Self-Defensive Response to Bone Disorder after Gastric Cancer Surgery

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Abstract

Background/Aims: Changes in estradiol that inhibits bone resorption were examined to investigate the *in vivo* defensive response to progression of bone disorder after gastric cancer surgery.

Materials and Methods: Women who might show effects of menstruation were excluded because estradiol was examined. The subjects were 17 men with a mean age of 60.4 years who had undergone gastrectomy because of gastric cancer and were followed as outpatients. Microdensitometry was used to evaluate bone disorder. The duration after surgery until bone assessment was a mean of 3.5 years. The surgical procedure was total gastrectomy with Roux-Y reconstruction in 4 patients and subtotal gastrectomy with Billroth-I reconstruction in 9 patients and with Billroth-II reconstruction in 4 patients.

Results: Bone disorder requiring treatment was observed in 6 out of the 17 patients (35.3%). Estradiol showed higher than normal values in 10 patients (58.8%). The incidence of bone disorder was high in patients with high estradiol levels, but the difference was not significant. Blood levels of estradiol in patients with bone disorder requiring treatment were high but again the difference was not significant ($P = 0.119$).

Conclusions: Although the difference was not statistically significant, the increase in estradiol observed in patients with progressive bone disorder suggested to be caused by *in vivo* inhibition of enhanced bone metabolism after gastric cancer surgery.

Keywords: self-defensive response, estradiol, bone disorder, gastric cancer surgery

Abbreviations: ECLIA; electrochemiluminescent immunoassay, MD; Microdensitometry

INTRODUCTION

Several reports have appeared since bone metabolic disorders after gastric surgery were first reported by Sarasin[1,3,6,7,9,11,13,14,16,17,18,19]. The causes given for bone metabolic disorders after gastric cancer surgery included defective absorption of calcium and vitamin D because of gastrectomy[6,7] and reduced food consumption[14]. However, doubts remain whether the body should initiate a defensive reaction to the progression of bone disorder caused by such metabolic changes or not. Therefore, we investigated changes in estradiol that suppresses bone resorption by inhibition of osteoclasts[4,5,12].

MATERIALS and METHODS

Women who might show effects of menstruation were excluded because estradiol was examined. The subjects were 17 men with a mean age of 60.4 ± 12.3 years (age range: 35 to 80 years) who had undergone gastrectomy for gastric cancer and were followed as outpatients without recurrence. The patient characteristics were as follows. The duration after surgery until bone assessment was a mean of 3.5 ± 3.8 years (0.2 to 13.8 years). The period was less than 2 years in 9 patients (57.7 ± 13.4 years of age) and 2 years or longer in 8 patients (63.5 ± 11.0 years of age). The surgical procedure was total gastrectomy with Roux-Y reconstruction in 4 patients, Billroth-I reconstruction in 9 patients and Billroth-II reconstruction in 4 patients (Table 1).

Informed consent was obtained from all patients beforehand for participation in bone tests and blood sampling. Estradiol was measured by the electrochemiluminescent immunoassay (ECLIA) (normal range: 13-42 pg/mL). Microdensitometry (MD) was applied for assessment of bone disorder. Radiographs were simultaneously taken of the second metacarpal bone and an aluminum step wedge, and the images were analyzed by computer for evaluation

of six microdensitometric parameters. Then the severity of bone disorder was expressed in terms of the scores for each of the 6 parameters, and the total score was used for overall evaluation of bone disorder (normal, initial, Grade I, II, III). The results obtained by this method are reported to show a good correlation with the results of the vertebral evaluation method developed in the Jikei University School of Medicine. Bone disorder of Grade I or worse is considered to require treatment[8].

Statistical analysis was conducted using Student's *t*-test with $P < 0.05$ taken as significant.

RESULTS

1) Bone atrophy

Bone disorder requiring treatment was observed in 6 out of the 17 patients (35.3%). Bone atrophy was evaluated as normal in 10 patients (58.8%), initial stage in 1 patient (5.9%), Grade I in 3 (17.6%) and Grade III in 3 patients (17.6%).

