Bone Metabolism Following Gastric Surgery : Microdensitometry and Single-Photon Absorptiometry

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IMAMURA, M., YAMAUCHI, H., FUKUSHIMA, K., SASAKI, I. and OUCHI, A. *Bone Metabolism Following Gastric Surgery : Microdensitometry and Single-Photon Absorptiometry*. Tohoku J. exp. Med., 1988, **156** (3), 237-249 — The impairment of bone metabolism was investigated in patients who underwent gastrectomy or vagotomy with drainage two or more years ago. Serum biochemical analysis, microdensitometry of the 2nd metacarpal bone, and measurements of bone mineral content of the radius (measured 1/3 distally) using single-photon absorptiometry were performed at follow-up examination. Although serum levels of calcium, phosphorus and alkaline phosphatase were within normal range, alkaline phosphatase levels were slightly higher for the Billroth II group than for Billroth I. Twenty-eight of 50 gastrectomy cases (56%), and four of 10 vagotomy cases (40%) showed pathologically thin bone: microdensitometric (MD) scores were greater than 3. The Billroth II group showed a far higher frequency of greater MD scores than Billroth I. The MD scores showed significant positive relationship with the age at follow-up, but did not correlate well with the length of the postoperative period. Radial bone mineral content (BMC) was lower in patients with Billroth II anastomosis, or with total or proximal gastrectomy, than in those undergoing Billroth I. These results suggest that metabolic bone disorders following gastric surgery can be detected by MD score and BMC of appendicular bones. However, there was not sufficient resolution with these parameters to detect any bone changes in patients treated with active vitamin D₃. ———— gastrectomy; vagotomy; bone metabolism; microdensitometry; 1 α -hydroxyvitamin D₃

Disturbances in both calcium and bone metabolism have long been pointed out as typical sequelae following gastrectomy. In 1941, Sarasin first reported the change in bone after gastrectomy as osteomalacia. Through the 1950's and 1960's, many researchers investigated the metabolic bone diseases following gastrectomy (Nicolaysen and Ragård 1955; Baird and Oleesky 1957; Morgan et al. 1965; Thompson et al. 1966) and in 1969, Morgan and Pulvertaft compared bone

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Received July 1, 1988; revision accepted for publication September 21, 1988.

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metabolism following vagotomy and drainage with that after gastrectomy. Recently, the metabolic bone changes subsequent to gastrectomy have been seen more frequently, because the life span has been lengthening, and because it has become possible to diagnose bone changes more precisely through the development of new methods, such as single- or dual- photon absorptiometry. In this study, the impairment of bone metabolism was investigated by follow-up examination of patients who underwent gastrectomy or vagotomy with drainage. In addition, the effect of 1α -hydroxyvitamin D₃ on bone metabolism was studied by oral administration to patients with thin bones.

SUBJECTS AND METHODS

Of the patients who underwent gastric surgery two or more years ago, at the First Department of Surgery, Tohoku University School of Medicine, sixty patients approved follow-up study, and gave informed consent. Primary diseases and operative methods are summarized in Table 1. Surgery for proximal gastrectomy included anastomosis of the end of the esophagus to the side of the remaining stomach, and pyloroplasty. The pylorus-preserving gastrectomy (Maki et al. 1967) was a distal gastrectomy, with the antrum transected 1.5 cm orally from the pyloric ring, and gastrogastrostomy. Vagotomized patients underwent selective or truncal vagotomy accompanied by pyloroplasty, i.e., the whole stomach was preserved and the food stream was not changed.

Details of subjects for each operative procedure are shown in Table 2. The mean age of the vagotomy group was significantly lower, and the follow-up period in the group with pylorus-preserving gastrectomy significantly longer than in the other groups.

In our series, no patients had a past history of diabetes mellitus, oophorectomy, steroid therapy, hyperparathyroidism, liver cirrhosis, renal dysfunction or massive small bowel resection. Some patients had been taking pancreatic enzyme or lactase supplements.

