Plasma levels and intestinal absorption of 25-hydroxyvitamin D in patients with small bowel resection

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SUMMARY Plasma levels of 25-hydroxyvitamin D (25-OHD) were found to be significantly reduced in a group of patients with small bowel resection when compared with normal controls. Plasma levels of 25-OHD after an oral dose of 25-hydroxy vitamin D₃ (25-OHD₃) were also reduced in the patient group. Dietary intake of vitamin D tended to be low in many patients, but seasonal variation of plasma 25-OHD levels indicated normal exposure to sunlight in most of the patients studied. It is suggested that these studies provide some evidence for malabsorption of 25-OHD after small bowel resection, which, it is postulated, may be due to interruption of the enterohepatic circulation of bile acids and of 25-OHD. These factors may contribute towards the low plasma levels of 25-OHD found in the patient group.

Osteomalacia is known to occur in some patients with small bowel disease, although its mechanism is not fully understood, and such patients may demonstrate resistance to treatment with large parenteral doses of vitamin D. Up to now, very few studies of vitamin D metabolism have been reported in patients with small bowel disease. Undetectable plasma levels of vitamin D-like activity were found in three patients with idiopathic steatorrhoea and tetany (Thompson *et al.*, 1965), and, using orally administered tritiated vitamin D, reduced intestinal absorption of the parent vitamin was demonstrated in five patients with coeliac disease (Thompson *et al.*, 1966). In a study of absorption of unlabelled 25-hydroxyvitamin D₃ (25-OHD₃) a patient with visceral scleroderma was shown to have reduced intestinal absorption of this metabolite (Stamp, 1974).

The major circulating form of vitamin D, 25-hydroxyvitamin D (25-OHD), is formed by 25-hydroxylation of vitamin D₂ and vitamin D₃ in the liver (Ponchon *et al.*, 1969), and can now be accurately measured by a competitive protein-binding assay (Haddad and Chyu, 1971). In this study, the plasma levels of 25-OHD and intestinal absorption of 25-OHD₃ have been investigated in a group of patients with small bowel resection.

Methods

Thirty-eight patients, 25 female and 13 male, who had undergone some form of small bowel resection were studied. Their mean age was 41.9 years (range 21-77 years). The cause of resection was Crohn's disease in 34 patients, radiation enteritis in two, carcinoid tumour in one, and a congenital abnormality in one. In 28 patients the length of small bowel resected had been documented, and this ranged from 15-189 cm (mean 84.3 cm). Ileal resection had been carried out in 34 patients, jejunal resection in one, and in the remaining three patients part of both ileum and jejunum had been resected. In 18 patients the remaining length of small bowel had been measured at operation, and ranged from 140-390 cm (mean 223 cm). Ten of the 38 patients were known to have active disease affecting the small bowel at the time of study.

None of the patients or controls studied was taking vitamin D, calcium supplements, or any drug known to induce hepatic microsomal enzymes.

Normal control values were provided by 22 male and eight female healthy adult volunteers, mean age 31.0 years (range 23-60 years).

Plasma levels of 25-OHD were measured by a method modified from Edelstein *et al.* (1974), using the rat kidney cytosol binding protein described by

Haddad and Chyu (1971). The mean coefficient of variation of the assay in this laboratory is $\pm 7\%$ with an average recovery of added 25-OHD₃ of $96.3\% \pm 1.2\%$ (mean $\pm$ SEM). All assays were carried out in triplicate, and all the samples were assayed twice. All samples taken for plasma 25-OHD levels (Fig. 1) were taken between November 1974 and February 1975.

Intestinal absorption of 25-OHD₃ was measured in 15 of the patients using the method described by Stamp (1974): 10 μ g/kg body weight of 25-OHD₃ as a solution in propylene glycol were given orally and plasma levels of 25-OHD were measured just before,

and at four, eight, and 24 hours after the dose. All timing of meals was standardised.

Dietary vitamin D intake was assessed in 30 of the patients by an experienced dietician.

Results

Plasma 25-OHD levels in the two groups are shown in Fig. 1. The mean level in the 30 patients was 9.9 ± 0.86 ng/ml (mean $\pm$ SEM) with a range of 1.3–24.1 ng/ml, compared with a mean level of 18.3 ± 0.9 ng/ml in the control group (range 11.0–29.7 ng/ml). The difference between the two groups was highly significant ($P < 0.0005$).

When only those patients with a known remaining small bowel length of 390 cm or less were considered the mean plasma 25-OHD level was lower (8.5 ± 1.2 ng/ml). No significant correlation was found between remaining small bowel length and plasma 25-OHD levels in this group (Fig. 2).

In 20 of the patients plasma 25-OHD levels were also measured during the summer months (July–September 1975), and the results are shown in Fig. 3. Nearly all the patients studied showed a rise of plasma 25-OHD levels during the summer months and this rise correlated well with the individual's known exposure to sunlight.

The results of 25-OHD₃ absorption tests in 15 patients and 15 normal controls are shown in Fig. 4, expressed as the mean levels $\pm$ SEM in each group, and in the Table. The mean plasma levels of 25-OHD in the patients at four hours and eight hours were significantly lower than those in the control group ($P < 0.0005$), although the difference in levels at 24 hours was less marked ($P < 0.01$). It can be seen from the Table that there was a large range of values in each group.

