Regulation of vitamin D and calcium metabolism after gastrectomy

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SUMMARY Fifteen men, who had undergone Billroth I gastrectomy and 19 men who had undergone Billroth II gastrectomy were studied with respect to vitamin D and other indices of calcium metabolism. The Billroth I group had hypocalcaemia, raised concentration of serum alkaline phosphatase, and reduced bone mineral content. The same biochemical disturbances were found in the Billroth II group, but bone mineral content was normal. In neither of the groups was found signs of increased bone resorption. The calcium absorption was situated in the lower part of the normal range and the fractional absorption and elimination rates were normal. The 25OHD concentrations in both groups were reduced ($p < 0.05-0.01$) and the $1,25(\text{OH})_2\text{D}$ concentrations raised ($p < 0.01-0.001$). The $1,25(\text{OH})_2\text{D}$ concentrations were inversely related to bone mineral content, but directly related to signs of bone turnover and calcium absorption. We suggest that the high $1,25(\text{OH})_2\text{D}$ concentration is the result of a compensatory process with the aim of preventing hypocalcaemia.

While most studies on postgastrectomy bone disease show that the disease is of osteomalacic nature,¹⁻³ there is disagreement with respect to its pathogenesis. Deficient dietary intake of calcium and vitamin D^{4,5} and various maldigestive or malabsorptive conditions caused by steatorrhoea⁶⁻⁷ are considered causative factors. Study results vary, however, and the literature concerning calcium absorption is particularly conflicting.⁸⁻¹¹ Findings of low 25OHD concentrations¹²⁻¹⁵ support the opinion that vitamin D deficiency is a contributory cause.

Whatever the cause, manifest bone disease can develop in two different ways; gradually over several years, finally reaching a symptomatological stage, or as the result of a sudden breakdown in compensatory processes that have hitherto been able to maintain almost normal bone composition. The lack of relationship between the time since operation and manifestation of bone disease^{1,13} favours the latter view, but no studies have been undertaken with the aim of investigating the regulation of the calcium and vitamin D metabolism after gastric resection.

We present here an investigation in which the

altered calcium metabolism after gastrectomy is reassessed from a pathophysiological point of view.

Methods

PATIENTS AND CONTROLS

We contacted 171 men who had undergone partial gastrectomy three to 14 years before at Glostrup Hospital. Of these 59 had had more than one operation and 61 were excluded for the following reasons: neoplasms (27), liver disease or alcohol addiction (seven), diabetes mellitus (four), immobility (four), lack of cooperation (nine), other diseases (six), and treatment with certain medications (four). Of the 51 who met the inclusion criteria eight had left the district and 35 of the remaining 43 were willing to participate. The study finally comprised 34 (Table 1) who were without conditions known to affect calcium metabolism and who had normal serum aspartate aminotransferase (ASAT) and serum creatinine concentrations. All gave their informed consent. Half of the patients were randomly selected for calcium absorption test. They constituted a true sample of the whole population (Table 1 and 2).

Serum alkaline phosphatase, calcium absorption, and urine values were compared with those in

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Table 1 Comparability of the Billroth I and Billroth II gastrectomy groups. Data for the subpopulation are given in brackets.

	Billroth I n=15 (8)	Billroth II n=19 (9)
Age (yr)	60.8±8.7 (63.4±8.8)	60.7±11.8 (57.7±9.5)
Interval since operation (yr)	8.8±2.2 (9.6±2.4)	10.4±2.9 (9.8±3.2)
Height (cm)	172±8 (172±6)	174±5 (175±6)
Present weight (kg)	69.5±11.1 (70.9±9.5)	76.0±9.2 (77.6±9.9)
Weight at time of operation (kg)	62.0±9.3* (64.6±8.8)	71.8±7.3 (71.3±7.6)

* = $p < 0.01$ (Billroth I versus Billroth II gastrectomy groups).

healthy age-matched men (Table 2). Vitamin D metabolite concentrations were compared with values in 20 persons (seven women and 13 men) aged 31.5 ± 5.7 (Fig. 1). As reference groups for bone mineral content values we used 74 healthy men, aged 40–90 years (mean 56.7 years); and 32 men, aged 26–85 years (mean 46.2 years) served as reference group for the remaining variables (Table 2).

