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Bone Disorders Following Total Gastrectomy

GEROLD WETSCHER, MD, ELIZABETH REDMOND, MD, CHRISTINE WATFAH, MD, GALEN PERDIKIS, MD, MICHAEL GADENSTÄTTER, MD, and RUDOLPH POINTNER, MD

Bone disorders following gastrectomy were studied by measuring absolute and relative bone mineral density of the Wards triangle, serum 1,25-$(OH)_2$-D, alkaline phosphatase, and total serum calcium. The subjects were 20 males who had undergone total gastrectomy not more than three months previously (group A_1). Seventeen of these patients were reviewed three years later (group A_2). Absolute and relative bone density were significantly lower in group A_2 than in A_1 (0.52 ± 0.011 g/cm^2 versus 0.6 ± 0.014 g/cm^2, $P < 0.01$ and $85.5 \pm 1.4\%$ age-matched control versus $95 \pm 1.3\%$, $P < 0.01$). 1,25-$(OH)_2$-D was significantly lower in group A_2 than in group A_1 (14.3 ± 0.97 pg/ml versus 20.6 ± 1.02 pg/ml, $P < 0.01$). There was no difference in alkaline phosphatase and calcium serum concentration. The mean weight loss was $6.26 \pm 0.57\%$ over the follow-up period, and weight loss correlated with absolute and relative bone density ($r = -0.74$, $P < 0.01$). There was a positive correlation between 1,25-$(OH)_2$-D and absolute or relative bone density ($r = 0.67$, $r = 0.62$ and $P < 0.01$). These data suggest that bone density decrease has already occurred three years after total gastrectomy and is positively correlated to 1,25-$(OH)_2$-D deficiency. As no differences in serum alkaline phosphatase and serum calcium concentration were found, these factors are of little value for the early detection of postgastrectomy bone disorders, whereas weight loss is a valuable screening parameter.

KEY WORDS: gastrectomy; bone disorders; vitamin D deficiency.

Partial and total gastrectomy may lead to bone disorders such as osteoporosis and osteomalacia in about 50–70% of patients, according to the more recent literature (1–4). They occur 3–10 years after operation and result in a decrease of bone mineral content in up to 25% of patients compared to age- and sex-matched controls (3). There is a two- to threefold increase in the rate of fractures over the subsequent 20 years (5).

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From the Second Department of Surgery, University of Innsbruck, Innsbruck, Austria; Department of Surgery, Creighton University, Omaha, Nebraska; Department of Nuclear Medicine, University of Innsbruck, Innsbruck, Austria; and Department of Surgery, Zell am See, Austria.

Address for reprint requests: Dr. Gerold Wetscher, 2nd Department of Surgery, University of Innsbruck, Anichstrasse 35, 6020 Innsbruck, Austria.

The cause is thought to be malnutrition and malabsorption with consequent calcium and vitamin D deficiency (1, 2). Postgastrectomy patients are known to avoid dairy products, as milk often leads to abdominal pain, bloating, and diarrhea, and therefore they have a decreased vitamin D and calcium uptake (1, 2). In addition gastrectomy leads to lipid malabsorption with consequent steatorrhea and reduced vitamin D and calcium absorption. More than 30% of postgastrectomy patients will complain of steatorrhea. Inactivation of pancreatic lipase by bacterial overgrowth and a delay of pancreatic enzymes reaching the food due to the presence of an afferent loop are also considered to play a role in the development of postgastrectomy malabsorption (1). The role of vitamin D and calcium deficiency in the pathophysiology of postgastrectomy bone disorders remains a matter for debate.

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TABLE 1. BONE DISORDERS FOLLOWING TOTAL GASTRECTOMY*

	Group A_1	*Group A_2*
Age (yr)	67 (42–79)	70 (45–81)
Postoperative interval	3 months	3 years
Weight loss (%)		6.26 ± 0.57
Bone density (g/cm^2)†	0.6 ± 0.014	0.52 ± 0.011
Bone density (%)†	95 ± 1.3	85.5 ± 1.4
1,25-$(OH)_2$-D (pg/ml)†	20.6 ± 1.02	14.3 ± 0.97
Alkaline phosphatase (units/liter)	154.2 ± 2.14	152 ± 3.08
Serum calcium (mmol/ml)	2.37 ± 0.02	2.35 ± 0.05

*Results are means ±SEM. Relative bone density is expressed as percentage compared to age-matched controls. 1,25-$(OH)_2$-D level below 20 pg/ml was considered to be pathologic. No significant differences in alkaline phosphatase and serum calcium concentrations levels were found.
†$P < 0.01$.

