SMALL INTESTINE

Vitamin D status and measurements of markers of bone metabolism in patients with small intestinal resection

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Background and aims: Vitamin D deficiency is common in patients with small intestinal resection and may lead to secondary hypersecretion of parathyroid hormone (PTH), which in turn may result in increased bone turnover rate and loss of bone mineral. The aims of this study were to investigate the prevalence of vitamin D deficiency, as assessed by low serum concentrations of 25-hydroxyvitamin D (25(OH)D) in patients with small intestinal resection and to explore the relation of 25(OH)D to PTH, markers of bone turnover rate, and bone mineral density (BMD) in these patients.

Patients: Forty two patients with small intestinal resection, a faecal energy excretion of more than 2.0 MJ/day, and a mean length of the remaining small intestine of 199 cm were included. Diagnoses were Crohn's disease (n=35) and other (n=7).

Methods: 25(OH)D was analysed by radioimmunoassay and bone turnover rate was assessed by measurement of serum osteocalcin, serum alkaline phosphatase, urine pyridinoline, and urine deoxypyridinoline. BMD was measured by dual energy x ray absorptiometry.

Results: Mean 25(OH)D concentration was 13.4 (SD 9.7) ng/ml, which was significantly below the reference mean of 26.4 (SD 13.2) ng/ml ($p<0.001$). Vitamin D deficiency (25(OH)D concentration ≤ 8 ng/ml) was found in 38.1% of patients and was accompanied by raised concentrations of PTH and significantly increased markers of bone resorption ($p<0.05$). Low 25(OH)D concentrations correlated significantly with lower BMD z scores of the spine ($r=0.38$; $p=0.02$) and hip ($r=0.33$; $p=0.04$).

Conclusions: We found reduced 25(OH)D concentrations in patients with small intestinal resection, and showed that a deficient 25(OH)D concentration is associated with significantly increased markers of bone resorption and decreased BMD values.

Vitamin D is essential for active intestinal calcium absorption and plays a central role in maintaining calcium homeostasis and skeletal integrity. Vitamin D is derived mainly from cutaneous synthesis in the presence of ultraviolet sunlight while dietary intake constitutes a minor fraction.¹ Deficiency of vitamin D, as assessed by low serum concentrations of the major circulating metabolite 25-hydroxyvitamin D (25(OH)D), is very common in patients with small intestinal resection, with a reported prevalence of up to 65%.²⁻⁵ The pathogenesis of vitamin D deficiency in these patients remains unclear but is thought to result primarily from fat soluble vitamin malabsorption due to steatorrhoea² although lack of adequate sunlight exposure, reduced dietary intake of vitamin D, and perhaps a disrupted enterohepatic circulation of vitamin D⁶ may also contribute.

25(OH)D is converted in the kidney, stimulated by parathyroid hormone (PTH), to the hormonally active metabolite 1,25-dihydroxyvitamin D (1,25 (OH)₂D), and plasma levels of 1,25 (OH)₂D are maintained within the normal range until the 25(OH)D concentration becomes extremely low. However, secondary PTH hypersecretion associated with vitamin D deficiency or less severe degrees of vitamin D insufficiency is associated with an increased bone turnover rate through PTH mediated actions on bone resorbing cells, which may result in loss of bone mineral.⁷⁻¹⁵

The bone turnover rate can be reliably assessed by surrogate measures of osteoblast and osteoclast function in blood and urine. Sensitive indicators of bone resorption rate are the 3-OH pyridinium derivatives, pyridinoline and deoxypyridinoline, crosslinks found in mature collagen chains.¹⁶⁻¹⁸ Serum osteocalcin, a non-collagenous protein secreted by osteoblasts, and serum total alkaline phosphatase, are considered useful indices of bone formation rate.¹⁸⁻²⁰

The aims of this cross sectional study were to assess to prevalence of vitamin D deficiency in patients with small intestinal resection and to examine the relation of 25(OH)D to PTH, biochemical markers of bone turnover rate, and bone mineral density in these patients.

