Jejunal and Ileal Adaptation to Alterations in Dietary Calcium

CHANGES IN CALCIUM AND MAGNESIUM ABSORPTION AND PATHOGENETIC ROLE OF PARATHYROID HORMONE AND 1,25-DIHYDROXYVITAMIN D

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ABSTRACT Previous balance studies have shown that fractional calcium absorption is increased by a low and reduced by a high calcium diet. The present studies were done to determine which segment of the small intestine is most sensitive to alterations in dietary calcium, and to see if dietary calcium intake has an effect on the intestinal absorption of another divalent cation, magnesium. Absorption was measured during constant perfusion of 30-cm segments of jejunum and ileum of normal subjects after 4 or 8 wk of a high (1,900 mg/d) or a low (200 mg/d) calcium diet. We found that calcium absorption rate was higher when subjects had been on a low than when they had been on a high calcium diet; the ileum responded more rapidly and more completely than the jejunum. Similar results were obtained with magnesium, but only the difference in the ileum was statistically significant. Sodium and xylose absorption were not influenced by dietary calcium intake. The serum concentrations of parathyroid hormone and 1,25-dihydroxyvitamin D were higher on the low than on the high calcium diet. We conclude that the ileum is more sensitive than the jejunum to changes in dietary calcium intake, and that ileal adaptation probably plays a major role in protecting the body against a deficiency or excess of body calcium that otherwise would occur when dietary calcium is abnormally low or high. Calcium intake influences ileal magnesium absorption in a similar fashion; it is not known whether or not this serves a protective function. Our data are compatible with the concept that adaptation to dietary calcium intake is mediated by changes in the serum concentration of parathyroid hormone and 1,25-dihydroxyvitamin D.

INTRODUCTION

It is known from previous balance studies that the intestine adapts its rate of calcium absorption in response to the amount of calcium in the diet (1–3). Thus, the fraction of dietary calcium that is absorbed is relatively high when calcium intake is low, and relatively low when calcium intake is high. This adaptation mitigates the effect of calcium intake on calcium absorption rate; within limits, calcium absorption is relatively constant regardless of calcium intake. It is generally believed that intestinal adaptation to dietary calcium intake is mediated by changes in the serum concentration of parathyroid hormone (PTH)[1] and 1,25-dihydroxyvitamin D (1,25-$(OH)_2$-D) (4, 5), although this has not been substantiated in humans.

Studies in animals have yielded conflicting evidence in regard to the area of the intestine which is most responsible for intestinal adaptation, one study in rats suggesting the ileum was more important than the jejunum (6), and another study in rats reaching the opposite conclusion (7). Comparable studies in humans have not been performed, although the question is of obvious importance when considering calcium balance in patients with regional or generalized intestinal disease.

Therefore, the major purpose of the present experiment was to learn whether the jejunum or ileum was

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[1] *Abbreviations used in this paper*: 1,25-$(OH)_2$-D, 1,25-dihydroxyvitamin D; PTH, parathyroid hormone.

most sensitive to changes in dietary calcium, with respect to the absorption rate of calcium. Since the absorption of magnesium, as well as the absorption of calcium, may be under the control of vitamin D (8), we also studied the absorption rate of magnesium after subjects had ingested a low vs. a high calcium diet. The serum concentrations of PTH and 1,25-$(OH)_2$-D were also measured.

METHODS

Subjects. 13 normal healthy volunteers who had no history of gastrointestinal, hepatic, renal, or endocrine disease were selected for study. The group consisted of five females and eight males with a mean age of 28 (range, 22–35 yr). None were on chronic medication.

Informed written consent was obtained from each subject, and these experiments were approved by the Human Research Review Committees of the University of Texas Health Science Center at Dallas, and Baylor University Medical Center.

Protocol. 10 of the subjects were randomly assigned to either a low or high calcium diet for 4 wk, after which absorption studies were performed. They were then switched to the opposite diet for 4 wk, and the absorption studies were then repeated.

After the above studies were completed and analyzed, it seemed necessary to reconfirm some of our earlier work (9) showing that longer periods of adherence to a low and high calcium diet would cause jejunal adaptation (Discussion). Therefore, three subjects were randomly assigned to either the low or high calcium diet for 8 wk (two received the low, one the high calcium diet). Absorption studies were performed at 4 and 8 wk. Afterwards, they were switched to the opposite diet for 8 wk; absorption studies were again done at 4 and 8 wk.

