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ORIGINAL PAPER

Evidence for metabolic origin of absorptive hypercalciuria Type II

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Abstract The objective of this retrospective data analysis was to test the hypothesis that absorptive hypercalciuria Type II (AH-II) is a less severe variant of absorptive hypercalciuria Type I (AH-I), a common cause of calcareous stones. 24-h urinary calcium obtained on constant metabolic diets was retrieved from several data sources, including those of the authors and another group. On a low calcium diet (10 mmol calcium), 35 patients with AH-II were compared with 70 non-stone formers (NSF) and 76 patients with AH-I. On a high calcium diet (25 mmol calcium/day), 10 patients with AH-II were compared with 35 NSF and 32 with AH-I. On a low calcium diet for all participants, 24-h urinary calcium in AH-II (4.13 ± 0.63 mmol/day) was significantly higher than in NSF (3.06 ± 1.17 mmol/day), but significantly lower than in AH-I (6.11 ± 1.14 mmol/day) ($p < 0.001$). In a smaller subset, fractional intestinal calcium absorption in AH-II (65.0 ± 11.1%) was intermediate between NSF (50.0 ± 6.4%) and AH-I (71.0 ± 6.7%) ($p < 0.001$ between AH-II and other groups). On a high calcium diet, the rise in urinary calcium in AH-II was significantly higher than in NSF, but not as marked as in AH-I. Estimated calcium balance in AH-II was similar to NSF, but significantly more positive than AH-I. In conclusion, AH-II shares with AH-I the same metabolic disturbance(s) stimulating intestinal absorption and renal excretion of calcium but to a lesser degree. Bone might be spared in AH-II.

Keywords Hypercalciuria · Urolithiasis · Absorptive hypercalciuria

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Introduction

Following the original description of absorptive hypercalciuria as a cause of calcium stones by Nordin et al. [1], we used as the provisional diagnostic criteria of this condition the presence of hypercalciuria (≥5 mmol/day on a diet restricted in calcium, sodium and phosphorus) with normal serum calcium and parathyroid function [2]. The invariable finding of high intestinal calcium absorption (by a radioisotopic method or calciuric response to single oral calcium load) lent support to the pathogenetic scheme implicating "absorptive" origin of hypercalciuria.

In 1980, we separated absorptive hypercalciuria into two forms [3]. Absorptive hypercalciuria Type I (AH-I) referred to patients who fulfilled the above diagnostic triad of high intestinal calcium absorption, hypercalciuria, and normal parathyroid function. We coined a term absorptive hypercalciuria Type II (AH-II) to describe those who had high intestinal calcium absorption and normal parathyroid function, but normal urinary calcium (<5 mmol/day on a constant restricted diet). We inferred that AH-II represented a less severe variant of AH-I based on circumferential findings.

By retrospective data analysis of published reports and unpublished studies, we offer justification for consideration of AH-II as a part of the syndrome of absorptive hypercalciuria.

Materials and methods

Sources of data

We obtained data for this analysis from several sources (Table 1). All studies were conducted while participants were kept on constant metabolic diets.

Table 1 Sources of data for evaluation on two calcium intakes

	No. of subjects or patients		
	NSF	AH-I	AH-II
10 mmol Ca/day			
Protocol #2-10-73	35	44	25
Broadus et al. [6]	25	29	7
Matsumoto et al. [8]	10		
Unpublished data		3	3
Total	55	76	35
25 mmol Ca/day			
Broadus et al. [6]	25	29	7
Matsumoto et al. [8]	10		
Unpublished data		3	3
Total	35	32	10

Unpublished data from protocol #2-10-73 on an intake of 10 mmol calcium/day in non-stone formers (NSF), AH-I and AH-II

From February 1973 to November 1976, all patients with recurrent calcium urolithiasis referred to the Mineral Metabolism group at the University of Texas Southwestern Medical Center were evaluated using an inpatient protocol (#2-10-73). While kept on a "constant restricted diet" or "low calcium diet" [10 mmol Ca (or 400 mg), 100 mmol sodium and 26 mmol phosphorus/day], the participants underwent the following tests: (a) 24-h urinary calcium, (b) serum calcium, (c) urinary cyclic AMP and/or serum PTH, (d) fractional calcium absorption (from fecal recovery of orally administered ^{47}Ca mixed with a stable calcium load of 2.5 mmol) [2], and (e) calciuric response over 4 h following 25 mmol oral calcium load [4]. Estimated calcium balance was calculated by the difference in absorbed calcium (Ca_A) and corresponding 24-h urinary calcium (Ca_{UV}) [2, 5]. Ca_A represented the product of fractional calcium absorption and the dietary calcium of 10 mmol/day.

