Original Paper

NEPHRON

Nephron 2001;89:384–390

Accepted: October 24, 2000

Prolonged Dietary Calcium Restriction: A Diagnostic Approach in Idiopathic Hypercalciuria

Dominik Müller Paul Eggert

Children's Hospital, University of Kiel, Germany

Key Words

Hypercalciuria · Calcium restriction · Calcitriol · Parathyroid hormone

Abstract

Background: Although frequently observed, the etiology of idiopathic hypercalciuria (IHC) remains largely unknown. A common hypothesis postulates intestinal hyperabsorption and/or a primary renal leak as the pathophysiological basis. The aim of our study was to investigate the regulation pattern of calcium homeostasis in patients with IHC by using a prolonged period of calcium restriction. ***Methods:*** Twenty-seven patients with IHC were investigated. After a 3-week run-in period (dietary calcium content 700–1,000 mg/24 h), a standard calcium reduced diet (300 mg/24 h) was given for 4 weeks. Thereafter, the participants received again a normal calcium-containing diet. Values for urinary calcium, PTH and calcitriol levels of all participants were obtained at different phases of the study. Forty-three healthy persons served as controls. ***Results:*** During calcium restriction, two distinct groups were identified. One group displayed an increase (n = 12) in urinary calcium excretion, the second (n = 15) a marked reduction, respectively. In both groups, the values during calcium restriction were significantly different from baseline ($p < 0.01$). In the first group, the increase of urinary calcium excretion was accompanied by an increase of PTH and calcitriol. These values were also significantly different from baseline values ($p < 0.01$). The control group showed decreasing calcium excretion during oral restriction ($p < 0.01$). ***Conclusion:*** Prolonged calcium restriction proved to be useful in distinguishing apparently two major forms of IHC. The fact that one group displayed the same excretion pattern as the control group raises the question if this group just represents the upper limit of a physiological range. These findings may shed new light on diagnosis, pathogenesis and treatment of patients with IHC.

Introduction

Hypercalciuria (> 0.1 mmol/kg body weight per 24 h or 600 μmol/mmol creatinine) is termed 'idiopathic' if plasma calcium levels are within normal ranges and if known causes for normocalcemic hypercalciuria are excluded. Symptoms of idiopathic hypercalciuria (IHC, McKusick 143870) may vary broadly. Asymptomatic patients account for the largest portion, some of them, especially children, present with abdominal crampy pain and micro-

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Paul Eggert
University Children's Hospital
Schwanenweg 20
D–24105 Kiel (Germany)
Tel. +49 431 597 1810, Fax +49 431 597 1831, E-Mail p.eggert@pediatrics.uni-kiel.de

hematuria, others with nephrocalcinosis and recurrent kidney stones [1, 2]. However, due to the high prevalence and the close relation to calcium-related kidney stone disease, the socioeconomic impact is rather high [3]. Different concepts for the elevated calcium excretion have been postulated. A common hypothesis predicts increased intestinal absorption of calcium on one hand and a primary renal loss on the other hand as the underlying pathomechanism. For the differentiation of both forms, an oral calcium-loading test is widely used [4]. In this approach, the amount of excreted calcium after a standardized oral calcium load gives clues about the origin of hypercalciuria. However, concerns have been raised regarding the specificity and sensitivity of this method [1]. Furthermore, the whole concept of two distinct entities has become a major point of discussion [5]. Finally, two other concepts focus on increased resorption of bone and on alterations of the plasma arachidonic content as the primary event of IHC [6, 7]. The aim of the study presented was therefore to assess the regulation pattern of calcium homeostasis without the manipulation of an oral calcium load. For this purpose, we used a prolonged period of oral calcium restriction in patients with IHC.