Vitamin D concentrations were measured by a previously described method.¹⁶ The method

involves extraction with methanol/dichloromethane and separation and purification by means of Sephadex LH-20, Lipidex 5000 chromatography and high pressure chromatography. The 25OHD fraction is measured by ultraviolet detection whereas the dihydroxylated metabolite $1,25(\text{OH})_2\text{D}$ was quantitated by a cytosol receptor assay. Inter-assay variations (CV%) are 11% and 13%, respectively. All blood samples for vitamin D analysis were taken during the same two months (February and March) because of seasonal variations in 25OHD. Parathyroid hormone (PTH) was measured by double antibody technique with determination of the C terminal fragments. Intra-assay variation is 10%. Calcium, magnesium, phosphate, ASAT, and alkaline phosphatase concentrations were measured by routine techniques (atomic absorption, colorimetry, and enzymatically). Calcium and magnesium concentrations were corrected to a protein concentration of 70 g/l.¹⁷

Calcium and creatinine were measured in 24 hour and fasting urine by means of SMA-6 autoanalyser, and hydroxyproline was measured in fasting urine spectrophotometrically by a previous described method.¹⁸ Interassay variation is 9%.

Bone mineral content was measured by single photon absorptiometry on the distal part of the forearm. The mean of 12 scans, six on each arm was expressed as percentage of a 10 year grouped

Table 2 Biochemical findings in gastrectomised patients compared with controls. Data for the subpopulations are given in brackets. Values are given as mean $\pm$ 1 SD.

	Billroth I n=15	Billroth II n=19	Controls
Bone mineral content (%)	89.4±12.4* (91.7±12.8)	100.7±19.4 (105.7±16.5)	100±16.4 (n=74)
<i>Serum values</i>			
Calcium (mmol/l)	2.39±0.07† (2.39±0.08)	2.42±0.07 (2.43±0.07)	2.47±0.09 (n=32)
Phosphate (mmol/l)	1.0±0.1 (1.0±0.1)	1.1±0.1 (1.1±0.2)	1.1±0.2 (n=32)
Magnesium (mmol/l)	0.82±0.05 (0.82±0.05)	0.83±0.06 (0.84±0.05)	0.85±0.07 (n=32)
Alkaline phosphatase (U/l)	206±61† (225±67)	187±51* (171±40)	154±26 (n=15)
<i>Urine values</i>			
24-hour Ca/Cr (mmol/mmol)	0.30±0.18 (0.29±0.21)	0.31±0.14 (0.32±0.16)	0.38±0.15 (n=17)
Fasting Ca/Cr (mmol/mmol)	0.18±0.11 (0.16±0.11)	0.20±0.15 (0.18±0.13)	0.20±0.11 (n=17)
Fasting HPR/Cr (mmol/mmol)	0.011±0.003 (0.011±0.003)	0.012±0.002 (0.011±0.002)	0.011±0.004 (n=17)
<i>Calcium absorption</i>			
Fract 60 min $\times$ 20% LBM	(27.7±5.4)	(26.4±6.4)	32.1±10.4 (n=11)
Time delay (min)	(7.0±2.7)*	(7.6±2.5)*	11.5±4.7 (n=11)
Fract abs rate (h^{-1})	(1.5±0.4)	(2.2±1.2)	1.8±0.9 (n=11)
Fract elim rate (h^{-1})	(0.27±0.11)	(0.21±0.10)	0.2±0.10 (n=11)

* = $p < 0.05$. † = $p < 0.01$ (patients versus controls).