Figure 5 shows the dietary vitamin D intake in 30 of the patients with small bowel resection. The mean dietary intake in the group was 1.75 μ g/day, which is lower than the recommended daily intake of 2.5 μ g/day, and 10 of these patients were taking less than 1.0 μ g/day in their diet.

Levels of serum calcium, phosphate, and alkaline phosphatase were normal in all patients apart from three, who had marginally raised alkaline phosphatase levels of 16, 17, and 19 KA units/dl, (normal range 4–13 KA units/dl) in association with normal 5-nucleotidase levels. One of these patients was also hypocalcaemic, with a corrected serum calcium of 1.85 mmol/l (normal range 2.25–2.55 mmol/l).

Discussion

This study has demonstrated for the first time that patients who have undergone small bowel resection

Fig. 1 Plasma 25-OHD levels in 38 patients with small bowel resection and 30 healthy adults. — — — Mean value for each group. I $\pm$ SEM.

Fig 2

Fig. 2 Plasma 25-OHD levels related to remaining small bowel length in 18 patients with small bowel resection. - - - - Lower limit of normal.

Fig. 3 Seasonal variation of plasma 25-OHD levels in 20 patients with small bowel resection.

Fig. 4 Mean plasma 25-OHD levels after oral administration of 25-OHD₃, 10 µg/kg body weight, in 15 patients with small bowel resection and 15 healthy adults. Results are expressed as mean values for each group ± SEM.

tend to have significantly lower plasma levels of 25-OHD than normal, healthy people, measured at the same time of year. It also provides evidence suggesting that these patients have a significant impairment of absorption of orally administered 25-OHD₃.

The reduced plasma level of 25-OHD in winter in

the patient group is probably multifactorial. Dietary intake of vitamin D tended to be low in this group but many patients were taking adequate amounts of the vitamin in their diet, and no significant correlation was found between dietary intake and plasma 25-OHD levels. Thus, it seems probable that dietary deficiency of vitamin D is at most only a contributory factor towards the low plasma 25-OHD levels.

The marked rise in plasma 25-OHD levels seen in the majority of patients during the summer months indicates that as a group they have normal amounts of exposure to sunlight, since the increases in plasma levels seen were very similar to those reported in normal people during the summer (McLaughlin *et al.*, 1974; Stamp and Round, 1974), and that these patients are able to synthesise adequate amounts of vitamin D endogenously if provided with sufficient amounts of ultraviolet light. Thus, it seems that they are much more likely to become vitamin D deficient during the winter months.

The lower plasma levels of 25-OHD in the patients after an oral dose of 25-OHD₃ provides evidence of malabsorption of the metabolite after small intestinal resection. However, plasma 25-OHD levels after an oral dose will be affected not only by intestinal absorption of the metabolite, but also by the rate of further metabolism and of tissue uptake of 25-OHD. These latter two factors are known to be influenced by circulating parathyroid hormone, phosphate, and 25-OHD levels, and also by tissue stores of vitamin D, and the less rapid rate of fall of plasma 25-OHD levels in the patients between eight and 24 hours compared with the controls may well reflect these regulating factors. Demonstration of increased faecal excretion of 25-OHD would be necessary to provide unequivocal evidence of malabsorption in these patients.

An obligatory role of bile acids in vitamin D absorption was suggested as early as the 1930s (Greaves and Schmidt, 1933; Heymann, 1937), and later work using radioactive preparations of vitamin D has confirmed this in rats (Schacter *et al.*, 1964), and man (Thompson *et al.*, 1966; Avioli *et al.*, 1967; Blomstrand and Forsgren, 1967). Interruption

Table Results of 25-OHD₃ absorption tests in 15 patients and 15 normal controls

	Time after oral dose (hr)		
	4	8	24
Mean plasma 25-OHD ng/ml ± SEM			
Patients	78.8 ± 9.5	87.1 ± 6.7	69.4 ± 7.0
Controls	124.6 ± 5.4	135.6 ± 6.3	93.8 ± 6.8
Range ng/ml			
Patients	32-140	56-136	32-117
Controls	78-155	103-186	56-143

Fig. 5 Estimated daily dietary intake of vitamin D in 30 patients with small bowel resection. - - - - Mean value for the group.

of the enterohepatic circulation of bile acids after ileal resection could thus produce malabsorption of 25-OHD in the patients studied, most of whom had had large enough ileal resections to produce significant bile acid malabsorption. Recently, some direct evidence has been provided for an enterohepatic circulation of 25-OHD in man (Arnaud *et al.*, 1975), and interruption of this circulation after small bowel resection may well lead to further faecal loss of 25-OHD. This continuous increased faecal loss of the metabolite may be important in the production of low plasma 25-OHD levels in these patients, particularly in the winter months when endogenous vitamin D synthesis is at a minimum.

The importance of these findings and their

relationship to metabolic bone disease can best be assessed by histological examination of bone, and this study is in progress. Vitamin D deficiency is not synonymous with osteomalacia, and other factors are involved in the development of the bone disease, particularly calcium and phosphate ions. However, information concerning vitamin D absorption and metabolism in small bowel disease may well facilitate a better understanding of the mechanisms involved in the development of osteomalacia in some of these patients and enable the present methods of treatment to be improved.

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