There were 35 NSF (19 men and 16 women), 44 patients with AH-I (39 men and 5 women) and 25 (20 men and 5 women) with AH-II. All patients with AH-I or AH-II had normal serum calcium and urinary cyclic AMP and/or serum PTH, and high 4-h urinary calcium post-1 g calcium load $\geq$0.56 mmol/mmol creatinine (or 0.2 mg/mg). However, 24-h urinary calcium was $\geq$5 mmol/day in AH-I, but was less than this value in AH-II, following the diagnostic separation we had described in 1980 [3].

Published report by Broadus et al. [6] on dietary calcium intake of 10 mmol and 25 mmol/day in NSF, AH-I and AH-II

Broadus et al. [6] reported on 25 NSF (14 men and 11 women) and 36 patients (22 men and 14 women) with absorptive hypercalciuria. They included all patients with exaggerated calciuric response to oral calcium load and normal parathyroid function [7], regardless of 24-h urinary calcium. For this report, we categorized the patients into AH-I or AH-II, depending on whether their 24-h urinary calcium on a constant restricted diet (containing 10 mmol calcium/day) was $\geq$5 or <5 mmol/day, respectively. There were 29 patients with AH-I and 7 with AH-II.

From all subjects and patients, Broadus et al. [6] obtained 24-h urinary calcium on two diets. A "low calcium diet" contained 10 mmol (400 mg) calcium, 26 mmol phosphorus and 69–109 mmol sodium/day. A "high calcium diet" contained 25 mmol (1,000 mg) calcium/day and the same amounts of other components.

Published report by Matsumoto et al. [8] on dietary intake of 10 mmol and 25 mmol/day in NSF

A 24-h urinary calcium was obtained from 10 healthy NSF kept on both low calcium (10 mmol calcium, 100 mmol sodium, and 26 mmol phosphorus/day) and high calcium diet (25 mmol calcium, 100 mmol sodium and 42 mmol phosphorus/day).

Data from an unpublished study by Sakhaee et al. on dietary calcium intake of 10 mmol and 25 mmol calcium/day in AH-I and AH-II

One of the authors of this report (K.S.) evaluated three patients with AH-I (2 men, 1 woman) and three with AH-II (2 men, 1 woman), while they were kept on low and high calcium diets.

Kappa coefficient of agreement between two methods for detecting AH-II

From a previously published study [9], 916 patients with idiopathic calcium oxalate nephrolithiasis (with normal serum calcium and PTH) had all data necessary for the diagnosis of AH-II by the following two methods. Method 1 was the published criteria [3], comprised of: 24-h urinary calcium following 25 mmol calcium load $\geq$ 0.56 mmol/mmol creatinine and 24-h urinary calcium on instructed restricted diet <5 mmol/day. Method 2 was a potentially simpler approach, with 24-h urinary calcium $\geq$5 mmol/day on a random diet (with customary intakes of calcium, sodium, and animal proteins), but <5 mmol/day on an instructed low calcium diet. We retrieved the numbers of patients with and without AH-II by both methods for the calculation of kappa coefficient of agreement.

Statistical analysis

Kappa measure of agreement has a value of zero if there is no more agreement between two judges or tests as can be expected on the basis of chance. Kappa has a value of 1 if there is perfect agreement. Kappa values lower than 0.4 represent poor agreement. Kappa coefficients were calculated with Epi Info 6 (Center for Disease Control and Prevention, Atlanta, GA).

Mean and standard deviation of data from multiple studies were estimated by weighted averages of the individual study means and standard deviations on the basis of sample size. *t* tests were performed with SAS release 9.1 (SAS Institute, Cary, NC) to determine differences between groups. Bonferroni corrections were applied to adjust for multiple testing.

Results

Table 1 shows the number of NSF, patients with AH-I and AH-II from various data sources, who had been evaluated on an intake of 10 and 25 mmol calcium/day.

