Sensitivity of parathyroid hormone response to calcium intake

Dear Sir:

In a recent issue of the Journal, Martini and Wood (1) concluded that calcium carbonate, milk, and calcium-fortified orange juice are approximately equivalent with regard to calcium bioavailability. Their conclusion was based mainly on the results of the use of a pharmacodynamic method, i.e., a decrease in serum parathyroid hormone (PTH) in response to the absorptive calcemia produced by each of the 3 sources. Although their conclusion may well be correct, it is questionable whether their data are adequate to support it.

It is troubling that their measurements of serum calcium did not detect the absorptive calcemia responsible for the decrease in PTH. Others (2, 3) have shown that calcemia is detectable, with a 1% change in serum calcium evoking an ∼10% change in PTH. Thus, the decrease in PTH 2 h after intake of the calcium carbonate and orange juice sources (∼36%) should have been associated with a 3–4% increase in serum calcium. Although the data of Martini and Wood fail to show even a hint of an increase in serum calcium, such an increase must have occurred, as indicated not only by the PTH response they described but also by the increase in urinary calcium excretion found at the 4-h time point.

The authors reported decremental areas under the curve (AUCs) for PTH (as a percentage of baseline). An equivalent treatment is to normalize each set to its own baseline. The time course of such relative PTH values for the 4 h over which Martini and Wood conducted their experiment is shown in Figure 1; these values are derived from the data in their Table 2. As is visually evident, the time course for milk differs considerably from that of the other 2 sources. As can be calculated from the data in Table 2 of their article, the decremental relative AUCs for the 3 sources are −1.00 for calcium carbonate, −0.67 for milk, and −1.14 for the calcium-fortified orange juice. These values cannot be easily converted to the percentage decrements reported in their article, and it is not possible to harmonize the reported decrements with the data in Figure 1. As is evident in Figure 1, calcium carbonate and fortified orange juice cannot have the same AUC value, as Martini and Wood reported. Moreover, the difference between milk and calcium-fortified orange juice is substantial. In this case, it looks as if milk is being absorbed more slowly than are the other sources, and one can only wonder what the time course of PTH might have looked like after the 4-h time point at which Martini and Wood stopped their measurements.

On the basis of the data in Figure 1 and on the results of other similar studies, 4 h is not long enough to assess AUC accurately. Factors that change the rate of gastric emptying, for example, will hasten or delay calcium entry into the system, and an adequate comparison between sources requires following the PTH curve until it returns to a value similar to baseline.

My extensive laboratory experience with the PTH response during absorptive calcemia over the past several years has convinced me that, although it greatly amplifies the calcemic signal, the PTH response is sufficiently variable from person to person and from time to time to be relatively insensitive as a means of detecting differences in absorption between calcium sources. This is certainly even more true if the time course is not long enough to capture the full AUC.

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REFERENCES


Reply to RP Heaney

Dear Sir:

In his letter about our recent article (1), Heaney points out his concern that acute postprandial suppression of parathyroid hormone (PTH) concentrations should not be used as a measure of calcium bioavailability. We had similar concerns, which led us to
measure a battery of potential calcium-dependent biomarkers as indicators of calcium bioavailability. We measured serum calcium, urinary calcium, plasma PTH, serum 1,25-dihydroxyvitamin D, and serum and urinary N-telopeptide collagen cross-links, as markers of bone-resorption response, in postmenopausal women both after an acute calcium load and after 7 d of a high calcium intake from 3 different sources. Thus, as we stated in the Discussion of our article (1) “on the basis of our acute and longer-term studies of several biomarkers of calcium and bone metabolism, we conclude that calcium bioavailability from milk, calcium-fortified orange juice, and a calcium carbonate supplement is equivalent.” Despite apparent (but not statistically significant) differences in the acute PTH response between milk and the other 2 dietary calcium sources, we have yet to see compelling enough evidence that collectively would cause us to change these conclusions.

In addition, Heaney’s letter points out that we observed a postprandial decrease in the plasma PTH concentration of Δ36%, with no evident increase in serum calcium. He suggests that we should have seen a 3–4% increase in postprandial serum calcium associated with the observed change in PTH. As stated in our article, we also expected to see a reciprocal relation between the changes in serum calcium and PTH. We note, however, that the relation between serum calcium and PTH can be more complex than Heaney’s suggestion of a 1% increase in serum calcium to a 10% decrease in PTH. For example, in a study of calcium bioavailability from calcium carbonate, Heller et al (2) reported a decrease in PTH in postmenopausal women 1 h after the consumption of a calcium carbonate supplement (Os-Cal; Smith-Kline-Beecham, Pittsburgh) but no concomitant increase in serum calcium. Moreover, in the same study, a modest increase (0.2 mg/dL) in serum calcium was observed at later time points; however, little additional decreases in PTH were evident. The change in the relation between serum calcium and PTH in Heaney et al’s (3) calcium bioavailability study in postmenopausal women suggests that this association can be complex. A compilation of data from the study of Heaney et al is shown in Table 1, which illustrates the association observed after the consumption of calcium carbonate.