At follow-up, peripheral blood was taken to measure plasma levels of substances related

TABLE 1. *Primary diseases and operative methods*

	Gastric cancer	Gastric ulcer	Duodenal ulcer	Miscellaneous	Total
	cases				
Subtotal gastrectomy*					
Billroth I	14				14
Billroth II	11	1		1	13
Total gastrectomy					
Interposition	1			1	2
Roux-Y	5				5
Proximal gastrectomy	5				5
Pylorus-preserving gastrectomy		11			11
Vagotomy†			10		10
Total	36	12	10	2	60

*These cases include 2 individuals who underwent distal gastrectomy.

†Truncal or selective vagotomy with pyloroplasty.

TABLE 2. *Details of subjects*

Operative method	<i>n</i>	Age (years) (mean & range)	Sex (M : F)	Years after surgery (mean & range)
Subtotal gastrectomy ¹⁾				
Billroth I	14	61(52~69)	9 : 5	7(2~15)
Billroth II	13	66(44~84)	5 : 8	8(3~26)
Total gastrectomy	7	62(45~78)	3 : 4	7(3~11)
Proximal gastrectomy	5	63(50~70)	3 : 2	6(2~9)
Pylorus-preserving gastrectomy	11	64(50~80)	9 : 2	*17(8~22)
Vagotomy ²⁾	10	*44(28~63)	7 : 3	10(3~17)

¹⁾These cases include 2 individuals who underwent distal gastrectomy.

²⁾Truncal or selective vagotomy with pyloroplasty.

M, male; F, female.

*p < 0.05 compared to the other groups.

to bone metabolism, including calcium, phosphorus and alkaline phosphatase. x-ray studies of both hands were performed, using an aluminium step wedge (Gray scale), and measurements were made at the midportion of the second metacarpal bone by the microdensitometric method of Inoue et al. (1983). The density of the bone was expressed in terms of a microdensitometric (MD) score. The MD score was calculated from the changes in six parameters: ratio of width of cortex, width of bone marrow, density index of cortex, density index of medulla, density index per bone width and densitometric pattern. Changes in these parameters were evaluated as follows: changes of less than 1 standard deviation (s.d.) from the regression line of healthy controls (matched for age and sex) were expressed as a change of one point; less than 2 s.d. as two points; and over 2 s.d. as three points. Zero scores indicate values close to those of controls, as defined for each parameter by Inoue et al. (1983). The total of points for the six parameters gives the MD score. The severity of bone changes was classified according to MD score: 0-3, normal; 4-6, slight change; 7-9, moderate change; and more than 10, severe change.

Bone mineral content was measured by single-photon absorptiometry, using ¹²⁵I (278 Bone Densitometer, Norland Co., Fort Atkinson, WI, USA), at a site one-third of the forearm length from the distal end of the radius of the non-dominant side. Measurements were repeated two or three times and the mean value was taken. Bone mineral content was calculated as bone mineral mass per unit area (gram/cm²) in the radiation beam path (Cameron et al. 1968). The method is quite reproducible, with a coefficient of variation of about 2.5%.

The results were expressed as mean ± s.d. or s.e. For statistical analysis, Student's *t*-test was used, and differences with a *p* value of less than 0.05 were considered significant.