Methods

The study had a prospective design. Every patient presenting with IHC at the University Children's Hospital in Kiel, Germany, during the years 1998 and 1999 was included. Before entering the study, all patients were tested clinically and biochemically to exclude underlying diseases like hyperparathyroidism, Bartter's syndrome, Dent's disease, renal tubular acidosis or familial hypomagnesemia with hypercalciuria and nephrocalcinosis (paracellin-1 defect). None of the patients ever took corticosteroids, furosemide, additional vitamin D or other drugs that are known to cause hypercalciuria. None of the patients received thiazides prior to the study. Glomerular filtration rate was estimated by calculation of creatinine clearance. IHC was diagnosed if the calcium excretion exceeded 0.1 mmol/l per kg body weight in three consecutive complete 24-hour collections. Once enrolled in the study, the patients received a 3-week lasting diet containing 700–1,000 mg of calcium per 24 h. No other dietary restrictions were made during the study. After this period, all participants received a calcium-reduced diet containing 300 mg/24 h for the following 4 weeks. Then the normal calcium-containing diet was given again. Blood samples were drawn and analyzed for parathyroid hormone (determined as intact PTH, iPTH) and calcitriol after 3, 7 and 9 weeks. All blood samples were drawn prior to breakfast. Complete 24-hour urinary samples were obtained at weeks 0, 3, 4, 5, 6, 7, 8 and 9, respectively. Forty-three normal, healthy children and adults served as controls. They received the same diets as the patients; urine was collected in the same way as described above.

Calcitriol and iPTH were determined by means of standard RIA procedures on an autoanalyzer (Beckman, Germany). Determinations for creatinine, sodium, uric acid and oxalate were carried out using an automated analyzer (Hitachi 911; Boehringer Mannheim, Germany). Urinary excretion of sodium and uric acid were calculated as related to glomerular filtration rate. Statistical analysis was performed using the Wilcoxon signed rank test. The level of significance was set at $p = 0.01$. For the control group, data were described as mean and standard deviation after passing the test for standard (gaussian) distribution. Two standard deviations were considered as the upper and lower limit of the normal range, respectively.

Results

Twenty-seven patients with IHC were enrolled in the study. The mean age was 8.5 years (median 9.4, range 4.2–22.5). Fifteen of the patients were male, 12 were females. Creatinine clearance revealed normal values in all patients (mean and median 114 ml/min/1.73 m^2, range 107–124). The clinical symptoms of the patients: 2 had calcium oxalate kidney stones, 2 had nephrocalcinosis, 5 had microhematuria, 4 had recurrent urinary tract infections, 7 had recurrent abdominal cramps, 19 were free of symptoms (some patients reported more than one symptom). Measured at the end of the run-in period, urinary excretion of oxalate, sodium and uric acid were not significantly different between patients and controls ($p > 0.01$; table 1).

The urinary calcium excretion of all patients remained elevated (>0.1 mmol/kg/24 h) under the normal diet but changed markedly under low calcium diet. Twelve patients (group 1) did not drop with their excretion but rather displayed a significant increase of urinary calcium over their baseline values (fig. 1). When a normal diet was given again, urinary calcium excretion returned back to baseline values. By contrast, the remaining 15 patients showed a decreasing urinary calcium excretion (group 2), reaching at the end of the diet period values within the normal range (<0.1 mmol/kg body weight per 24 h). When a normal diet was introduced again, their urinary calcium values returned similarly to group 1 back to baseline values. The two groups also showed characteristic and significant differences in their responses to the low calcium diet regarding PTH and calcitriol. While PTH levels in group 1 were significantly different when determined at weeks 3 and 7, they were not significantly different in group 2 (fig. 2). When compared for week 7 (low calcium diet) and week 9 (normal calcium diet), the differences were significant different again. Accordingly, the changes in group 2 were not significantly different. For groups 1 and 2, the same significant changes were observed with respect to changes in plasma calcitriol (fig. 3). These results are summarized in table 2. In the control group,