Similarly in some sense to our abovementioned observations about the findings of Heller et al (2), what struck us about Heaney’s observations was the apparent discordance between the degree of absorptive calcemia and the changes in PTH. For example, as can be seen in column 2 of Table 1, an increase in serum calcium of <2% was observed within 1 h after consumption of the calcium supplement; however, a striking 40% decrease in PTH was observed. If one then examines the data in the third column of Table 1, which shows the postprandial response at 3 h, serum calcium is 6% greater than the baseline value (ie, Δ3 times the observed increase at 1 h); however, PTH decreased to only slightly more than its nadir, ie, to 48% of baseline. Finally, by 5 h postprandially (column 4 of Table 1), PTH began to return toward baseline, despite no change in serum calcium between 3 and 5 h. Our conclusion from the data of both Heller et al (2) and Heaney et al (3) is that the relation of serum calcium and PTH can be complex and that PTH can change with no or little observed change in serum calcium.

The degree of absorptive calcemia after consumption of a calcium-supplement source may be influenced by the composition of the test meal. For example, Heaney et al (3) found a 0.15-mg/dL change in serum calcium 1 h after ingestion of the calcium carbonate supplement and a 0.6-mg/dL increase at 3 h. In contrast, Heller et al (2) found no increase in serum calcium 1 h after the ingestion of a calcium carbonate supplement. By 2 and 5 h postprandially, Heller et al’s (2) observed calcemic response (<0.2–0.3 mg/dL above baseline) was much lower than that observed by Heaney et al (3). A comparison of the 2 studies indicated that the simpler test meal (white bread, butter, and beverage) used by Heaney et al (3) was associated with the highest calcemic response (0.6 mg/dL compared with 0.2 mg/dL), perhaps reflecting the more complex meal (farina, sugar, egg, bread, and beverage) used by Heller et al (2). In our own study (1), the largest calcemic difference was only 0.12 mg/dL above baseline serum calcium concentrations 2 and 4 h after ingestion of the calcium carbonate supplement. Our test meal was the most complex (wheat bread, jelly, butter, eggs, mushrooms, green peppers, soybean oil, seasoning, and beverage) and may have influenced the poor calcemic response to calcium supplementation. Finally, additional undetected factors in a group of study subjects may affect the mean postprandial calcemic response observed in any study. For example, Heller et al (2) noted that one-third of their older subjects had poor calcemic responses after calcium carbonate treatment that were not different from the response to placebo. Unfortunately, it was not possible to determine from the published data whether the same subjects would also be classified as nonresponders on the basis of other biomarkers of calcium absorption.

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Iron bis-glycine chelate competes for the nonheme-iron absorption pathway

Dear Sir:

Pizarro et al (1) reported that iron bis-glycine chelate (Fe-bis-gly) ionizes in stomach acid to free iron cations, which are absorbed from the intestinal lumen via the nonheme-iron pathway. They stated that these findings contradict those of previously published articles (2–4). If Fe-bis-gly were to hydrolyze before the absorption of its iron component, the released iron cations would compete with iron absorbed from FeSO₄, and the rates of absorption would depend on the relative amounts of free iron dissociated from each source by acid digestion. Several research studies have shown that iron from Fe-bis-gly is preferentially absorbed over iron from FeSO₄ (5–8). The results of studies that used radiolaabeled iron indicate that Fe-bis-gly is absorbed intact (4).