RESULTS

Laboratory data

As shown in Table 3, serum levels of calcium, phosphorus, alkaline phosphatase, urea N, creatinine and total protein were all within their normal range in each operative group. Both glutamic-oxaloacetic transferase and glutamic-pyruvic transferase levels were slightly elevated in some groups but as mentioned previously, no patients suffered from acute hepatitis, or liver cirrhosis. Alkaline

TABLE 3. *Plasma levels of substances relating to bone metabolism*

Operative method	<i>n</i>	Ca	P (mg/ 100 ml)	ALP	GOT	GPT (IU/ liter)	BUN	Crea- tinine (mg/ 100 ml)	TP (g/ 100 ml)
Subtotal gastrectomy									
Billroth I	14	9.2±0.3	3.3±0.6	97±28	25±5	15±5	15±5	0.7±0.2	7.8±0.6
Billroth II	13	9.0±0.3	3.4±0.5	112±21	34±19	27±24	14±3	0.6±0.2	7.5±0.7
Total gastrectomy	7	8.9±0.3	3.7±0.3	102±23	42±24	28±18	12±4	0.5±0.1	7.6±0.4
Proximal gastrectomy	5	9.1±0.4	3.8±0.2	94±22	26±10	23±10	15±3	0.5±0.1	7.7±0.7
Pylorus-preserving gastrectomy	11	9.1±0.3	3.0±0.4	108±30	36±19	31±36	16±4	0.8±0.2	7.6±0.5
Vagotomy	10	9.1±0.6	3.1±0.5	115±62	32±28	35±43	13±4	0.8±0.1	7.3±0.6
Normal range		8.6~10.5	2.6~4.9	30~130	10~34	3~28	7~19	0.3~0.9	6.8~8.2

n, number of cases

Ca, calcium; P, phosphorus; ALP, alkaline phosphatase; GOT, glutamic-oxaloacetic transferase; GPT, glutamic-pyruvic transferase; BUN, blood urea N; TP, total protein.

Each value represents mean±s.d.

phosphatase levels were slightly higher for the Billroth II group than for Billroth I.

MD scores for each operative method

As shown in Table 4., there were 14 cases (23%) of slight change in MD score, 10 (17%) of moderate change, and eight (13%) of severe change. In all, 53% (32 of 60 cases) had scores greater than 3, representing pathologically thin bone.

28 of 50 gastrectomy cases (56%), and four of 10 vagotomy cases (40%) had MD scores greater than 3. Comparing the MD score in each operative group, the

TABLE 4. *Operative methods and microdensitometric scores*

Operative method	<i>n</i>	Normal (0-3)	Slight change (4-6)	Moderate change (7-9)	Severe change (10≤)	Frequency of score ≥4
Subtotal gastrectomy						
Billroth I	14	9	2	3	0	5/14(36%)
Billroth II	13	4	3	2	4	9/13(69)
Total gastrectomy	7	4	1	1	1	3/7(43)
Proximal gastrectomy	5	2	0	1	2	3/5(60)
Pylorus-preserving gastrectomy	11	3	6	1	1	8/11(73)
Vagotomy	10	6	2	2	0	4/10(40)
Total	60	28 (47%)	14 (23)	10 (17)	8 (13)	32/60 (53%)

Billroth II group showed a far higher frequency of scores greater than 3 than the Billroth I group, and also more cases of moderate or severe change. The pylorus-preserving gastrectomy group showed a high frequency of scores greater than 3, although the operative procedure is similar to Billroth I. In the vagotomy group, the changes in MD score were slight or moderate.

As depicted in Fig. 1, the MD scores for the Billroth II group were significantly higher than those for either Billroth I or vagotomy. The MD scores for the proximal gastrectomy group were also significantly higher than those for Billroth I.

MD scores and age at follow-up study

In Fig. 2, the MD scores showed an apparent increase with the age of patients, but there were no statistical difference among the age groups. However, patients who underwent gastrectomy showed a significant positive correlation between age and MD score, as depicted in Fig. 3. The r values were 0.428 ($p < 0.01$) for all cases, 0.427 ($p < 0.05$) for males, and 0.467 ($p < 0.05$) for females.

MD scores and postoperative period

The patients who had undergone gastrectomy were divided into five groups, according to the period elapsed after surgery. As shown in Table 5, there were no statistically significant differences among these groups, but the frequency of MD scores greater than 3 tended to increase with postoperative time. There was no

Fig. 1. Microdensitometric (MD) scores (mean $\pm$ S.E.) of the second metacarpal bone for each operative method. Normal range of MD score (0-3) is shaded. Significant differences ($p < 0.05$): vs. Billroth I group (*); vs. Vagotomy group (†).