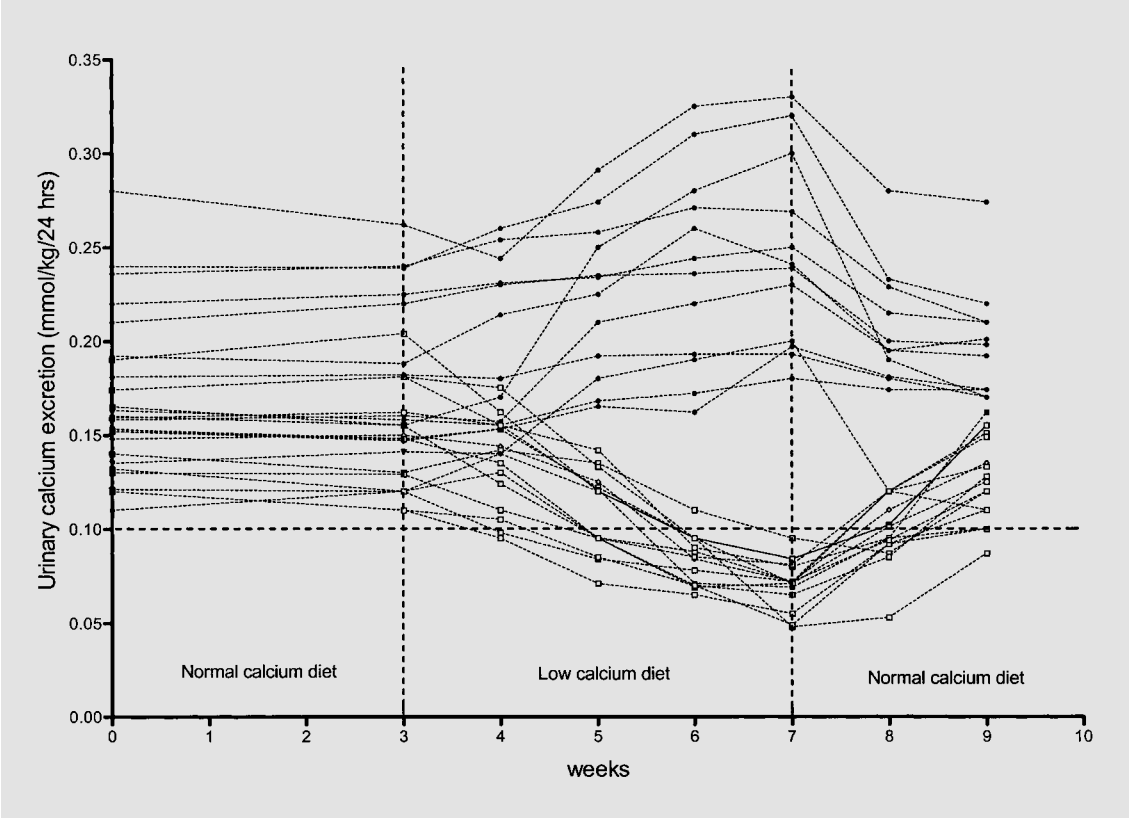

Fig. 1. Urinary calcium excretion of 27 patients with IHC. The data are given for each individual during the course of the study (filled circles: group 1; open boxes: group 2). After a run-in period of 3 weeks, the low calcium diet lasted for 4 weeks. After that, a normal calcium-containing diet was given again. Vertical lines indicate changing of the calcium diet. The upper limit of reference ranges is indicated by a dotted line.

Table 1. Values for fractional sodium excretion, fractional uric acid and urinary oxalate excretion of group 1, group 2 and controls at week 3 of the study

	Group 1 (n = 12)	Group 2 (n = 15)	Controls (n = 43)	p (group 1/C)	p (group 2/C)
FE Na, %	0.67 (0.49–0.82)	0.62 (0.44–0.93)	0.65 (0.55–0.72)	n.s.	n.s.
Oxalate, mg/24 h/1.73 m^2	56.4 (29.5–110.2)	61.7 (36.4–103.3)	55.3 (34.4–96.5)	n.s.	n.s.
FE uric acid, %	8.3 (5.7–11.4)	8.8 (5.2–12.1)	7.9 (6.1–10.2)	n.s.	n.s.

Probability (p) values were calculated for differences between group 1 and the controls and group 2 and the controls. Data are given as median, maximum and minimum, respectively. Statistical analysis is given as p values (the level of significance was set at $p < 0.01$; n.s. = not significant).