Data from the study by Pizarro et al support the intact absorption of Fe-bis-gly by a pathway other than nonheme absorption, on the basis of the following observations: 1) Fe-bis-gly was not directly measured—its effects were surmised on the basis of the absorption of radiolabeled iron from either FeSO₄ or lyophilized hemoglobin both in and out of the presence of unlabeled Fe-bis-gly; 2) ingested Fe-bis-gly does not need to participate in the absorption pathway of FeSO₄ when the 2 compounds are administered together—it is absorbed independently via the mucosal cell receptors that consistently work best for it; 3) there was no significant difference in the absorption of radiolabeled iron from FeSO₄ that had no enteric protection, whether Fe-bis-gly was present or not, which indicated that there was no competition for the nonheme FeSO₄ pathway; 4) absorption of radiolabeled iron from hemoglobin was significantly enhanced (P < 0.01) in the presence of Fe-bis-gly, which indicated an augmenting effect of Fe-bis-gly on the heme uptake pathway; and 5) when FeSO₄ and Fe-bis-gly were administered together with enteric protection, iron absorption from FeSO₄ was significantly suppressed (P < 0.001). This finding indicates that the iron requirements of the mucosal cells in a high-pH environment were being met by the absorption of iron as Fe-bis-gly, given that there was no other alimentary iron present (because the test subjects had fasted overnight and were prevented from eating for 4 h after dosing).

Bovell-Benjamin et al (4) used different radioisotopes to label the iron in each of FeSO₄ and Fe-bis-gly. They compared the absorption of the 2 sources in whole-maize meal porridge consumed by 10 noniron-deficient, nonanemic, fasted men. After initial whole-blood samples were taken, all of the men received porridge containing ⁵⁹FeSO₄ on day 1 and porridge with ⁵⁵Fe-bis-gly on day 2. On day 14, three 10-mL fasting blood samples were drawn from each test subject, and the contents of both radiolabeled iron compounds were measured in the same samples. On day 16, the same men were given porridge containing both labeled iron sources; blood samples were recovered on day 31 for the measurement of ⁵⁹FeSO₄ and ⁵⁵Fe-bis-gly. Results from the combined tests showed that the absorption of iron from ⁵⁵Fe-bis-gly was 4.7 times that of iron from ⁵⁹FeSO₄, even though both ⁵⁹FeSO₄ and ⁵⁵Fe-bis-gly were obviously down-regulated (r = 0.99, P < 0.001) by iron stores in the individual men. The percentage of iron absorbed from each iron source was unaffected by the presence of the other iron source. This finding indicates that there was no cross-exchange of iron between the 2 sources and that Fe-bis-gly was absorbed intact, because FeSO₄ must release iron before its uptake. This study showed that the characteristics of iron absorption from FeSO₄ and from Fe-bis-gly are different, with Fe-bis-gly being favored when doses of phytate are high.

On the basis of the findings of Pizarro et al, Fe-bis-gly has a relation with the heme-absorbing pathway. Heme is also a chelate, the chelating ligand being cyclic porphyrin. Heme iron is far more bioavailable than are inorganic sources of iron. In a diet containing only 6% of the total iron as heme, 30% of the iron absorbed was acquired from heme, to the exclusion of other dietary sources (9). Pizarro et al found that heme absorption increased significantly (P < 0.01) in the presence of Fe-bis-gly. This indicates that the 2 sources were mutually compatible. Clearly, the uptake of one of the iron compounds was influenced by the presence of the other, which was the criterion that Bovell-Benjamin et al (4) used to assess iron absorption from iron sources. On the basis of this criterion and according to the data of Pizarro et al, heme and Fe-bis-gly share similar absorption properties.

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The results of our study (1) show that an important fraction of iron from iron bis-glycine chelate (Fe-bis-gly) is delivered to the stomach or duodenum and forms part of the nonheme-iron pool. We do not think that the results of our study contradict those of previously published studies (2–4).

Pineda supports the existence of special nonheme-iron receptors, which take up iron from an iron chelate pool at the intestinal mucosal surface (4, 5). Data from our study do not support this hypothesis. Furthermore, there is neither direct scientific evidence that shows the presence of the intact Fe-bis-gly within the enterocyte nor evidence of the existence of a specific receptor. Differences in the absorption of nonheme-iron sources do not necessarily indicate the existence of different absorption pathways. Differences could be explained on the basis of physical and chemical characteristics that determine different iron bioavailabilities. There is growing evidence that supports the hypothesis, first proposed by Olivares et al (2), that a significant but not quantified fraction of iron from Fe-bis-gly is dissociated in the gastrointestinal tract, where it can interact with other dietary constituents and enter the common nonheme-iron pool (4, 6, 7). This hypothesis is supported by studies that showed that 1) iron from Fe-bis-gly is affected by inhibitors and enhancers in the diet, as occurs with nonheme iron but not with heme iron, which is absorbed intact (2, 3, 8), and 2) iron from Fe-bis-gly competes for the nonheme-iron absorption pathway but not for the heme-iron absorption pathway (1). The results of our study, discussed by Pineda in his letter, provide strong evidence supporting our hypothesis. Our study was designed to show the competition of a small trace (0.5 mg) of a labeled ionic iron (ferrous sulfate) and heme iron (hemoglobin) with increasing doses of Fe-bis-gly. We labeled ferrous sulfate and hemoglobin, an approach widely used to assess competition for intestinal uptake, because both compounds have well-known absorption pathways. Whenever 2 compounds compete for the same absorption pathway, their dose-response curves are alike. Pineda argued that the results of the study performed by Bovell-Benjamin et al (4) support the lack of competition between Fe-bis-gly and nonheme iron. However, we believe that the design of this study did not allow for the characterization of competition because only one low dose of iron (1 mg) with a ratio of Fe-bis-gly to ferrous sulfate of 1:1 was administered. Competition between the 2 compounds cannot be observed under this condition because, despite the greater bioavailability of iron from Fe-bis-gly, the quantity of available iron at this dose and ratio would not be sufficient to saturate the receptors and transporters of iron in the enterocyte. In contrast, this ratio ranged from 1:10 to 1:200 in our study.