24-h urinary calcium on an intake of 10 mmol Ca/day

In protocol #2-10-73, the mean urinary calcium in 35 NSF was well below 5 mmol/day, whereas it was considerably above this value and significantly higher in 44 patients with AH-I (Fig. 1, first column in left panel). Similar differences were disclosed when comparing 25 NSF (from Broadus et al. and Matsumoto et al.) with 32 patients with AH-I (from Broadus et al. and unpublished data) (Fig. 1, second column). When all sources were combined, urinary calcium in 76 patients with AH-I of 6.11 ± 1.14 mmol/day was significantly higher than in 70 NSF of 3.06 ± 1.17 mmol/day ($p < 0.001$). The upper normal limit (defined as mean + 2 SD in NSF) was 5.14 mmol (206 mg)/day for the combined data sources. In 35 patients with AH-II, the mean urinary calcium of 4.13 ± 0.63 mmol/day was significantly higher than that of 70 NSF ($p < 0.001$), but significantly lower than in 76 patients with AH-I ($p < 0.001$).

24-h urinary calcium on an intake of 25 mmol Ca/day

In NSF, the mean urinary calcium on an intake of 25 mmol calcium/day was significantly higher than on an intake of 10 mmol calcium/day (4.39 ± 1.50 mmol/day, $n = 35$ vs. 3.06 ± 1.17 mmol/day, $n = 70$, $p < 0.001$) (Fig. 1). On an intake of 25 mmol calcium/day, urinary calcium was much higher in 32 patients with AH-I than in 35 NSF (9.38 ± 1.27 vs. 4.39 ± 1.50 mmol/day, $p < 0.001$) (Fig. 1, right panel). In 10 patients with AH-II, urinary calcium of 7.01 ± 1.47 mmol/day was significantly higher than in 35 NSF but significantly lower than in 32 with AH-I (both $p < 0.001$).

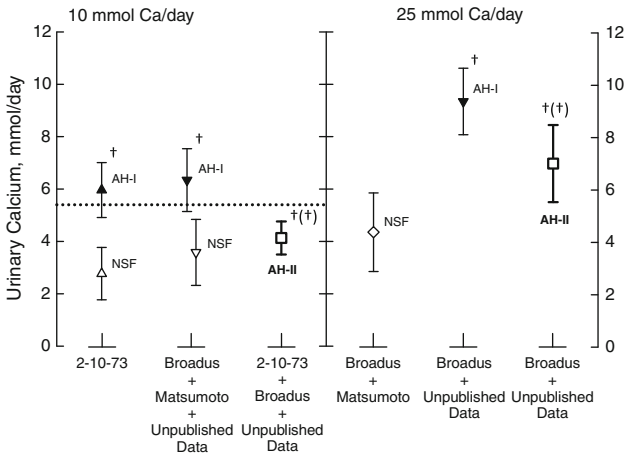

Fig. 1 24-h urinary calcium on an intake of 10 and 25 mmol calcium/day in non-stone formers (NSF), patients with absorptive hypercalciuria Type I (AH-I) and Type II (AH-II). Data were retrieved from various sources. *Symbols* and *bars* indicate mean ± SD. On a diet of 10 mmol calcium/day (*left panel*), *the dashed horizontal line* indicates upper normal limit, or mean + 2 SD in NSF (for the combined data). Significant difference between NSF and AH-I is indicated by † for $p < 0.001$ for the separate data sources. For the combined data, significant difference between AH-II and NSF is shown by † and between AH-II and AH-I by (†) for $p < 0.001$. On a diet of 25 mmol calcium/day, † indicates $p < 0.001$ for the difference between NSF and AH-I and between NSF and AH-II. (†) indicates the same level of significance between AH-II and AH-I

Comparison of data between three groups from protocol #2-10-73 on an intake of 10 mmol calcium/day

24-h urinary calcium was significantly higher in both AH-I and AH-II than in NSF ($p < 0.001$, Table 2). The value in 25 patients with AH-II was intermediate between the other two groups, being significantly higher than in 35 NSF, but significantly lower than in 44 patients with AH-I ($p < 0.001$).