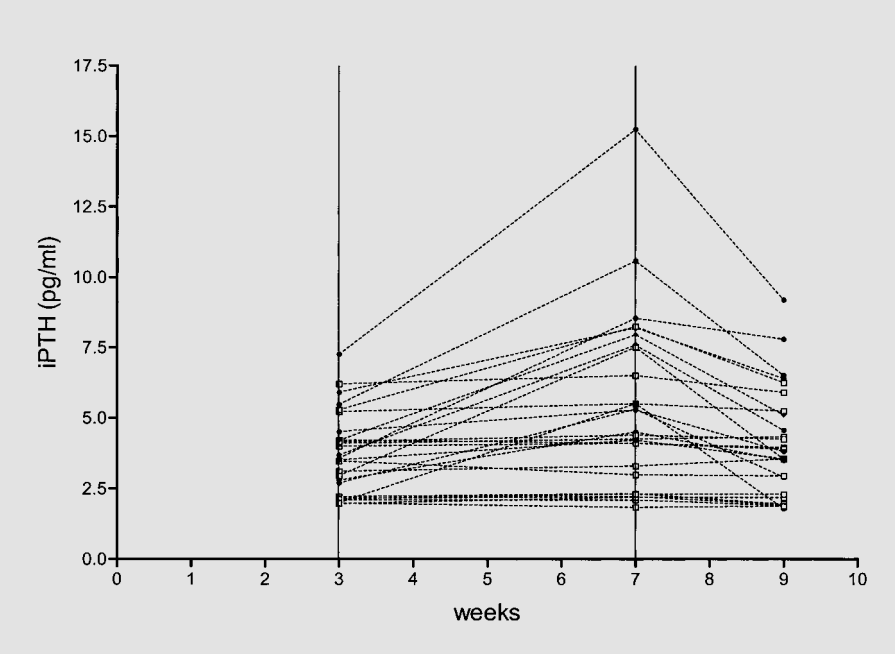

Fig. 2. PTH (pg/ml) levels during the study. Blood samples were taken at weeks 3, 7 and 10, respectively. Data are given for each individual (filled circles: group 1; open boxes: group 2).

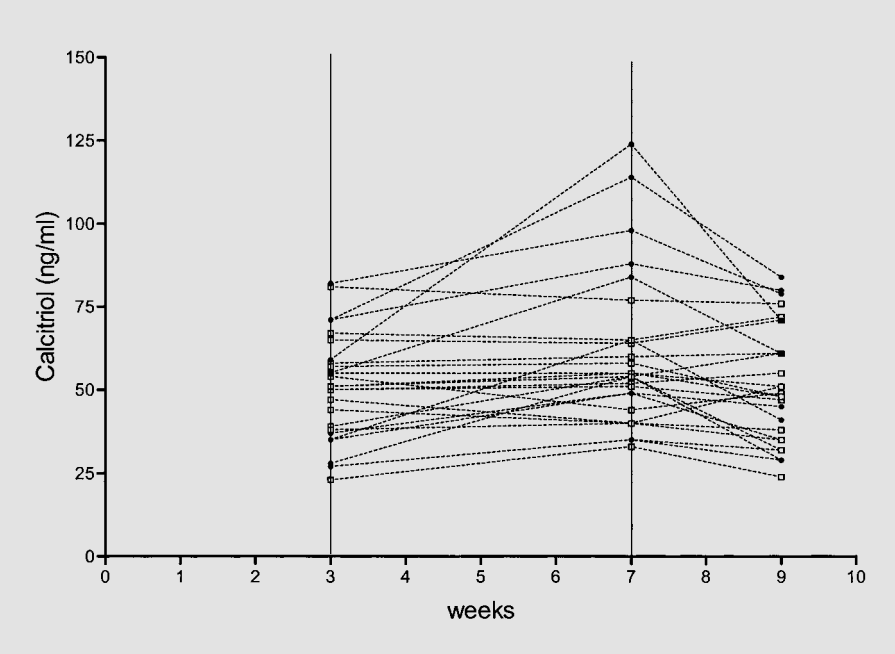

Fig. 3. Calcitriol (ng/ml) during the study. Blood samples were taken at weeks 3, 7, and 9, respectively. Data are given for each individual (filled circles: group 1; open boxes: group 2).

20 females and 23 males were included. The age ranged from 4.1 to 31.2 years, (mean 10.3). Urinary excretion of calcium dropped in the same way as in group 2 and increased again to baseline levels after administration of a regular calcium-containing diet (fig. 4). The values during low calcium diet were significantly different from the beginning and end of the study ($p < 0.01$).