Kozawa et al described decreased levels of 25-(OH)-D_3 and 24,25-$(OH)_2$-D_3 but increased 1,25-$(OH)_2$-D_3, which is intriguing as it is known that 1,25-$(OH)_2$-D_3 is the most active vitamin D metabolite (6). These results are supported by a study by Bisballe et al (4), who found the levels of vitamin D metabolites to be similar. Tovey et al (1) and Hirota (7) reported decreased 25-(OH)-D_3 in only a small number of patients with postgastrectomy bone disorders and Nishimura et al (3) found 25-(OH)-D_3 deficiency in only 29% of their patients, whereas 60% were within the normal range and 11% had elevated 25-(OH)-D_3 levels. Bisballe et al (4) reported decreased serum calcium levels, whereas Nishimura's study showed these to be at the lower end of the normal range. Alkaline phosphatase was found to be increased in most of the studies (3, 4, 8). The aim of our study was to investigate the influence of total gastrectomy on the vitamin D metabolite 1,25-$(OH)_2$-D and bone density in a prospective trial and to evaluate diagnostic criteria to enable early detection of changes in bone mineralization.

MATERIALS AND METHODS

A series of 20 male patients who underwent total gastrectomy at the University Hospital of Innsbruck not more than three months previously (group A_1) were studied. The indication for surgery was gastric cancer in all of the patients. In each patient an accurate history with regard to nutritional behavior, dumping syndrome, and diarrhea was obtained. Patients were also evaluated in terms of bone pains and fractures in the period since gastrectomy. The weight was compared to the preoperative weight and results are expressed as percentage of the preoperative weight loss. Total serum calcium, serum alkaline phosphatase, and 1,25-$(OH)_2$-D [= 1,25-$(OH)_2$-D_2 + 1,25-$(OH)_2$-D_3] serum concentrations were assayed. 1,25-$(OH)_2$-D measurements were performed in

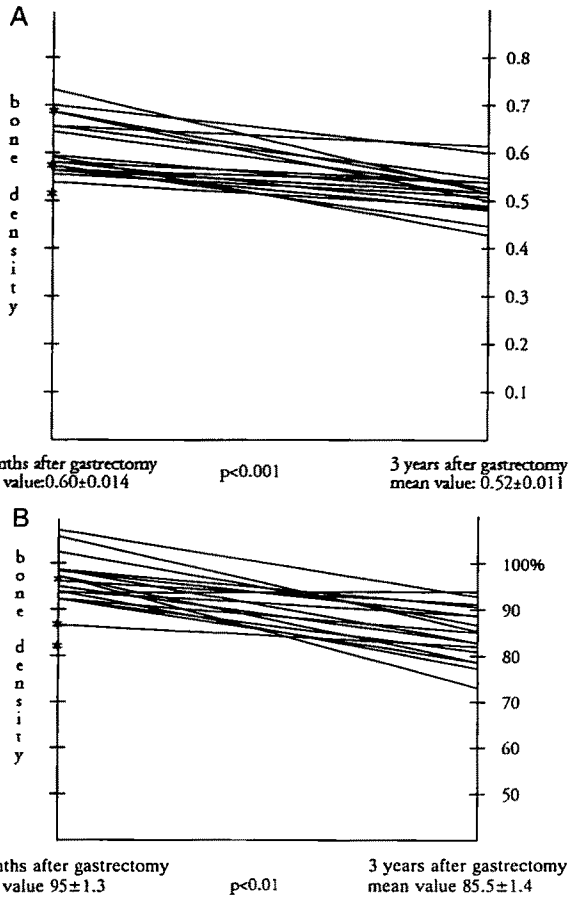

Fig 1. (A) Absolute bone density values (g/cm^2) in each patient three months and three years postoperatively. *Findings of those patients who died. (B) Relative bone density in percentage in each patient compared to age matched controls three months and three years postoperatively. *Findings of those patients who died.

the laboratory of the department of pediatrics of the University Hospital of Innsbruck by means of a competitive radioreceptor binding assay (9). Values of less than 20 pg/ml were considered to be pathologic (normal range 20–60 pg/ml). The detection limit was 2.2 pg/ml.