Fig. 2. MD scores (mean $\pm$ s.e.) of the second metacarpal bone for different age groups. There were no significant differences between any of the groups.

Fig. 3. The relationship between MD score of the second metacarpal bone and age of patient at examination. Male subjects ($n=29$) are indicated by closed circles, females ($n=21$) by open circles. Normal range of MD score is shaded.

correlation between MD scores and years after gastrectomy (this result not shown).

Bone mineral content for each operative method

Bone mineral content tended to be lower in patients with the Billroth II anastomosis, or with total or proximal gastrectomy, than in those who underwent the Billroth I anastomosis (Table 6). In those cases where the MD score was greater than 3, bone mineral content was lower in the Billroth II group than in Billroth I, although the difference was not statistically significant.

Relationship among MD scores, bone mineral content, and alkaline phosphatase levels

All three parameters were significantly correlated (Figs. 4 to 6).

TABLE 5. *Microdensitometric (MD) score in relation to years after gastrectomy*

Years after gastrectomy	<i>n</i>	MD score (mean $\pm$ S.E.)	Frequency of score ≥ 4
2 $\leq$ < 5	13	4.8 $\pm$ 1.3	6/13 (46%)
5 $\leq$ < 10	19	4.7 $\pm$ 1.0	9/19 (47)
10 $\leq$ < 15	6	5.2 $\pm$ 1.5	4/ 6 (67)
15 $\leq$ < 20	8	5.0 $\pm$ 1.3	5/ 8 (63)
20 $\leq$	4	6.8 $\pm$ 1.6	4/ 4 (100)

TABLE 6. *Operative methods and bone mineral content (BMC)*

Operative method	<i>n</i>	BMC (g/cm ²)	Cases of MD score ≥ 4	
			<i>n</i>	BMC(g/cm ²)
Subtotal gastrectomy				
Billroth I	14	0.60 $\pm$ 0.08	5	0.58 $\pm$ 0.06
Billroth II	11	0.54 $\pm$ 0.12	7	0.47 $\pm$ 0.09
Total gastrectomy	5	0.53 $\pm$ 0.11	2	0.53
Proximal gastrectomy	4	0.53 $\pm$ 0.08	2	0.48

Each value denotes mean $\pm$ S.D.

Changes in MD scores and bone mineral content after administration of 1 α -hydroxyvitamin D₃

1 α -hydroxyvitamin D₃ was administered orally (1.0~1.5 μ g/day) to 14 patients with MD sores greater than 4. As shown in Fig. 7, MD scores tended to decrease in some cases, but they mostly remained unchanged within the observa-

Fig. 4. The relationship between MD score of the second metacarpal bone and serum alkaline phosphatase level.

Fig. 5. The relationship between bone mineral content (BMC) and serum alkaline phosphatase level. BMC was measured using single photon absorptiometry, at a site one-third of the forearm length from the distal end of the radius of the non-dominant side.

Fig. 6. The relationship between MD score of the second metacarpal bone and bone mineral content of the radius (measured one-third of the forearm length from the distal end; non-dominant side).

tion period (≤ 1 year). Radial bone mineral content (Fig. 8) showed a tendency to increase in a few cases, but remained more or less unchanged in the rest.

DISCUSSION

Metabolic bone diseases following gastrectomy have been known for many years in both humans and dogs (Bussabarger et al. 1938; Sarasin 1941), and have been investigated by considering the impairment of the absorption of ingested

Fig. 7. Changes in MD score after oral administration of 1α -hydroxyvitamin D_3 (1.0 – $1.5 \mu\text{g/day}$), in 14 cases with MD scores greater than 4. Shaded area represents normal range.