Discussion

The etiology of IHC is still unsolved, but a widely accepted hypothesis suggests the existence of a renal and an intestinal (or hyperabsorptive) form [4, 8, 9]. According to this model, a renal calcium leak would cause hypercalciuria leading to secondary hyperparathyroidism, in-

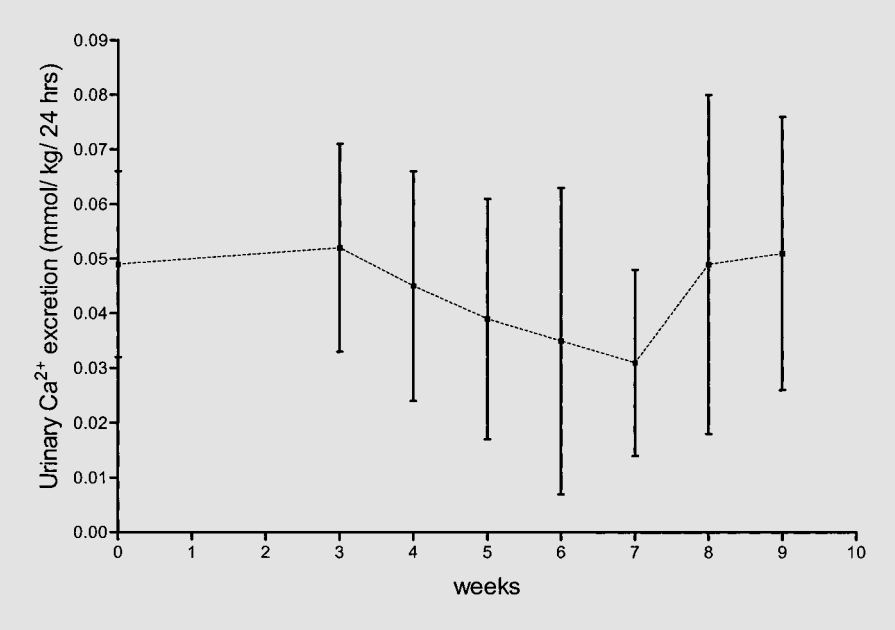

Fig. 4. Urinary calcium excretion (mmol/kg body weight/24 h) of 43 healthy individuals under the study conditions. Data are presented as mean ± 2 SD.

Table 2. Values for urinary calcium excretion, plasma calcitriol and serum PTH during the course of the study

	Week 3	Week 7	Week 9	p (3/7)	p (7/9)	p (3/9)
Urinary calcium, mmol/kg/24 h						
Group 1	0.163 (0.11–0.24)	0.230 (0.18–0.32)	0.174 (0.11–0.22)	0.003	0.003	n.s.
Group 2	0.144 (0.1–0.24)	0.720 (0.26–0.056)	0.131 (0.087–0.21)	0.007	0.005	n.s.
Calcitriol, ng/ml						
Group 1	37 (27–82)	54 (35–114)	41 (29–84)	0.003	0.004	n.s.
Group 2	52 (23–81)	54 (33–124)	51 (24–76)	n.s.	n.s.	n.s.
iPTH, pg/ml						
Group 1	3.57 (2.0–7.2)	7.51 (4.2–15.2)	3.8 (1.8–9.2)	0.003	0.005	n.s.
Group 2	3.47 (1.9–6.2)	3.3 (1.8–10.5)	3.5 (1.8–6.5)	n.s.	n.s.	n.s.

Data are given as median, maximum and minimum. Results of statistical analysis are given as p values (the level of significance was set at $p < 0.01$; n.s. = not significant). For week 3 (normal diet), week 7 (low calcium diet) and week 9 (normal diet), the different data were compared within each group.

creased calcitriol production and subsequently, secondary intestinal hyperabsorption. Primary intestinal hyperabsorption on the other hand would raise serum calcium levels and thereby deliver an increased filtered load to the tubule, suppressing the PTH secretion thus leading to subsequent hypercalciuria. Depending on the dietary status of the affected individual, mobilization of bone-bound calcium could be another additional mechanism of compensation. According to the above-mentioned hypothesis, a reasonable way to separate the two putative forms is provided by testing specific conditions, which – according to the hypothetical models of hypercalciuria – should reveal predictable reactions. Several attempts have been made to characterize hypercalciuria during the fasting state and by its response to thiazides [10]. An unequivocal differentiation, however, could not be achieved. In 1975,