4-h urinary calcium after an oral load of 25 mmol calcium was significantly higher in AH-I and AH-II than in NSF (Table 2). There was no significant difference between AH-I and AH-II. Fractional (intestinal) calcium absorption was significantly higher in AH-I than in NSF, with nearly a total separation of individual values between the groups at a value of 61%. In AH-II, it was significantly higher than in NSF though significantly lower than in AH-I. Eighteen of 25 patients with AH-II had high fractional intestinal calcium absorption >61%. $Ca_A - Ca_{UV}$ in AH-II was 2.3-fold higher than in AH-I ($p < 0.001$), but not significantly different from NSF.

Kappa coefficient of agreement

There was a poor agreement (kappa coefficient of 0.399) between the published method [3] for diagnosing AH-II

Table 2 Data from 2-10-73 (restricted diet)

	NSF	AH-I	AH-II
Urinary Ca (mmol/day)	2.77 ± 1.00	5.96 ± 1.05†	4.07 ± 0.67$^{\dagger(\dagger)}$
4-h urinary Ca, post-Ca load (mmol/mmol creatinine)	0.34 ± 0.11	0.76 ± 0.20†	0.73 ± 0.14†
Fractional Ca absorption (%)	50.0 ± 6.4	71.0 ± 6.7†	65.0 ± 11.1$^{\dagger(*)}$
$Ca_A - Ca_{UV}$ (mmol/day)	2.46 ± 0.76	1.13 ± 0.97†	2.42 ± 0.9$^{(\dagger)}$

Data are presented as mean ± SD

$Ca_A - Ca_{UV}$ difference in absorbed calcium and urinary calcium

Statistical significance versus non-stone formers (NSF) is indicated by * for $p < 0.05$ and † for $p < 0.001$. Symbols in parenthesis indicate statistical significance versus AH-I

(requiring fast and calcium load test) and the simple method based on 24-h urinary calcium on random and restricted diets.

Discussion

The objective of this retrospective analysis was to explore the biochemical presentation of stone-forming patients with AH-II, considered to be a less severe variant of AH-I [3]. Many patients with this poorly investigated variant were shown to share certain features with those of AH-I, indicative of disturbance(s) in intestinal calcium absorption.

Our original definition of absorptive hypercalciuria in 1974 required a triad of high intestinal absorption of calcium, hypercalciuria (≥5 mmol/day on a constant restricted diet with calcium intake of 10 mmol/day), and normal parathyroid function among patients with calcareous stones [2]. The goal of our ambulatory diagnostic protocol in 1980 [3] was to categorize all referred patients with stones into different medical causes. When we encountered some patients who shared the above features but presented with normocalciuria, we subcategorized absorptive hypercalciuria into two variants—Type I with hypercalciuria and Type II with normocalciuria.

Since then, our pathophysiological exploration has focused on AH-I, believing that this variant would more clearly reveal underlying mechanisms for the high intestinal absorption and renal excretion of calcium. On the other hand, AH-II was largely ignored.

In this retrospective data analysis, we offer several lines of evidence suggesting that AH-II might share some of the underlying metabolic disturbances of AH-I. For this purpose, we took only the data obtained on constant metabolic diets to exclude the role of other dietary factors on intestinal absorption and renal excretion of calcium [10, 11].

First, compared to NSF, patients with AH-II had significantly higher 24-h urinary calcium on a low calcium diet (10 mmol calcium, 100 mmol sodium and 26 mmol phosphorus). Even though their individual urinary calcium was less than 5 mmol/day as previously defined [3], the mean urinary calcium was nearly 50% higher than that of NSF. Second, fractional calcium absorption from a stable calcium load of 2.5 mmol was increased (above the upper normal limit) in 72% of patients with AH-II. Third, consistent with how this entity was defined [3], all patients with AH-II had an exaggerated 4-h calciuric response to a single oral calcium load of 25 mmol. Fourth, by combining data from our group and elsewhere [6], this report showed a differing response to a high calcium intake (25 mmol calcium/day) during a constant dietary setting. While 24-h urinary calcium rose modestly in NSF when calcium intake was increased from 10 to 25 mmol/day, it increased markedly in patients with AH-I. The rise in urinary calcium in AH-II was intermediate between NSF and AH-I.