Diet. The prescribed low calcium diet contained ~300 mg calcium, 200 mg magnesium, and 100 meq sodium/d. The high calcium diet was identical in all respects except for supplemental calcium in the form of calcium glubionate (Neo-Calglucon, Dorsey Laboratories, Lincoln, Neb.), 1,656 mg elemental calcium per d, given in four equally divided doses with meals and with a bedtime snack, to provide a total calcium intake of ~2,000 mg/d. A dietician instructed each subject in achieving the desired intake at home. A daily diet diary was maintained, and each subject reviewed their intake weekly with the dietician, who calculated intake according to reference texts (10, 11). Subjects were instructed to further revise their diet if deviations were noted at the weekly reviews.

After 25 d on each diet (and after 52 d on each diet for three subjects), the subjects were admitted to the General Clinical Research Center where they received, for 3 d, a constant metabolic diet of the same composition (and same calcium supplementation if they had been on a high calcium diet at home). After an overnight fast, they underwent jejunal and ileal intestinal perfusion studies on the 29th and 30th d (and after the 56th and 57th d for three subjects). Subjects ingested the same metabolic diet (and calcium supplementation if on a high calcium diet) following the jejunal study, prior to ileal perfusion.

Urine and blood samples. On admission to the General Clinical Research Center after 4 wk of the low and 4 wk of the high calcium diet, urine was collected in 24-h pools daily for 3 d before the jejunal perfusion study. Urine samples were analyzed for calcium, magnesium, and sodium. Fasting blood samples were drawn for measurement of calcium, magnesium, albumin, alkaline phosphatase, PTH and 1,25-$(OH)_2$-D at 7:00 a.m., immediately before the jejunal perfusion.

Intestinal perfusion studies. Subjects were intubated with a triple-lumen polyvinyl tube, as previously described (12–14). They underwent jejunal perfusion, for which the infusion site was placed under fluoroscopic control at the ligament of Treitz (70–90 cm from the incisors). This was followed 24 h later by an ileal study, where the infusion site was in the midileum (150–200 cm from the incisors). Test solutions were prewarmed to 37°C, gassed with 5% CO_2 and 95% O_2, and infused at a constant rate of 10 ml/min with a peristaltic pump (Desaga multichannel peristaltic pump, Brinkman Instruments, Inc., Westbury, N. Y.). After a 40-min equilibration period, sampling from collection sites located 10 and 40 cm from the infusion site was begun and continued for a 1-h period. The collection rate was 1.5 ml/min at each site, and sampling was staggered, i.e., the distal collection was started and stopped 10 min after the proximal collection, based on previous estimates of transit time of fluid through segments of human small intestine (15).

For each jejunal or ileal perfusion study, two test solutions were perfused in random order. Both solutions contained 0.5% polyethylene glycol (PEG, a nonabsorbable volume marker), 135 mM NaCl, 5 mM KCl, and 10 mM D-xylose. In addition, the two test solutions contained either 5 mM calcium gluconate or 5 mM magnesium chloride. Osmolality of the test solutions was 290 mosmol/kg. Net absorption of sodium, D-xylose, calcium and magnesium was calculated by standard nonabsorbable marker equations. Results are expressed as the mean±SE. The concentrations of solutes in the perfusate represent the arithmetic mean of the concentration determined at the proximal and distal ends of the test segment.

Analysis of samples. Perfusion samples were analyzed for PEG and D-xylose by methods previously described (16). Serum calcium, albumin, and alkaline phosphatase were analyzed by an autoanalyzer, and serum magnesium by atomic absorption spectrophotometry. In urine and perfusion samples, sodium was analyzed by flame photometry, and calcium and magnesium by atomic absorption spectrophotometry.