Fig. 8. Changes in bone mineral content (BMC) after oral administration of 1α -hydroxyvitamin D_3 (1.0 – $1.5 \mu\text{g/kg}$), in 10 cases showing MD scores greater than 4.

calcium or vitamin D in the upper small intestine (Nicolaysen and Ragård 1955; Imawari et al. 1980). In agreement with the findings of Klein et al. (1987), most cases with high MD scores in the present study were asymptomatic: they maintained body weight, and were relatively well-nourished. Accordingly, it seems that the reported frequency of bone disorders after gastrectomy is influenced by the method of follow-up study, or by the technique used for diagnosis.

Persuasive explanations for the relationship between gastric surgery and metabolic bone diseases have yet to be given. Many causal factors have been

proposed, such as age, sex, period since surgery, operative method, maldigestion of fat, malabsorption of calcium and vitamin D, duodenal bypass, rapid intestinal transit, and milk intolerance (Baird and Oleesky 1957; Thompson et al. 1966; Gregory and Van Uelft 1972; Kocián et al. 1973; Smith et al. 1976; Gertner et al. 1977; Fukuda et al. 1979; Kaplan 1983; Klein et al. 1987; Nishimura et al. 1988). In our series, the MD scores increased gradually as subjects became older, and there was a close correlation between the MD scores and the age of patients at follow-up study. Regarding the time elapsed after surgery, the frequency of cases showing high MD scores increased with postoperative period, although mean MD scores remained around the same values. It would seem, then, that metabolic bone disorders are more closely related to the age at follow-up study than to the period after surgery. Therefore, other considerations are necessary when assessing the factors affecting postgastrectomy osteopenia: for example, postmenopausal osteodystrophy in elderly female subjects (Davis 1987).

Metabolic bone diseases develop differently according to the operative method. Like other reports (Eddy 1971; Fukuda et al. 1979; Pääkkönen et al. 1984; Nishimura et al. 1988), in the present study the incidence of bone disorders was higher in cases undergoing Billroth II reconstruction than in those undergoing Billroth I. Suggested reasons for this difference include duodenal bypass of food and shortened intestinal transit time (Pääkkönen et al. 1984; Klein et al. 1987). It is probable that these changes result in the malabsorption of fat-soluble vitamins, such as vitamin D, as well as calcium, in the upper small intestine. In the group which underwent the pylorus-preserving gastrectomy (a procedure which was devised in our department to improve postgastrectomy disorders such as rapid gastric emptying), many cases showed a slight change in the MD score. The high frequency of scores greater than 3 is thought to be related to the longer period since surgery in this group compared with other groups. 40% of vagotomized patients showed slight elevation of MD scores. This result is very interesting because gastric resection was not included, the subjects were significantly younger, and the ratio of male to female was higher compared with other gastrectomy groups. Moreover, the mean follow-up period of the vagotomy group was longer than that of the cases of Morgan and Pulvertaft (1969), who suggested that the incidence of thin bones in vagotomized cases might be the same as in patients without surgery. It is suggested here, then, that vagotomy itself can be a cause of osteopenia. The impairment may be related to the relatively high incidence of diarrhea after vagotomy (O'Leary et al. 1976), resulting in malabsorption of calcium, vitamin D and other nutrients.

It has also been reported that the development of bone disorders is more common and severe, and occurs earlier, after total gastrectomy than after distal gastrectomy (Nishimura et al. 1988). In our series, though the number of subjects was small, there were no significant differences in either the MD score or bone mineral content between the subtotal or distal gastrectomy groups and the total

gastrectomy group.