Bone mineral density of the Wards triangle of the left femur was measured using a Lunar DP3 dual-photon densitometer with a gandolineum-153 source (DPA). These measurements were performed in the Department of Nuclear Medicine of the University of Innsbruck. Results are expressed as grams per square centimeter (absolute bone density) and as percentage of the normal age-matched data as provided by the Lunar Corporation and are adjusted for height.

Exclusion criteria were tumors extending beyond stage II, tumor recurrence, primary hyperparathyroidism, steroid medication, and previous calcium, vitamin D, or other forms of therapy known to influence bone mineralization. Patients received no calcium or vitamin D supplements postoperatively. Of these 20 patients, 17 were

followed up for three years (group A_2) and results were compared to those of group A_1.

For statistical analysis the Student's t test was used. Results are expressed as mean ± SEM. To demonstrate the relation between vitamin D deficiency and bone density, results of 1,25-$(OH)_2$-D concentration of group A_2 have been correlated to bone density measurements of patients in group A_2. To evaluate the importance of weight loss as a diagnostic guide for the detection of postgastrectomy patients at high risk of development of bone disorders, weight loss has been correlated to bone density and vitamin D levels. The linear correlation test has been used. Results are expressed as correlation coefficient (r), and the P value is quoted also.

RESULTS

The median age of group A_1 was 67 years (range: 42–79 years) and of group A_2 70 years (range: 45–81 years). All patients who were followed up were in good health and denied symptoms of the dumping syndrome. Diarrhea and dyspepsia were absent but most patients found it necessary to avoid milk or dairy products. There were no fractures noted during the interval after surgery in any of the patients. Three patients in group A_2 admitted to intermittent low back pain. These symptoms were present before surgery. Radiographic examinations in these three patients revealed no signs of osteoporosis or osteomalacia in the lumbar region but marked degenerative changes. The most frequent clinical sign was weight loss. This was present in all patients of group A_2. The mean weight loss was 6.26 ± 0.57%.

Three patients had to be excluded from the study due to tumor recurrence. The results are shown in Table 1. The absolute bone density was 0.60 ± 0.014 g/cm^2 in group A_1 and 0.52 ± 0.011 g/cm^2 in group A_2, a difference of 13.4%. The relative bone density was 95 ± 1.3% in A_1 and 85.5 ± 1.4% in A_2, a difference of 10.1%. Both differences are statistically significant ($P < 0.01$) (Figure 1A and B).

1,25-$(OH)_2$-D serum levels were 20.6 ± 1.02 pg/ml in A_1 and 14.3 ± 0.97 pg/ml in A_2, which is significantly different ($P < 0.01$) (Figure 2).

No significant differences were found in serum calcium levels and serum alkaline phosphatase levels. Serum calcium (normal value 2.10–2.6 mmol/liter) was borderline decreased in one patient in group A_1 (2.09 mmol/liter) and slightly elevated in another patient in group A_1 (2.63 mmol/liter) and in two patients in group A_2 (2.65 and 2.68 mmol/liter). No calcium deficiency was found in patients in group A_2. The serum alkaline levels were slightly elevated above the normal value of 170 units/liter in two patients of group A_1 (179 and 184 units/liter) and in one patient of group A_2 (181 units/liter).

A positive correlation was found between serum 1,25-$(OH)_2$-D levels and absolute or relative bone density findings of group A_2 ($r = 0.67$, $r = 0.62$ and $P < 0.01$) (Figure 3A and B). There is a negative correlation between weight loss and absolute or relative bone density ($r = -0.74$, $P < 0.01$) (Figure 4A and B).

DISCUSSION

Bone disorders after gastrectomy, such as osteoporosis and osteomalacia, are well recognized, affecting up to 70% of patients, and may be seen as early as three years following surgery (1–8). Our prospective study demonstrates that three years after operation a bone mineral loss of 13.4% occurs that is accompanied by a 30% depletion of 1,25-$(OH)_2$-D. The decrease of bone mineralization is similar to the results reported by Nishimura et al (3). Bone mineralization decreases progressively with age, especially in women (3), therefore one might argue that our observed results are due to the three-year difference in age between the first investigation and the follow-up study rather than due to gastrectomy. However, the influence of age is minimized by comparing absolute bone values with age-matched controls, which can be expressed as a percentage of the normal values (relative bone density).