Determination of PTH in the serum was done by a modification of the Iso-Tex PTH radioimmunoassay system (Iso-Tex Diagnostics, Inc., Friendswood, Tex.). The antiserum, guinea pig anti-b PTH, is directed against the carboxy-terminus fragment of the PTH molecule. Diluted culture medium from human parathyroid adenoma (provided by Dr. B. Roos) was used as the standard. In this laboratory, this assay provided detectable values in 90% of 56 normal subjects tested, and there was a significant ($P < 0.001$) negative correlation between serum calcium and PTH concentration ($r = -0.4336$). Normal range in subjects with normal serum calcium is less than 36 μleq/ml. Inter- and intra-assay variations are 15 and 8%, respectively. Values above the normal range, or inappropriately high values with respect to serum calcium, were found in 95% of 70 patients with proven primary hyperparathyroidism.

Serum 1,25-$(OH)_2$-D was determined by a modification (17) of the technique of Brumbaugh et al. (18) and of Eisman et al. (19). Initial extraction was performed in dichloromethane, and final purification was accomplished on a Glenco high pressure liquid chromatograph (19). Purified samples were assayed using the chromatin receptor system (18). Each sample was assayed in triplicate; results were acceptable only if replicate values agreed within 10%. Inter- and intra-assay variations are 12 and 8%, respectively. The limit of detection is 8 pg/ml with the normal range for 23 adults (mean age 29 yr) being 20–50 pg/ml (mean±SD = 34±8 pg/ml). The validity of this assay is supported by the demonstration of elevated concentrations of 1,25-$(OH)_2$-D in 15 patients with primary hyperparathyroid-

ism and low to undetectable values in 6 patients with hypoparathyroidism and 8 patients with chronic renal failure.

Statistical analysis. Data were analyzed statistically by the paired *t* test. Values are presented as mean±SEM.

RESULTS

Calculated dietary results (Table I). On the high calcium diet, calculated calcium intake (from diet history and prescribed calcium supplementation) was 1,878±21 mg/d, and on the low calcium diet it was 198±13 mg/d. Calculated intake of magnesium and sodium were similar on the two diets.

Effect of 4 wk of high vs. low calcium diet on urinary excretion and serum concentration of calcium and magnesium (Table I). 24 h urinary calcium was significantly higher (by an average of 64 mg/d) after 4 wk of the high than after 4 wk of the low calcium diet ($P < 0.0025$). Urinary magnesium was greater after 4 wk of the low than after 4 wk of the high calcium diet, but the difference did not reach statistical significance ($P < 0.10$, >0.05). Urinary sodium excretion approximated the calculated intake on both the high and low calcium diet.

Changes in dietary calcium intake for 4 wk did not alter significantly the serum concentration of calcium, magnesium, albumin or alkaline phosphatase.

Effect of 4 wk of high vs. low calcium diet on serum concentrations of PTH and 1,25-$(OH)_2$-D (Table I). Serum concentration of PTH after 4 wk on a high calcium diet was significantly lower than that after 4 wk on a low calcium diet ($P < 0.005$), even though changes were very small and occurred within the normal range. Similarly, serum 1,25-$(OH)_2$-D concentration was significantly lower on the high compared to the low calcium diet ($P < 0.025$).

TABLE I
Calculated Dietary Intake and Urinary and Serum Chemistries after 4 wk on a Low and High Calcium Diet

	Low calcium diet	High calcium diet
Calculated dietary		
Calcium, *mg/d*	198±13	1878±21§
Magnesium, *mg/d*	173±12	173±12
Sodium, *meq/d*	92±7	87±7
Urinary		
Calcium, *mg/d*	138±18	202±23§
Magnesium, *mg/d*	101±7	87±10
Sodium, *meq/d*	102±9	87±12
Serum		
Calcium, *mg/dl*	9.4±0.1	9.4±0.1
Magnesium, *mg/dl*	2.0±0.1	2.1±0.1
Albumin, *g/dl*	4.2±0.1	4.3±0.1
Alkaline phosphatase, *IU*	64±5	65±5
Parathyroid hormone, *μl eq/ml*	16.8±3.8	14.9±3.3‡
1,25-$(OH)_2$-D, *pg/ml*	44.2±0.7	27.2±0.2*

Statistical significance by paired *t* test of difference in values between low and high calcium diet: * $P < 0.025$; ‡ $P < 0.005$; § $P < 0.0025$. Urinary and serum chemistries were obtained during a constant metabolic regimen.