It is known that gastrectomized patients often suffer from lactose intolerance, resulting in the reduced intake of milk or milk products, which contain a large quantity of calcium (Birge et al. 1967). In this study, eight of 14 patients who were given 1α -hydroxyvitamin D_3 supplement, complained of diarrhea and/or abdominal discomfort after drinking milk. Lactase preparation (Tilactase®) was given *t.i.d.* for these cases, and effectively improved milk intolerance in six of the eight cases (75%). Both before and after administration of lactase preparation, however, no marked changes in serum calcium levels and in MD scores were observed. Therefore, it is supposed that either much longer observation is necessary, or the involvement of other parameters must be considered, in order to detect the effect of the improvement of milk intolerance on bone metabolism.

Many investigators have reported that the metabolic bone disorders after gastrectomy have the histological characteristics of osteomalacia (Baird and Oleesky 1957; Morgan et al. 1965; Gertner et al. 1977), but others have indicated osteoporosis, or a combination of osteomalacia and osteoporosis (Bussabarger et al. 1938; Deller et al. 1963). These skeletal disorders are histologically quite different, so it would seem that a bone biopsy is necessary to diagnose correctly the pathological bone change. As mentioned previously, the frequency of the osteopenic state partly depends upon the parameters used for diagnosis. In the present study, blood biochemical analysis, and measurements of MD scores and of bone mineral content were performed. There were close relationships among MD scores, bone mineral content, and serum alkaline phosphatase levels. Therefore, it is considered that measurements of these three parameters are very useful in defining the osteopenic state after gastric surgery. On the other hand, serum levels of both calcium and phosphorus were within their normal range in each operative group, and remained almost unchanged during the period of 1α -hydroxyvitamin D_3 administration. Although serum concentrations of active forms of vitamin D_3 (such as 25-hydroxy-, $1\alpha \cdot 25$ -dihydroxy-, or $24 \cdot 25$ -dihydroxy vitamin D_3) were not measured, the functioning of the liver and kidneys, which play important roles in the activation of vitamin D_3 (Ponchon et al. 1969; Fraser and Kodicek 1970), were not impaired in our cases. Consequently, it would seem to be inappropriate to try to diagnose the osteopenic state from changes in serum levels of calcium, phosphorus or active vitamin D_3 .

For the treatment of postgastrectomy osteopenia, patients with high MD scores were given 1α -hydroxyvitamin D_3 . They were observed by measuring MD scores at the midportion of the second metacarpal bone, and bone mineral content at a site one-third of the forearm length from the distal end of the radius; and by checking blood biochemistry data. Within one year of observation, there were no remarkable changes in MD scores or bone mineral content. MD scores were determined from x-ray films of appendicular cortical bone, rather than axial trabecular bone which is metabolically more active, and much affected by sub-

stances in the blood. Although not indicated in the results, in this study bone mineral content was measured at two different sites on the radius, 1/3 and 1/6 distally, by single photon absorptiometry. The results were similar for both sites, so it would seem preferable to take measurements even more distally, or in an axial trabecular bone, in order to detect the changes in bone mineral content after administration of 1α -hydroxyvitamin D_3 . Dual photon absorptiometry, which can precisely detect changes in bone mineral content (Mazess 1986; Davis 1987), has recently become available in some institutes. It is hoped that this useful new technique will become a commonly used method in the near future.

As mentioned above, many patients suffered from lactose intolerance after gastrectomy, but were able to take milk after lactase supplement. Presumably, lactase supplement following gastrectomy will be very effective in preventing postoperative osteodystrophy by enabling patients to take milk, and therefore calcium, without discomfort. The problem of lactose intolerance is more acute in Japan, because the habit of drinking milk is less common than in Europe or America, and because intestinal lactase activity is much lower.

In conclusion, it is considered that metabolic bone disorders following gastric surgery have a close relationship with operative procedure, age at examination, and postoperative period. There were significant correlations among MD scores, bone mineral content and serum alkaline phosphatase levels, which seem to be valuable parameters reflecting well the bone changes after gastric surgery. During the relatively short observation period, the oral administration of 1α -hydroxyvitamin D_3 to patients with thin bones produced no obvious changes in peripheral cortical bones.

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