The observed decrease of 1,25-$(OH)_2$-D is in contrast to other studies in which increased levels of

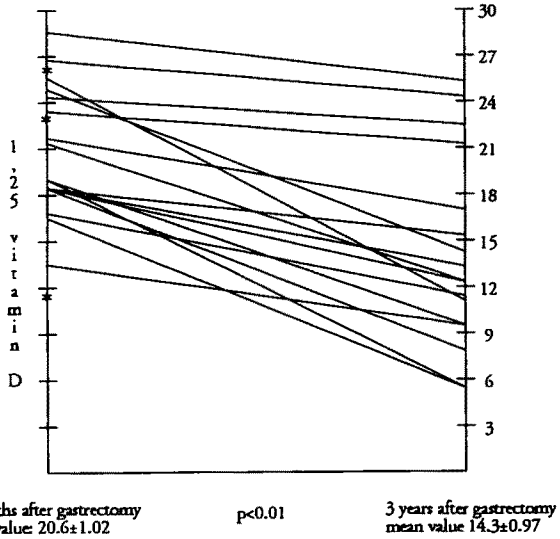

Fig 2. 1,25-$(OH)_2$-D in each of the patients three months and three years postoperatively. *Findings of those patients who died.

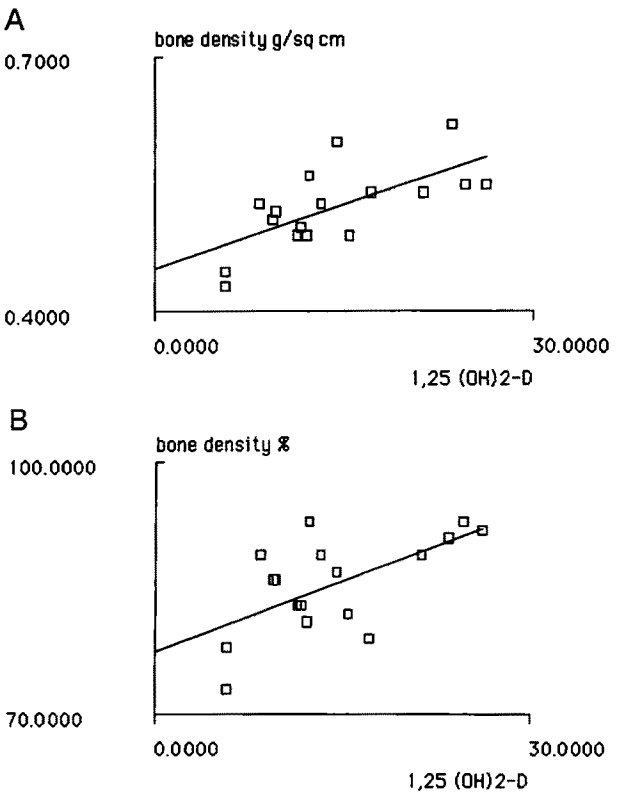

Fig 3. (A) Correlation between 1,25-$(OH)_2$-D as the independent variable and absolute bone density as the dependent variable ($r = 0.67$; $P < 0.01$). (B) Correlation between 1,25-$(OH)_2$-D as the independent variable and relative bone density as the dependent variable ($r = 0.62$; $P < 0.01$).