Fig. 1 Serum 25OHD and 1,25(OH)₂D concentrations after Billroth gastrectomies compared with normal values.

sex-matched reference population. The bone mineral content measurement has a long term reproducibility of 1.4%,¹⁹ and it is highly correlated to total body calcium in both gastrectomised patients and normal subjects.²⁰

Calcium absorption was measured by a slight modification of the single isotope technique described by Marshall and Nordin.^{21, 22} The oral tracer of 10 μ Ci ⁴⁷Ca with a carrier dose of 20 mg calcium ion as CaCl₂ in 250 ml water was given to the fasting subjects between 8 and 10 am. Blood samples were taken after 10, 20, 40, 60, 90 and 120 minutes and the absorbed fractions were corrected for lean body mass²⁰ calculated by the formula of Boddy *et al.*²³ The time delay Δt , the absorbed fractions, and the constant fractional absorption and elimination rates were calculated by a non-linear curve fitting programme using a two component model.²⁴

CALCULATIONS AND STATISTICS

The following statistical tests were used: calculation of mean values and standard deviation (SD); Student's *t* test for unpaired observations, except for calcium absorption for which Wilcoxon's rank sum test was used; and tests of linear correlation.

Results

Hypocalcaemia, raised serum alkaline phosphatase, and lower than normal bone mineral content were found in the Billroth I gastrectomy group. The biochemical findings were similar in the Billroth II group but the mean values for bone mineral content

were normal. The mean calcium and hydroxyproline excretions were similar in both groups and did not differ from the normal mean values (Table 2).

The mean calcium absorption curves were almost identical and were situated in the lower part of the normal range (Fig. 2). The only significant differences from normal were a shorter time delay in both gastrectomy groups and a correspondingly increased absorbed fraction after 10 minutes in the Billroth II group (Table 1, and Fig. 2). The calculated fractional absorption and elimination rates were of similar magnitude in both patients and controls (Table 2). In neither group was the absorbed fraction (after 60 minutes and corrected for lean body mass (F_{60})), related to age or interval since operation.

Fig. 2 Intestinal calcium absorption expressed as fraction of oral ⁴⁷Ca dose $\times$ 20% of lean body mass. Values are given as mean $\pm$ 1 SD.

* = $p < 0.05$ (Wilcoxon's rank sum test).

Figure 1 shows the individual concentrations of vitamin D metabolites for both the patient groups and the controls. The mean serum 25OHD was decreased and the mean serum 1,25(OH)₂D was increased in both the patient groups compared with the normal subjects. Taking the patients as one group, three had a 25OHD concentration below the normal range (<4.9 ng/ml) and 16 had a 1,25(OH)₂D concentration above the normal range (>45.2 pg/ml). No significant correlations were observed between the two serum vitamin D metabolites, and none were significantly related to age or time since operation. The PTH concentrations were significantly higher in the Billroth I group ($0.34 \pm 0.11 \mu\text{g/l}$) than in the Billroth II group ($0.27 \pm 0.04 \mu\text{g/l}$), $p < 0.05$. Only two of the patients (both in the Billroth I group) had concentrations above the normal range.

Table 3 gives the linear coefficients of correlation between the relevant variables. The salient features are as follows: bone mineral content was inversely related to the serum 1,25(OH)₂D concentration and calcium absorption. Moreover, the serum 1,25(OH)₂D concentration was related to the serum alkaline phosphatase (estimate of bone formation), fasting urinary hydroxyproline/creatinine excretion (estimate of bone resorption), and calcium absorption.

Discussion

The Billroth I and Billroth II gastrectomy groups had an average bone mineral content value of 96% of the normal value, which is similar to the values of 95%³ and 93%² found in other studies. Because the local bone mineral content value is closely related to the total body mineral content,¹⁹ there does not seem to be much acceleration of bone loss during the first 10 years after gastric resection in otherwise healthy men. This is also supported by lack of biochemical signs of increased bone resorption. Although the patients in the two resection groups were identical with regard to age, height, and interval since operation, the body weight in the

Billroth I group were nearly 10 kg less than that in the Billroth II group at the time of operation and this difference largely persisted at the time of the study (Table 1). In spite of the lower bone mineral content values and greater biochemical alterations in the Billroth I group, no conclusion can be drawn about which type of resection carries the greater risk of osteopenia subsequently developing.