Effect of 4 and 8 wk of high vs. low calcium diet on net intestinal absorption of calcium (Table II). In the jejunum, mean calcium absorption in 13 subjects after 4 wk of a high calcium diet was approximately the same as that obtained after 4 wk on a low calcium diet (200 compared to 240 μmol/30 cm per h). The difference of 17% was not significantly significant. After 8 wk of dietary adherence in three subjects, calcium absorption in the jejunum was significantly less on the high than on the low calcium diet ($P < 0.05$).[2] The magnitude of this difference was 43%.

In the ileum, calcium absorption after only 4 wk of a high calcium diet in 13 subjects was significantly lower than the value obtained after 4 wk of a low calcium diet ($P < 0.05$). The magnitude of the difference was 45%. After three subjects were on these two diets for 8 weeks, the difference in ileal calcium absorption was even more striking, owing principally to a marked reduction of ileal calcium absorption while on the high calcium diet ($P < 0.01$).[2] The magnitude of this difference was 89%.

Although mean calcium absorption rates were higher (especially in the ileum) when the mean serum concentration of PTH and 1,25-$(OH)_2$-D were higher, among individual subjects there was no significant correlation between calcium absorption rate (in either segment of the intestine) and the serum concentration of PTH or 1,25-$(OH)_2$-D.

Effect of 4 wk of a high vs. low calcium diet on net intestinal absorption of magnesium (Table III). Jejunal magnesium absorption in 13 subjects was less after 4 wk of a high calcium diet than after 4 wk of a low calcium diet, but the difference did not reach statistical significance ($P < 0.15$). However, ileal magnesium absorption was significantly less after 4 wk of a high calcium diet than after 4 wk of a low calcium diet ($P < 0.05$), as was found for calcium absorption. The same trends were observed after 8 wk of each dietary regimen, but the differences in absorption did not reach statistical significance (with only three subjects for comparison).

Effect of dietary calcium on net intestinal absorption of D-xylose, sodium and water. D-xylose, sodium, and water absorption rates were similar, regardless of dietary calcium intake, as shown in Table IV.

[2] Calcium absorption decreased to a similar degree in each subject on a high compared to a low calcium diet for 8 wk. Thus, a statistically significant difference was obtained, in spite of the small number of observations.

TABLE II
Net Absorption Rate of Calcium in the Jejunum and Ileum After 4 and 8 Wk of a Low vs. High Calcium Diet

	Jejunum		Ileum	
wk	4 (n = 13)	8 (n = 3)	4 (n = 13)	8 (n = 3)
Low calcium diet, *μmol/30 cm per h*	240±20	210±10	200±30	180±40
High calcium diet, *μmol/30 cm per h*	200±30	120±20	110±20	20±30
Difference, %	17	43	45	89
P	NS	<0.05	<0.05	<0.01

Absorption expressed as micromoles per 30 cm per hour; luminal calcium concentration in test segment was not significantly different at any dietary period studied in the jejunum or ileum. Statistical analysis by paired t test.

DISCUSSION

One purpose of these experiments was to determine whether the jejunum or ileum was most sensitive to changes in dietary calcium, with respect to the absorption rate of calcium. The small bowel perfusion technique seems well suited to answer this question since absorption can be measured from segments of intestine under similar intraluminal conditions. For example, luminal calcium and sodium concentrations, pH and flow rate can be controlled within relatively narrow limits during intestinal perfusion of either jejunum or ileum, whereas this is not the case when absorption of calcium is studied after ingestion of test meals containing calcium.

In the present study, we initially measured calcium absorption after 4 wk of a low or a high calcium diet, because balance studies in man had shown that intestinal adaptation to changes in dietary calcium occur within this period of time (1). We found that after 4 wk on a low calcium diet, jejunal and ileal calcium absorption rates were approximately equal, and that a change from a low to a high calcium diet did not significantly alter calcium absorption in the jejunum but decreased ileal calcium absorption by 45%.