Pak et al. [4] developed a simple and easy-to-perform test. After some days of oral calcium restriction, patients are given an oral calcium load. If the urinary calcium excretion then rises rapidly, diagnosis of intestinal (hyperabsorptive) hypercalciuria can be made. If the excretion of calcium remains more or less constantly elevated, the diagnosis of renal hypercalciuria has to be made. Many concerns exist, however, about the accuracy of this test [11, 12]. Some investigators were unable to find distinct differences; others detected renal and absorptive hypercalciuria in the same patients when examined at different points of time [5]. Furthermore, the concerns about this test were supported by the findings in familial forms of IHC where different subtypes were found within the same family [13], and finally, the question has been brought up if renal and absorptive hypercalciuria may just represent the two ends of one broad spectrum [6].

At first glance our findings seem to confirm the existence of two principally different types of IHC. One subset of individuals (group 1) responds to a low calcium diet with a constant or even increasing urinary calcium loss and a compensatory rise in PTH and calcitriol. The second form (group 2) normalizes urinary calcium excretion under a low calcium diet. The corresponding PTH and calcitriol levels remain unaffected. This shows that prolonged dietary calcium restriction is able to reveal two major subtypes of IHC. Although other studies have been carried out in the past using dietary calcium restriction, our study is the first that extends the calcium restriction over a longer period. When compared to former studies, our data clearly demonstrate that a discrimination of different phenotypes is not possible after a short-lasting diet of e.g. 1 week. Although the calcium excretion is already distinct, the different patterns of PTH and calcitriol were not statistically significant before the second week of the diet. Coe et al. [14] were able to find two groups of patients with IHC, but did not find differences concerning PTH levels after 9 days of a low calcium diet. Based on this finding, they concluded that a clear differentiation of two entities is not reasonable. The extension of their important study for another week probably would have led to different findings.

Although the distinct patterns of calcium excretion as well as the course of PTH and calcitriol levels allow speculating on the underlying basis of our findings, it should be realized that even the groups identified might be heterogeneous and more detailed and extended studies are necessary to determine whether more subgroups exist. Regarding the different groups, it is tempting to assign the attributes 'renal' and 'intestinal'; on the other hand, one should realize that the molecular basis for such a classification still remains elusive. Today, some important candidate genes have already been excluded [15, 16]. Two other promising studies, reporting about putative susceptibility regions on chromosome 1q23.3-q24, and in close vicinity to the vitamin D receptor gene on chromosome 12, respectively, still await more detailed investigation [17, 18].

Another so far not reported finding correlated with this putative defect is represented by the increasing calcium excretion during the calcium-restricted diet. Even though the regulation mechanism is intact in these patients, the data suggest a certain hyperreactivity of the compensation mechanism. Increased sensitivity was also found in studies on genetically hypercalciuric rats, indicating a hyperresponsiveness of vitamin D receptor gene expression to calcitriol [19, 20]. Disordered control of calcitriol has also been postulated for humans with IHC [21]. For patients with IHC this could mean that an existing hyperresponsiveness to vitamin D does exist but is not relevant as long as the levels of calcitriol are within normal ranges.

It is interesting to see that group 2 showed the same pattern of urinary calcium excretion as the control group. The difference was made up by the absolute amounts of urinary calcium excreted. This raises the question if the type of IHC in group 2 rather constitutes the upper end of the physiological spectrum of calcium excretion than representing a primary pathological condition. It can be speculated if the uptake of calcium in these patients is regulated by the dietary amount of calcium itself.

Beyond these theoretical considerations, the data presented here have an important clinical impact. They demonstrate that it is crucial to determine in every patient the subtype of IHC. Only group 2 patients might be therapeutically influenced with a low calcium diet while a patient with group 1 form of IHC will impair severely by developing secondary hyperparathyroidism. This also stresses the importance of the recommendations for daily calcium intake [22].

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