MATERIAL AND METHODS

Patients

This work was carried out in conjunction with a study in which intestinal energy absorption was the principal outcome measure.²¹ Patients with small intestinal resection were eligible for entry into the study if they had intestinal malabsorption, defined as a faecal energy excretion of more than 2.0 MJ/day (measured at a previous admission). Patients with a peroperatively measured remnant small intestine of 200 cm or less from the ligament of Treitz, and patients with a small intestinal resection of more than 150 cm were also assumed to have a faecal energy excretion of more than 2.0 MJ/day and were included. Exclusion criteria were: current need for parenteral nutrition, evidence of inflammatory activity in patients with inflammatory bowel disease, renal impairment (defined as a creatinine clearance less than 35 ml/min), biochemical signs of liver cirrhosis, and intake of drugs that impair vitamin D activation or accelerates its clearance, such as cholestyramine or anticonvulsants. Patients were also excluded if the time elapsed since their last small intestinal

Abbreviations: BMD, bone mineral density; PTH, parathyroid hormone; 25(OH)D, 25-hydroxyvitamin D; 1,25 (OH)₂D, 1,25 dihydroxyvitamin D; T score, standard deviation score for bone mineral density (sex matched); z score, standard deviation score for bone mineral density (age, sex matched); DXA, dual energy x ray absorptiometry.

operation was less than two years. Based on information obtained from the case records, 76 patients were selected and invited by letter to participate in the study. Forty two patients (18 males, 24 females, of whom nine were postmenopausal) accepted the invitation. Clinical assessment included: weight, height, body mass index (weight/height²), data concerning time elapsed since last small intestinal surgery, length of remaining bowel (based on specification in the case records), as well as measurements of creatinine clearance and faecal fat excretion (procedures have been described previously^{21, 22}). On admission, patients were questioned about their habitual intake of calcium and vitamin D supplements but no effort was made to assess compliance with this treatment.

Biochemical measurements

All blood samples were obtained under fasting conditions, and samples were stored at -80°C until analysis.

Samples for measurement of 25(OH)D and 1,25 (OH)₂D were analysed by radioimmunoassay using an in house method.^{23, 24} The limits of detection were 5 ng/ml and 5 pg/ml, respectively. The inter- and intra-assay coefficients of variation for 25(OH)D measurements were 10.2% and 8.3%, respectively, and for 1,25 (OH)₂D measurements, 12.9% and 8.4%, respectively.

Intact serum PTH (1–84) was analysed with a two site IRMA technique using the Allegro immunoradiometric assay (Nichols Institute, San Juan Capistrano, USA). The inter- and intra- assay coefficients of variation were 6.5% and 7.8%, respectively. The manufacturer's recommendation for the normal range of PTH concentrations in White North European populations was used as a reference.

Serum osteocalcin and alkaline phosphatase were used as markers of bone formation. Serum osteocalcin was measured by a bovine ELISA assay (Dako, Copenhagen, Denmark) and the inter- and intra assay coefficients of variation were 5.3% and 3.1%, respectively. Serum alkaline phosphatase was measured using a standard hospital analytical technique.

Urine pyridinium crosslinks—that is, total urinary pyridinoline and total urinary doxypyridinoline—were used as markers of bone resorption. All urine samples were second voided specimens. Urinary deoxypyridinoline and urinary pyridinoline were analysed by a high performance liquid chromatography method with fluorescence detection after hydrolysis of urine.²⁵ The inter- and intra-assay coefficients of variation for urine pyridinium crosslinks were 13.3% and 5.7%, respectively. To compensate for the day to day variation in urinary volume, concentrations of pyridinoline and deoxypyridinoline were expressed as nmol/mmol creatinine as it was assumed that for each patient 24 hour urinary creatinine excretion was constant. Urinary excretion of creatinine was measured at 505 nm as a picric creatinine complex using a standard hospital analytical technique according to the method of Jaffe.

The concentration of calcium in aliquots of 24 hour urine samples was measured by atomic absorption spectrophotometry (model 3100; Perkin Elmer, Connecticut, USA).