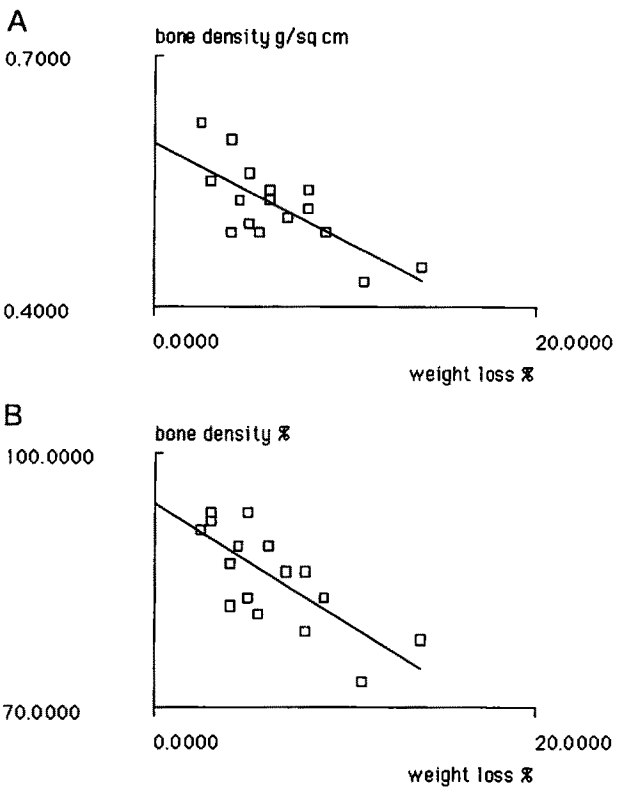

Fig 4. (A) Correlation between weight loss in percentage (independent variable) and absolute bone density (dependent variable) ($r = -0.74$; $P < 0.01$). (B) Correlation between weight loss in percentage (independent variable) and relative bone density (dependent variable) ($r = -0.74$; $P < 0.01$).

1,25-$(OH)_2$-D but decreased 25-(OH)-D_3 were detected following gastrectomy (4, 6, 8). The different findings regarding 1,25-$(OH)_2$-D are surprising as 1,25-$(OH)_2$-D is thought to be the most active vitamin D analog (4, 6). 1,25-$(OH)_2$-D is produced by hydroxylation of 25-(OH)-D_3, which is catalyzed by 1-α-hydroxylase in the kidney. The level of 1,25-$(OH)_2$-D therefore depends on the activity of 1-α-hydroxylase and the degree of 25-(OH)-D_3 depletion. As demonstrated by Habener and Potts (10) and Tanaka and DeLuca (11), the activity of 1-α-hydroxylase is increased by hyperparathyroidism and hypophosphatemia. Secondary hyperparathyroidism occurs in 25-(OH)-D_3 deficiency (4) and may be responsible for increased 1,25-$(OH)_2$-D levels as long as there is no severe depletion of 25-(OH)-D_3. Bisballe's patients had vitamin D supplements of 400–600 IU/day (4) and therefore only slightly decreased 25-(OH)-D_3 levels, which may still have been high enough to account for the 1,25-$(OH)_2$-D overproduction. Our patients were not given vitamin D or calcium supplements, and this may explain the decreased 1,25-$(OH)_2$-D levels. We did not measure 25-(OH)-D_3, so no conclusions can be made about the severity of 25-(OH)-D_3 deficiency that leads to 1,25-$(OH)_2$-D depletion.

No changes in serum calcium and alkaline phosphatase concentrations were noted in our patients throughout the follow-up period. This observation is in contrast to the studies of Bisballe et al (4) and Nishimura et al (3), who reported decreased calcium and increased alkaline phosphatase levels. However, the differences were only slight in their patient groups, and for the majority of the postgastrectomy patients it was within the normal range. From our own data and from data in the literature it can be concluded that serum calcium and alkaline phosphatase are of little value for screening postgastrectomy patients at high risk of development of bone disorders.

Weight loss is a common finding after gastrectomy (1). The average weight loss was more than 6% in our series of patients. Weight loss after gastrectomy is due to malabsorption and malnutrition

(1), and thus it has the same underlying pathophysiology as vitamin D deficiency with consequent bone disorders. Therefore weight loss is a useful screening factor for the detection of bone disorders following gastrectomy. This is supported by our data, which show a strong correlation between weight loss and the extent of bone mineralization.

SUMMARY

Bone disorders are common long-term complications after gastrectomy. We found that DPA is a good method to evaluate the loss of bone mineralization after gastrectomy as early as three years following operation. Weight loss is an indicator of risk for postgastrectomy patients developing bone disorders, whereas serum calcium levels and alkaline phosphatase are ineffective for this purpose.

We have shown that vitamin 1,25-$(OH)_2$-D is a causal factor in the development of bone disorders after gastrectomy and that gastrectomy without postoperative vitamin D supplements results in 1,25-$(OH)_2$-D deficiency. Therefore vitamin D supplements are required by postgastrectomy patients to prevent bone disorders. The recommended dose should be higher than 600 IU/day since Bisballe's study showed persistence of vitamin D deficiency and bone mineralization at this dose.

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