In accordance with the almost normal bone mass and the normal calcium excretion rate, we found no evidence of pronounced malabsorption. Estimation of calcium absorption by the single isotope test has shown both higher⁸⁻¹⁰ and lower¹⁰⁻¹¹ plasma ⁴⁷Ca concentrations after gastrectomy. A relation between test values and bone disease has been claimed by some authors¹⁰ and contradicted by others.¹¹ There is a similar disagreement about the role of steatorrhoea,⁸⁻¹¹ but increased faecal calcium has often been found in gastrectomised patients.⁹⁻¹⁰ In large population studies of healthy persons and patients with calcium metabolic disorders, including gastrectomised patients, the fraction absorbed after one or two hours, corrected for body weight, is closely related to calcium absorption measured by the balance method²¹ and using a greater carrier dose also with the double isotope test.²⁵ In the presence of severe intestinal malabsorption and delayed calcium absorption the curve may continue to rise for two to three hours and calcium absorption will be underestimated if the fraction absorbed is measured after only one or two hours. In this study, however, the maximum values were reached at the same time in the control group and the two patient groups. The two-compartment models may underestimate calcium absorption when calcium turnover is high, but the fractional elimination rates were similar in patients and controls, and the patients had no other signs of accelerated bone turnover. The dependency of the calcium absorption test on simultaneous intake of milk and fat has been evaluated by Arman²⁶ and Agnew.⁸ Despite the fact that this method, like other tracer methods, does not necessarily reflect the physiological events, we consider it useful in estimating calcium absorption.

Table 3 Coefficients of correlation between relevant calcium metabolic variables in 34 patients after partial gastrectomy.

	BMC	Ca	Alkaline Ph	FUOHPPro/Cr	25OHD	1,25(OH) ₂ D
Calcium absorption (n=17)	-0.48*	0.24	0.43	0.37	0.16	0.54*
1,25(OH) ₂ D	-0.38*	0.07	0.41*	0.42*	0.19	
25OHD	0.02	0.24	0.01	0.17		
FUOHPPro/Cr	0.09	0.12	0.17			
Alkaline phosphatase	-0.33	-0.05				
Calcium	0.16					

* = $p < 0.05$.

In spite of an inability to relate calcium absorption to a low calcium diet in the elderly, there is no clear evidence of a dependence between age and serum $1,25(\text{OH})_2\text{D}$ concentrations.²⁷ On the other hand, if such a relation does exist we have underestimated the increase in serum $1,25(\text{OH})_2\text{D}$ in our patients as the control group was younger than the patient groups.

Our present study confirms that gastrectomised patients have decreased serum 25OHD concentrations¹²⁻¹⁵ which is not related to bone mineral content^{2, 28} or time after operation.¹⁴⁻¹⁵ The exogenous vitamin D supply is probably the critical factor, but malabsorption and increased turnover might contribute to the low concentrations. The absorption of vitamin D and 25OHD has been found normal or just below the normal range after gastrectomies^{12, 29, 31} and a relation to fat excretion has been proposed.¹² Because 25OHD undergoes enterohepatic circulation,³² an impaired bile salt excretion or absorption might influence absorption, but none of the patients in this study had symptoms of liver disease and all had normal serum ASAT concentrations.

Our data clearly demonstrate that these patients as a group have raised $1,25(\text{OH})_2\text{D}$ concentrations. These raised concentrations cannot be explained by a concomitant increment of the PTH level. The significant relation between $1,25(\text{OH})_2\text{D}$ concentrations and calcium absorption, together with the almost normal bone mass, may indicate that the rise of the $1,25(\text{OH})_2\text{D}$ concentration is a compensatory process.

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