These 4-wk findings in the jejunum were somewhat inconsistent with an earlier study from our laboratory, which revealed that the jejunum adapted its rate of calcium absorption to 4–8 wk (average 6 wk) of a high vs. a low calcium diet (9). Therefore we did an additional 8-wk experiment in three subjects to confirm or refute our earlier findings. We found that jejunal calcium absorption was significantly less after 8 wk of a high compared to 8 wk of a low calcium diet in these three subjects. The difference in jejunal absorption rates after these two dietary periods was 43%. However, after 8 wk of a high vs. a low calcium diet, the difference in ileal calcium absorption was even more marked than in the jejunum (89% difference). These results suggest that the ileum is more sensitive than the jejunum to variations in dietary calcium intake, with respect to the absorption of calcium.

It is possible that the underlying mechanism of adaptation of the small intestine to a low and high calcium diet observed here could have resulted from an alteration of vitamin D metabolism. In the setting of dietary deprivation of calcium, the regulatory mechanism probably involves a small diminution in serum ionized calcium concentration which stimulates PTH secretion; this, in turn, results in enhanced conversion of 25-hy-

TABLE III
Net Absorption Rate of Magnesium in the Jejunum and Ileum after 4 wk of a Low vs. High Calcium Diet

	Jejunum	Ileum
	μmol/30 cm per h	
Low calcium diet	180±40	160±30
High calcium diet	110±30	100±30
P	NS	<0.05

Luminal magnesium concentration in test segment was not significantly different at either dietary period studied in the jejunum or ileum. Statistical analysis by paired t test.

TABLE IV
Net Absorption Rates of Xylose, Sodium, and Water in the Jejunum and Ileum after 4 Wk of a Low vs. High Calcium Diet

	Jejunum (n = 13)	Ileum (n = 13)
Xylose, *mmol/30 cm per h*		
Low calcium diet	1.08±0.70	0.46±0.06
High calcium diet	1.07±0.70	0.45±0.06
Sodium, *meq/30 cm per h*		
Low calcium diet	6.7±0.8	7.9±0.5
High calcium diet	5.6±1.1	7.6±0.7
Water, *ml/30 cm per h*		
Low calcium diet	48±5	51±5
High calcium diet	40±8	53±6

There was no significant difference by paired t test in the absorption rates of xylose, sodium, and water between the low and high calcium diet.

droxycholecalciferol to 1,25-$(OH)_2$-D by the kidney (20, 21). This potent vitamin D metabolite would then stimulate intestinal calcium absorption (22) to restore serum calcium to normal. This hypothesis is supported by the finding of significantly higher values for serum PTH and 1,25-$(OH)_2$-D (albeit only slightly in the case of PTH) after 4 wk of a low calcium diet, as compared to values obtained after 4 wk of a high calcium diet.

Another purpose of these experiments was to determine if intestinal adaptation to variations in dietary calcium is restricted to calcium or involves other ions as well. Our studies reveal that a low calcium diet enhanced magnesium absorption in both the jejunum and the ileum, although only the changes in the ileum were statistically significant. To our knowledge, this is the first demonstration that any type of variation in diet can influence the absorption of magnesium in man. Interestingly, variations in magnesium intake have been reported not to influence magnesium absorption when studied by *in situ* perfusion in rats (23). Our results support the above scheme for the intestinal adaptation process involving 1,25-$(OH)_2$-D, since we have previously shown that this vitamin D metabolite stimulates magnesium absorption in anephric humans (8).

Since intestinal absorption of xylose, sodium, and water was not influenced by dietary calcium intake, intestinal adaptation to dietary calcium is probably limited to vitamin D-dependent transport processes, rather than a general phenomenon as might occur with hyperplasia or hypertrophy of the intestinal mucosa.

