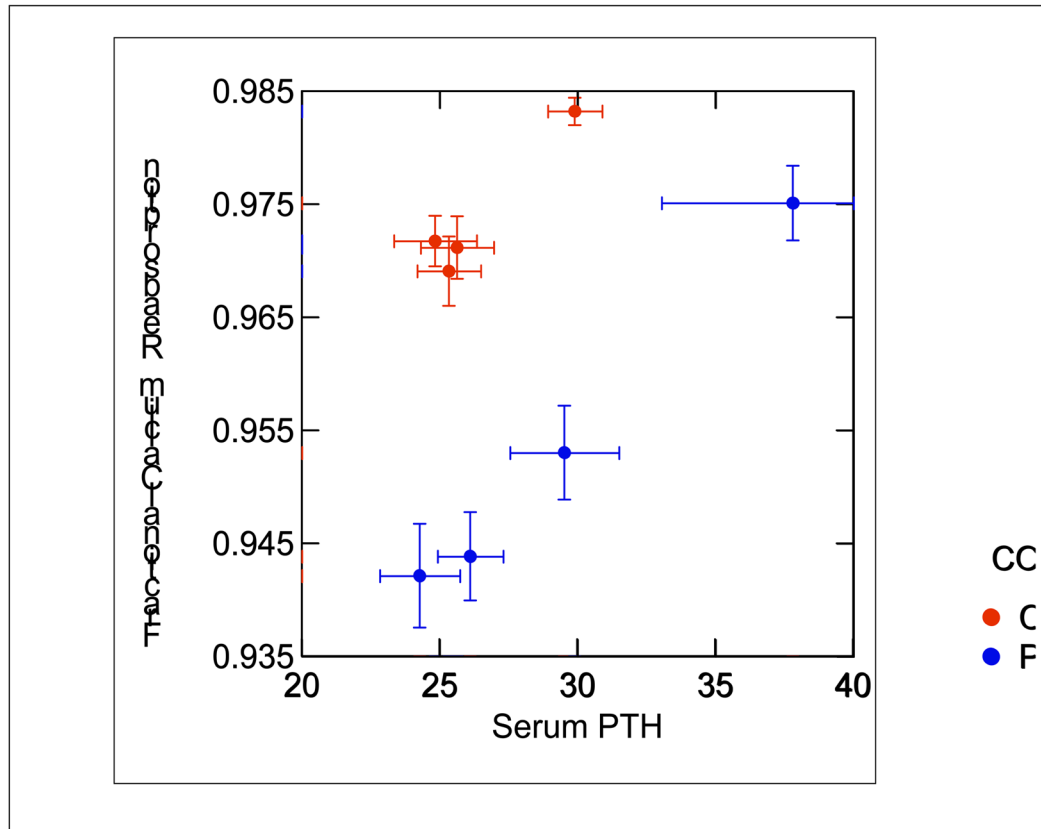reabsorption that accounts for hypercalciuria. (From reference [28]).

Figure 6. Serum PTH in IH (Black circles) and Normal Subjects (Grey circles)
Fasting (upper right values for each group) and during meals, values of PTH did not differ in
IH vs. normal. At all values of PTH, calcium reabsorption of IH was below normal (points are
± SEM). (From reference [28]).