Definition of vitamin D deficiency

Reference values of 25(OH)D were based on measurements obtained in 596 healthy subjects throughout the year, as described previously.²³ A subset of 384 healthy subjects, comparable in age and ethnic race, who had been investigated during the same season of the year (October through March) was selected from the reference population. Mean 25(OH)D concentration of the matched control group was 26.4 (SD 13.2) ng/ml.

We defined vitamin D deficiency as a 25(OH)D concentration ≤8 ng/ml. This definition was based on the approximate lower 5% limit of the reference population and from published data demonstrating that serum PTH concentrations are

generally increased in patients who have 25(OH)D concentrations ≤8 ng/ml.^{26–28} Based on reference values in the literature, we defined normal vitamin D status as 25(OH)D concentrations >15 ng/ml^{28, 29} whereas concentrations in the range 8–15 ng/ml were categorised as low normal.

Bone mineral density measurements

Assessment of bone mineral density (BMD) of the posterior-anterior spine and hip was performed by dual energy x ray absorptiometry (DXA) with a Norland XR-36 DXA densitometer (Norland Corporation, Fort Atkinson, Wisconsin, USA) according to the manufacturer's instructions. The host software was revision 2.5.2. and the scanner software revision 2.0.0. BMD was also expressed as a standard deviation score (z score) and BMD T score.³⁰ The reference population consisted of 696 normal healthy Danish women who had taken part in the Copenhagen Female Study. Norland supplied normal BMD values for men from a normal White European population. Osteopenia was defined according to the WHO recommendation³⁰ as a T score of less than -1.0 and osteoporosis as a T score of less than -2.5. In our laboratory, the precision error (spine phantom BMD coefficient of variation) was below 0.8%, and the short term in vivo coefficients of variation of BMD measurements were 1.1% and 1.5% for the lumbar spine and femoral neck, respectively.

Ethics

The Ethics Committee for Medical Research in Copenhagen, Denmark, approved the study protocol and the study was conducted in accordance with the Declaration of Helsinki of 1975, as revised in 1983. Written and oral informed consent was obtained from all patients prior to inclusion.

Statistics

Results are expressed as mean (SD) unless otherwise indicated. We used a one way ANOVA for between group comparisons and the Bonferroni method for post hoc analysis if the p value of the overall test was below 0.05. The χ^2 test was used to test the relation between categorical values. All statistical tests were two tailed, and a p value of less than 0.05 was considered statistically significant. Association between variables was established by Pearson's correlation coefficients. The SPSS statistical program version 11.0 (SPSS Inc., Chicago, Illinois, USA) was used for all analyses.

RESULTS

Patients demographics

The clinical characteristics of the patients are given in table 1. The study population was heterogeneous with respect to underlying disease but the majority of patients suffered from Crohn's disease. The average length of the remaining small intestine was 199 (70) cm, and the mean time elapsed since the last bowel resection was 11 (8) years. On average, patients absorbed 48% of ingested fat and excreted a mean of 47 g/day of fat in stools. Bone mineral density z scores of both the lumbar spine (-0.43 (1.36)) and hip (-0.70 (1.16)) were significantly reduced (p<0.05), and according to the criteria of the WHO,³⁰ 21% (9/42) of patients had osteoporosis and an additional 52% (22/42) had osteopenia. Most patients received some form of supplemental vitamin D but 27.9% (11/42) were not taking any supplements. The group of patients who had an oral intake of more than 400 IU/day received, on average, 825 IU/day (range 800–1000). None of the patients received activated forms of vitamin D supplements—for example, 25(OH)D or 1, alpha OH vitamin D. Four postmenopausal women were taking hormone replacement therapy but none was treated with bisphosphonates. None of the patients in this study had hypocalcaemia and none complained of bone tenderness, or bone or proximal muscle pain.