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REFERENCES

1. Leichsenring, J. M., L. M. Norris, S. A. Lameson, E. D. Wilson, and M. B. Patton. 1951. The effect of level of intake on calcium and phosphorus metabolism in college women. *J. Nutr.* **45:** 407–419.
2. Malm, O. J. 1958. Calcium requirement and adaptation in adult man. *Scand. J. Clin. Lab. Invest.* **10**(Suppl. 36): 108–199.
3. Heaney, R. P., P. D. Saville and R. R. Recker. 1975. Calcium absorption as a function of calcium intake. *J. Lab. Clin. Med.* **85:** 881–890.
4. Takana, Y., H. F. DeLuca, J. Omdahl, and M. F. Holick. 1971. Mechanism of action of 1,25-dihydroxycholecalciferol on intestinal calcium transport. *Proc. Natl. Acad. Sci. U. S. A.* **68:** 1286–1288.
5. Ribovich, M. L., and H. F. DeLuca. 1978. Adaptation of intestinal calcium absorption: Parathyroid hormone and vitamin D metabolism. *Arch. Biochem. Biophys.* **188:** 157–163.
6. Petith, M. M., and H. P. Schedl. 1976. Duodenal and ileal adaptation to dietary calcium restriction: In vivo studies in the rat. *Am. J. Physiol.* **231:** 865–871.
7. Kimberg, D. V., D. Schachter, and H. Schenker. 1961. Active transport of calcium by intestine: Effects of dietary calcium. *Am. J. Physiol.* **200:** 1256–1262.
8. Schmulen, C., M. Lerman, C. Y. C. Pak, J. Zerwekh, S. Morawski, J. S. Fordtran, and P. Vergne-Marini. 1980. Effect of 1,25-dihydroxy-vitamin D_3 therapy on intestinal absorption of magnesium in patients with chronic renal disease. *Am. J. Physiol.* **1:** G349–G352.
9. Ireland, P., and J. S. Fordtran. 1973. Effect of dietary calcium and age on jejunal calcium absorption in humans studied by intestinal perfusion. *J. Clin. Invest.* **52:** 2672–2681.
10. Watt, B. K., and A. L. Merrill. 1963. Composition of foods. U. S. Department of Agriculture Handbook, No. 8. Washington, D. C. 147–158.
11. Adams, C. F. 1975. Nutritive value of American foods. U. S. Department of Agriculture Handbook, No. 456. Washington, D. C.
12. Fordtran, J. S. 1966. Marker perfusion techniques for measuring intestinal absorption in man. *Gastroenterology.* **51:** 1089–1093.
13. Fordtran, J. S., F. C. Rector, and N. W. Carter. 1968. The mechanisms of sodium absorption in the human small intestine. *J. Clin. Invest.* **47:** 884–900.
14. Fordtran, J. S. 1969. Segmental perfusion techniques. *Gastroenterology.* **56:** 987–989.
15. Dillard, R. L., H. Eastman, and J. S. Fordtran. 1965. Volume-flow relationship during the transport of fluid through the human small intestine. *Gastroenterology* **49:** 58–66.
16. Fordtran, J. S., F. C. Rector, T. W. Locklear, and M. F. Ewton. 1967. Water and solute movement in the small intestine of patients with sprue. *J. Clin. Invest.* **46:** 287–298.
17. Zerwekh, J. E., L. A. Sanders, J. Townsend, and C. Y. C. Pak. 1980. Tumoral calcinosis: Evidence for concurrent defects in renal tubular phosphorus transport and in 1α,-25-dihydroxycholecalciferol synthesis. *Calcif. Tissue Int.* In press.
18. Brumbaugh, P. F., D. H. Haussler, R. Bressler, and M. R. Haussler. 1975. Radioreceptor assay for 1α,25-dihydroxyvitamin D_3. *Science (Wash. D. C.).* **183:** 1089–1091.
19. Eisman, J. A., A. J. Hamstra, B. E. Kream, and H. F. DeLuca. 1976. A sensitive, precise and convenient method for determination of 1,25-dihydroxyvitamin D in human plasma. *Arch. Biochem. Biophys.* **176:** 235–243.
20. Hughes, M. R., P. F. Brumbaugh, M. R. Haussler, J. E. Wergedal, and D. J. Baylink. 1975. Regulation of serum 1α,25-dihydroxyvitamin D_3 by calcium and phosphate in the rat. *Science (Wash. D. C.).* **190:** 578–580.
21. Garabedian, M., M. F. Holick, H. F. DeLuca, and I. T. Boyle. 1972. Control of 25-hydroxycholecalciferol metabolism by parathyroid glands. *Proc. Natl. Acad. Sci. U. S. A.* **69:** 1673–1676.
22. Omdahl, J. L., and H. F. DeLuca. 1973. Regulation of vitamin D metabolism and function. *Physiol. Rev.* **53:** 327–372.
23. Petich, M. M., and H. P. Schedl. 1978. Effects of magnesium deficiency on duodenal and ileal magnesium absorption and secretion. *Dig. Dis. Sci.* **23:** 1–5.