Another finding of considerable interest concerned estimated calcium balance, derived from the difference in absorbed calcium and corresponding 24-h urinary calcium. Absorbed calcium was calculated as the product of fractional calcium absorption (from 2.5 mmol stable calcium load) and the dietary calcium intake (10 mmol/day). It probably represented the total luminal to serosal uptake of calcium, exclusive of serosal to luminal secreted calcium on a low calcium diet [2, 5]. Thus, the estimated calcium balance by this method exceeded true calcium balance (obtained from direct measurement of calcium in diet, feces and urine) by the amount of net secreted calcium. In this study, we confirmed a prior report [2] showing that the estimated calcium balance was much lower in AH-I than in NSF. This study also revealed a new finding that the value in AH-II was nearly the same as in NSF, but significantly higher (by 2.3-fold) than in AH-I. The higher estimated calcium balance in AH-II than in AH-I might reflect a less efficient reabsorption of secreted calcium leaving a larger net secreted calcium. As another possibility, AH-II might be partially spared from bone loss that has been implicated in AH-I [12]; in other words, a lower amount of skeletal calcium might contribute to urinary excretion in AH-II than in AH-I. The exaggerated calciuric response to a single oral calcium load (25 mmol) in both variants suggests that the

skeletal contribution to urinary calcium might be obscured during a high calcium diet. Overall, this explanation is consistent with the finding of Coe et al. [13], revealing increased 24-h urinary calcium in hypercalciuric stone formers during severe calcium restriction.

Thus, compared to AH-I, AH-II had lower 24-h urinary calcium, fractional calcium absorption and 24-h urinary calcium on a high calcium intake, but an equivalent calciuric response to a single oral calcium load. AH-II also had higher estimated calcium balance, possibly indicating a less severe skeletal involvement. AH-II, therefore, shared some but not all the metabolic disturbance(s) associated with AH-I.

The above findings have diagnostic and therapeutic implications. As implied by the report of Broadus et al. [6], absorptive hypercalciuria might be detected from the difference in 24-h urinary calcium on calcium intakes of 10 and 25 mmol/day without the use of a cumbersome fast and calcium load test [4, 7]. AH-I would be revealed by exaggerated urinary calcium excretion on both low and high calcium diets, and AH-II by a borderline accentuated rise in urinary calcium on high calcium intake. This approach might have a practical value if it can be applied in an ambulatory setting using dietary instruction.

In our unpublished work, we recently showed that AH-I can be reliably diagnosed on the basis of high urinary calcium ($\geq$5 mmol/day) on both random (customary) and low calcium (instructed) diets in an ambulatory setting without the fast and calcium load test. This finding led us to explore whether AH-II might be detected from elevated urinary calcium on a random diet but normal urinary calcium (<5 mmol/day) on a low calcium diet. Unfortunately, kappa coefficient of agreement between the simple approach and the published criteria [3] was poor. Thus, we cannot substitute the random diet for the high calcium diet (25 mmol/day) in detecting AH-II.

Therapeutically, the use of low and high calcium diets might reveal those patients with AH-II with sufficient hypercalciuria to merit treatment with a hypocalciuric agent [14, 15]. From this report, many but not all patients with AH-II revealed sufficient hypercalciuria on a high calcium intake to qualify for treatment.

A strength of this report is the use of constant diets. As an example, the imposition of a low calcium diet permitted an almost complete separation of 24-h urinary calcium between AH-I and NSF at a value of 5 mmol calcium/day. This finding suggested that insufficient control of other dietary factors affecting calcium excretion [10, 11] could have accounted for a poor separation of 24-h urinary calcium between stone formers and NSF during a random diet [16, 17].

We acknowledge that the number of patients with AH-II who had undergone evaluation during an intake of 25 mmol calcium/day was small. Due to limited resources, the likelihood of evaluating additional patients in a constant dietary setting in the near future is small. We offer the available data to elicit interest in others for further exploration.

In summary, AH-II is not due to dietary indiscretions, but shares the same metabolic disturbance(s) as AH-I but to a lesser degree, with borderline disturbance(s) in intestinal absorption and renal excretion of calcium. A search for a simple ambulatory protocol for the diagnosis of AH-II, based on 24-h urine collections without the use of fast and calcium load test, is warranted. Moreover, measurement of bone mineral density is indicated to clarify whether or not bone might be spared in AH-II.

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