Our results showed that Fe-bis-gly did not compete with hemo- globin for the heme-iron absorption pathway. The mild decrease in the dose-response curve for competition between Fe-bis-gly and hemoglobin may have been due to the competition between a small fraction of nonheme iron dissociated from labeled hemo- globin and nonheme iron from Fe-bis-gly.

Differences in the magnitude observed between the dose-response curves of coated ferrous sulfate and Fe-bis-gly can be explained—as Pineda does in his letter—by differences in the bioavailability of both compounds under the environmental conditions of the duodenum. Both curves have a similar trend, with differences only in the magnitude of the changes in absorption of the tracer. If Fe-bis-gly did not compete with the tracer of ferrous sulfate, the trend of the curve would be different.

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Serum 25-hydroxyvitamin D response to oral vitamin D intake in children

Dear Sir:

In a recent issue of the Journal, Heaney et al (1) reported important new data on the requirement of oral vitamin D to maintain physiologic concentrations of circulating 25-hydroxyvitamin D [25(OH)D] in adults. Some years ago, an analysis was performed of serum concentrations of 25-hydroxyvitamin D2 [25(OH)D2] and 25-hydroxyvitamin D3 [25(OH)D3] in German pediatric patients (x age: 5.2 y; x body wt: 21.7 kg) with phenylketonuria (n = 3) or maple syrup urine disease (n = 3) during the winter (January–March) and summer (July–September) (2). All patients were free of diseases affecting vitamin D metabolism. They were supplemented daily with doses of 15.6–25.0 μg vitamin D2/d (mean: 19.6 μg vitamin D2/d) for a minimum of 1.5 y, which corresponded to a mean vitamin D2 intake of 1.37 μg · kg body wt−1 · d−1 in winter and of
1.27 μg · kg body wt⁻¹ · d⁻¹ in summer. Serum concentrations of 25(OH)D₃ and 25(OH)D₂ showed inverse seasonal variations (winter: 71.1 ± 33.6 and 25.3 ± 9.9 nmol/L; summer: 43.0 ± 22.5 and 62.5 ± 26.3 nmol/L, respectively). Normally, concentrations of 25(OH)D₃ in German children are close to zero (< 3 nmol/L). Therefore, serum concentrations of this metabolite reliably reflect the effects of supplementation. Increments per μg vitamin D₂/kg body wt were ≈60 nmol/L in winter and 39 nmol/L in summer. An oral intake of vitamin D₃ results in a 70% higher serum 25(OH)D concentration than does an oral intake of the same amount of vitamin D₂ (3). Considering these differences in the effects of oral vitamin D₂ and vitamin D₃ on serum 25(OH)D concentrations, the abovementioned data on 25(OH)D₂ increments and 25(OH)D₃ baseline concentrations in summer are in line with values calculated by Heaney et al in adults with baseline 25(OH)D concentrations of ≈70 nmol/L. Moreover, the earlier data indicate that an oral intake of vitamin D₂ results in relatively high serum 25(OH)D₂ concentrations when initial 25(OH)D₂ concentrations are low. The seasonal differences in serum 25(OH)D₂ increments support the assumption of Heaney et al (1) that the increment in serum 25(OH)D concentrations after vitamin D supplementation may depend on baseline 25(OH)D₂ concentrations (1). Together, the earlier data and the data of Heaney et al indicate that an oral dose of vitamin D₂ or vitamin D₃ would lead to a comparable increase in circulating 25(OH)D concentrations in children and adults when the initial 25(OH)D₃ concentrations in the groups are similar and when equivalent oral vitamin D doses expressed per kilogram body weight/d are given.

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