Table 1 Patient demographics

	All patients	S-25(OH)D concentration		
		Deficient (≤ 8 ng/ml)	Low normal (>8 and ≤ 15 ng/ml)	Normal (>15 ng/ml)
No of patients	42	16	10	16
Sex (pre women/post women/men) (n)	15/9/18	9/3/4	8/0/2	6/6/4
Diagnosis (CD/MT/Surg.) (n)	35/3/4	14/1/1	7/2/1	14/0/2
Age (y)	50.3 (12.3)	44.1 (12.2)*	52.2 (9.9)	55.2 (11.7)
Weight (kg)	62.8 (13.2)	60.6 (15.3)	71.1 (13.8)	59.8 (8.1)
Height (cm)	168.8 (9.3)	166.1 (8.0)	172.9 (11.0)	168.9 (9.0)
BMI (kg/m ²)	22.0 (3.9)	21.8 (4.4)	23.7 (3.6)	21.0 (3.4)
Renal creatinine clearance (ml/min)	79.4 (30.7)	77.9 (37.2)	93.8 (30.2)	71.3 (20.9)
Small bowel length (cm)	199.1 (70.6)	196.1 (73.6)	189.7 (92.4)	208.0 (54.1)
Remaining colon (%)	37.8 (40.8)	34.4 (42.7)	50.0 (40.8)	29.7 (39.0)
Faecal fat excretion (g/day)	46.9 (38.1)	43.2 (21.5)	47.9 (47.3)	50.0 (46.4)
Vitamin D suppl (none/PO/>PO/IM) (n)	11/14/10/7	7/5/2/2	2/4/3/1	2/5/5/4
Calcium suppl (0/500/1000/>2000 (mg/day)) (n)	16/7/17/2	6/2/5/3	7/2/0/1	3/3/5/5

Results are expressed as mean (SD).

*Significantly different from the normal group ($p>0.05$, one way ANOVA).

S-25(OH)D, serum 25-hydroxyvitamin D; pre women, premenopausal women; post women, postmenopausal women; CD, Crohn's disease; MT, mesenteric thrombosis; Surg, complications related to surgery; BMI, body mass index; PO, per oral 400 IU/day; >PO, per oral >400 IU/day; IM, intramuscularly 100 000 IU/month.

Relationship between 25(OH)D concentrations and biochemical markers of bone turnover rate

Mean 25(OH)D concentration was 13.4 (9.7) ng/ml which was half that of the mean of the control population ($p<0.001$). Defining 8 ng/ml as the lower level of normal, 38.1% (16/42) of patients had deficient concentrations of 25(OH)D, 23.8% (10/42) had low normal values (>8 and ≤ 15 ng/ml), and only 38.1% (16/42) had normal 25(OH)D concentrations (>15 ng/ml). Lower 25(OH)D concentrations were associated with higher concentrations of both PTH and most of the markers of bone turnover rate; however, not all between group differences were statistically significant (table 2). In particular, markers of bone resorption (urinary pyridinoline and urinary deoxypyridinoline) were elevated and significantly increased in patients with vitamin D deficiency

compared with those with normal 25(OH)D concentrations ($p<0.05$ for both markers). In patients with low, low normal, and normal 25(OH)D concentrations, 25.0%, 30.0%, and 18.8% of patients, respectively, had serum alkaline phosphatase concentrations above the normal range. Although PTH concentrations were increased in patients with lower 25(OH)D levels, the inter-correlation was not significance (fig 1A). We found significant correlations between 25(OH)D concentration and both markers of bone resorption: urinary pyridinoline ($r=-0.34$; $p=0.04$) and urinary deoxypyridinoline ($r=-0.32$; $p<0.05$), respectively. There were significant inter-correlations among the studied markers of bone turnover rate, and thus urinary pyridinoline, urinary deoxypyridinoline, and serum alkaline phosphatase correlated significantly with each other ($p<0.05$ for all correlations) whereas

Table 2 Relationship between serum 25-hydroxyvitamin D (S-25(OH)D) concentration and mean levels of calcium regulating hormones, markers of bone turnover rate, and dual energy x ray absorptiometry measurements in 42 patients with small intestinal resection and normal renal function

	S-25(OH)D concentration		
	Deficient (≤ 8 ng/ml)	Low normal (>8 and ≤ 15 ng/ml)	Normal (>15 ng/ml)
Calcium regulating hormones			
S-25(OH) vitamin D (ng/ml)	5.6 (1.5)	11.0 (2.4)	22.7 (9.4)
S-1,25 (OH) ₂ vitamin D (pg/ml)	22.5 (8.6)	21.7 (9.2)	21.1 (7.3)
S-PTH (pg/ml)	47.1 (45.0)	53.8 (53.2)	27.6 (13.5)
S-ionised calcium (mmol/l)	1.27 (0.07)	1.24 (0.05)	1.26 (0.04)
S-phosphate (mmol/l)	1.01 (0.30)	1.04 (0.23)	1.00 (0.18)
Urine-calcium (mmol/day)	2.2 (1.6)	2.9 (2.1)	3.0 (3.2)
Markers of bone turnover rate			
S-alkaline phosphatase (IU/l)	278 (176)	245 (91)	220 (112)
S-osteocalcin (µg/l)	10.2 (6.1)	11.2 (3.5)	10.4 (1.8)
U-pyridinoline (nmol/mmol creatinine)	63.4 (36.4)*	43.7 (20.3)	37.8 (10.9)
U-deoxypyridinoline (nmol/mmol creatinine)	13.8 (7.9)*	11.0 (6.3)	8.0 (3.0)
Bone mineral density z scores			
Spinal BMD z score	-0.91 (0.94)†	-0.70 (1.43)	0.16 (1.49)
Hip BMD z score	-0.96 (1.18)†	-0.66 (1.35)	-0.50 (1.03)

Data are mean (SD)

*Significantly different from the normal group ($p>0.05$, one way ANOVA); †significantly below zero ($p<0.01$, Student's one sample *t* test).

Normal reference range: serum-1,25 dihydroxyvitamin D [S-1,25 (OH)₂ vitamin D] (17–43 pg/ml); serum parathyroid hormone [S-PTH] (10–50 pg/ml); serum ionised calcium (1.15–1.50 mmol/l); serum phosphate (0.80–1.50 mmol/l); serum alkaline phosphatase (80–275 IU/l); serum osteocalcin (2.9–10.4 µg/l); urinary pyridinoline/mmol of creatinine (17.2–60.4 nmol/mmol); urinary deoxypyridinoline/mmol of creatinine (3.8–22.2 nmol/mmol).

Figure 1 (A) Relationship between serum 25-hydroxyvitamin D concentration and parathyroid hormone (PTH) in 42 patients with small intestinal resection. Individual vitamin D supplementation is indicated: none; 400 IU/day orally (PO); >400 IU/day PO; 100 000 IU/month intramuscularly (IM). The horizontal line indicates the upper limit of normal for PTH; the vertical line indicates the lower limit of normal for 25-hydroxyvitamin D concentration. (B) Relationship between serum 25-hydroxyvitamin D concentration and spinal bone mineral density (BMD) z score.

serum osteocalcin correlated significantly only with serum alkaline phosphatase ($p=0.02$). All markers of bone turnover rate appeared to be strongly related to PTH. Thus there were significant correlations between PTH and serum alkaline phosphatase ($r=0.41$; $p<0.01$), serum osteocalcin ($r=0.75$; $p<0.01$), urinary pyridinoline ($r=0.35$; $p=0.03$), and urinary doxypyridinoline ($r=0.54$; $p<0.01$).

In addition, there was a significant correlation between PTH and serum ionised calcium ($r=-0.39$; $p=0.02$). Mean values of serum ionised calcium, serum phosphate, and serum 1,25(OH)₂D remained normal regardless of the level of 25(OH)D, and only one patient with deficient 25(OH)D concentrations presented with very low serum 1,25(OH)₂D concentration. This patient had very high levels of both PTH and markers of bone turnover rate but serum ionised calcium and serum phosphate were within the normal range. Lower 25(OH)D concentrations were associated with decreased spinal and hip BMD z score values, and there were significant correlations between 25(OH)D concentration and BMD z scores of the spine ($r=0.38$; $p=0.02$) and hip ($r=0.33$; $p=0.04$) (fig 1B). In addition, there were significant inverse correlations between spinal BMD z score and serum alkaline phosphatase ($r=-0.33$, $p=0.03$), urinary pyridinoline ($r=-0.35$, $p=0.03$), and urinary doxypyridinoline ($r=-0.35$, $p=0.03$). Hip BMD z score correlated significantly with serum alkaline phosphatase ($r=-0.38$, $p=0.02$) and urinary doxypyridinoline ($r=-0.34$, $p=0.04$).

A low 25(OH)D concentration was not significantly related to a high fat excretion, a short remaining small intestine, or old age ($p>0.05$ for all correlations). Two patients presented with moderate chronic hypomagnesaemia, one of whom had vitamin D deficiency and raised PTH concentrations and the other had normal 25(OH)D and PTH concentrations.

Influence of vitamin D supplements on 25(OH)D concentrations

Mean 25(OH)D concentration was 9.4 (7.2) ng/ml, 12.9 (7.5) ng/ml, 17.4 (14.6) ng/ml, and 14.9 (7.0) ng/ml in patients who received none ($n=11$), 400 IU/day orally ($n=14$), >400 IU/day orally ($n=10$), or 100 000 IU/month intramuscularly ($n=7$) of supplemental vitamin D, respectively. Thus mean 25(OH)D concentrations tended to increase with increasing daily doses of vitamin D but differences between treatment groups were not statistically significant. In this study, 63.6% (7/11) of patients who did not receive any vitamin D supplementation had deficient 25(OH)D concentrations whereas only 29% (9/31) of those who received some supplementary vitamin D had deficient concentrations ($p=0.04$).

DISCUSSION

We studied the prevalence of vitamin D deficiency in patients with small intestinal resection and severe intestinal malabsorption, as reflected by a mean faecal fat excretion of 46 g/day. Defining vitamin D deficiency as a 25(OH)D concentration of ≤ 8 ng/ml, approximately one third of patients were vitamin D deficient and a large number had low 25(OH)D concentrations. The high prevalence of vitamin D deficiency confirms previous observations in similar groups of patients.²⁻³ One study, however, reported normal 25(OH)D concentrations in small intestinal resected Crohn's disease patients³¹ but the relatively short intestinal resection of these patients may explain this conflicting finding.

Increased PTH secretion is one of the earliest signs of insufficient stores of vitamin D, a physiological response presumably mediated through changes in serum ionised calcium and serum 1,25(OH)₂D. In our study, although PTH was not significantly raised, clearly higher PTH concentrations were seen in patients with lower 25(OH)D concentrations. Concurrent with the increase in PTH, lower 25(OH)D concentrations were accompanied by higher concentrations of most of the markers of bone turnover rate. However, bone formation markers were only moderately elevated or unchanged whereas resorption markers (urinary pyridinoline and urinary doxypyridinoline) were significantly increased by approximately 70%. Changes in these markers of a similar magnitude have been reported in elderly women with vitamin D insufficiency.⁷ In our study, PTH correlated significantly with all of the markers of bone turnover rate, which strongly indicates that PTH hypersecretion is responsible for the accelerated bone turnover rate in patients with vitamin D deficiency. The fact that bone resorption markers were substantially more elevated probably reflects the fact that PTH primarily affects bone turnover rate by stimulating osteoclast mediated bone resorption.³²⁻³⁴

The increased PTH mediated bone resorption caused by vitamin D deficiency may disturb the bone remodelling process and result in a net loss of bone mineral.³²⁻³³ We found significant correlations between measurements of 25(OH)D and BMD z scores of both the spine and hip, supporting the fact that vitamin D deficiency adversely affects bone health in these patients. The finding of significant inverse correlations between markers of bone resorption and BMD z scores adds support to the contention that PTH hypersecretion plays an important role in the pathogenesis of bone mineral loss in patients with vitamin D deficiency. Although differences did not reach statistical significance, spinal and hip z scores were about 1.0 and 0.5 lower in patients with vitamin D deficiency

compared with patients with normal 25(OH)D concentrations. How does this translate into fracture risk when using BMD data generated in the normal population? For the individual patient of 50 years of age, a decrease in the hip z score of 0.5 corresponds to an increase in the 10 year probability of sustaining any osteoporotic fracture of approximately 25%.³⁵ Yet caution should be exercised when interpreting the significance of the findings given that a range of factors not accounted for in this study are known to affect BMD in these patients.

Long lasting and severe vitamin D deficiency with loss of 1,25 (OH)₂D leads to a defective mineralisation of bone, resulting in rickets or its adult equivalent osteomalacia. PTH is usually increased in this clinical condition but bone turnover rate is not generally increased, presumably as a consequence of excess unmineralised matrix blocking the bone resorbing action of osteoclasts.³⁶ Although in this study a large number of patients had deficient 25(OH)D concentrations, essentially all maintained a normal 1,25 (OH)₂D concentration, indicating sufficient substrate for hydroxylation, and none had sub-normal serum concentrations of calcium and phosphate or typical clinical signs of osteomalacia (that is, bone tenderness or proximal muscle pain). We therefore assumed that the vitamin D deficiency in our patients was moderate enough not to cause overt osteomalacia. However, as no bone biopsies were performed, we cannot exclude the possibility that a mild degree of osteomalacia may have contributed to the lower bone mass in some patients, as histological evidence of osteomalacia has been reported in patients with small intestinal resection in the absence of biochemical or clinical symptoms.³⁷

Chronic hypomagnesaemia, which may coexist in patients with severe intestinal malabsorption, is known to suppress the physiological PTH response to hypocalcaemia.³⁸ However, only a few patients presented with mild hypomagnesaemia and in these patients there were no indications of impaired PTH secretion.

Vitamin D deficiency is a well established risk factor for fracture rate in the elderly,³⁹⁻⁴¹ and although data are not available in patients with small intestinal resection, a similar relationship can be assumed. The high prevalence of vitamin D deficiency in patients with small intestinal resection calls for a more active strategy to combat this deficit. Cutaneous synthesis is considered the primary source of vitamin D but it is unlikely that solar radiation can be significantly increased in these patients, and given that only very few food items contain vitamin D it is also unlikely that dietary intake can be raised. Therefore, the most rational approach to reducing vitamin D deficiency is supplementation; uncertainty exists however about the optimum dose and route of administration (oral or parenteral). Previous studies on intestinal vitamin D absorption in patients with small intestinal resection have shown an inverse relationship between absorption of vitamin D and the degree of fat malabsorption.⁴²⁻⁴⁴ Although some authors⁴³ have questioned the efficacy of oral vitamin D supplementation, others have concluded that malabsorption of vitamin D is usually moderate enough so that conventional oral replacement therapy is appropriate in most patients.⁴²⁻⁴⁴ In our study, irrespective of the degree of fat malabsorption, any vitamin D supplementation was associated with significantly higher 25(OH)D concentrations. This study was not powered to detect the optimal dose of supplementary vitamin D but a dose of 400 IU/day orally, normally contained in a multivitamin tablet, was generally not sufficient to protect against vitamin D deficiency but it appeared that higher oral doses were protective in many patients. Intramuscular vitamin D injections of 100 000 IU of cholecalciferol monthly have long been used in patients with severe malabsorption, and although this treatment ensured adequate vitamin D stores in most patients, a few still had deficient 25(OH)D concentrations, presumably because of poor absorption from the injection site.

In conclusion, this study supports the fact that vitamin D deficiency is common in patients with small intestinal resection and is associated with increased PTH secretion and biochemical evidence of increased bone resorption. The data indicate that vitamin D deficiency is an important aetiological factor for bone disease commonly observed in these patients. On the basis of our findings, we recommend that patients with small intestinal resection and malabsorption should routinely receive oral supplements of vitamin D. Several activated forms of vitamin D (for example, 1, alpha OH vitamin D, 1,25 (OH)₂D₃, or 25(OH)D) have the advantage of being more easily absorbed from the gastrointestinal tract compared with the native vitamin.⁴²⁻⁴⁴ However, the use of these formulations requires monitoring of serum ionised calcium due to the risk of toxicity, and we therefore suggest supplementation with conventional vitamin D dosed individually. The currently accepted threshold that is regarded as safe and does not require monitoring of serum ionised calcium is 2000 IU daily.⁴⁵ Yet we would recommend that treatment in all patients should be guided by regular determinations of 25(OH)D and PTH in order to identify patients who need even higher doses of vitamin D, and parenteral supplements should be considered if oral treatment proves insufficient.

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