2) Estradiol and bone disorder

Estradiol showed higher than normal values in 10 patients (58.8%). When bone disorder was investigated by dividing the patients in a high estradiol group and a normal estradiol group, bone disorder in the high estradiol group was Grade III in 2 patients, grade I in 3 patients and normal in 5 patients. In the normal group, bone disorder was Grade III in 1 patient, initial stage in 1 patient and normal in 5 patients. The percentage of patients with Grade I or higher bone disorder requiring treatment was 5 out of 10 patients (50%) in the high estradiol group and 1 out of 7 patients (14.3%) in the normal group. The incidence of bone disorder was higher in the high estradiol group, but the difference was not significant (Table 2).

In patients with Grade I or Grade III bone disorder requiring treatment and patients with initial stage or normal bone disorder not requiring treatment, the blood levels of estradiol were 58.2 pg/mL and 44.3 pg/mL respectively. The value in patients requiring treatment was higher but the difference was not significant ($P = 0.119$) (Fig. 1).

In this study, a multivariate analysis was not performed because significant differences were not observed for any factors.

DISCUSSION

Various sequelae following gastric cancer surgery including the dumping syndrome have been reported. Recently reports on bone metabolic changes and a higher risk for bone fractures in patients after gastric cancer surgery have appeared[3,9,13,19]. We reported reduced food consumption[14] as a cause of bone disorder after gastric cancer surgery and the usefulness of vitamin D preparations in the treatment of bone disorder[15]. Doubts remain however because the body should initiate some kind of reaction to the prevent progression of bone disorder after gastric cancer surgery. Therefore, we investigated changes in estradiol that inhibits bone resorption to determine if an *in vivo* response to resist bone disorder occurs.

Estradiol is known to suppress the activity of osteoclasts by inhibition of IL-6 and to prevent osteoporosis by direct action on osteoblasts[5]. It has also been reported that estradiol inhibits bone metabolic turnover[4]. In women, a sharp reduction in bone mass is found around the time of menopause, which causes osteoporosis. Animal studies in male aromatase knockout mice have revealed reduced bone mass, which was normalized by estrogen replacement[10]. Reduced bone mass has also been reported several times in men with an aromatase gene mutation, suggesting the importance of estrogen in bone metabolism in men[2,12].

In the present study, only men were used as subjects to avoid the effect of menopause. Increases of estradiol above the normal range were found in about 60% of the male patients. This was a very interesting change considered to be a feedback reaction to inhibit bone loss or inhibition of the bone metabolic turnover rate.

CONCLUSIONS

Although it was not statistically significant, the elevation of estradiol observed in patients with progressive bone disorder suggested that *in vivo* inhibition of enhanced bone metabolism occurs after gastric cancer surgery.

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REFERENCES

- [1] E.M. Alhava, S. Aukee, P. Karjalainen, et al, The influence of calcium and calcium + vitamin D2 treatment on bone mineral after partial gastrectomy, Scand J Gastroenterol, 10(1975),689-693.
- [2] J.P. Bilezikian, A. Morishima, J. Bell, et al, Increased bone mass as a result of estrogen therapy in a man with aromatase deficiency, N Engl J Med, 339(1998), 599-603.
- [3] S. Bisballe, E.F. Eriksen, F. Melsen, et al, Osteopenia and osteomalacia after gastrectomy: interrelations between biochemical markers of bone remodeling, vitamin D metabolites, and bone histomorphometry, Gut, 32(1991),1303-1307.

[4] S. Eviö, A. Tiitinen, K. Laitinen, et al, Effect of Alendronate and Hormone Replacement Therapy, Alone and in Combination, on Bone Mass and Markers of Bone Turnover in Elderly Women with Osteoporosis, *J Clin Endocrinol Metab*, 89(2004),626-631.

[5] W.F. Ganong. Hormone control of calcium metabolism & the physiology of bone. In: Wiliam FG, ed. *Review of medical physiology*. 18th ed. Norwalk, Appleton & Lange, 1997.

[6] B. Harvald, A.R. Krogsgaard, P. Lous, Calcium deficiency following partial gastrectomy, *Acta Med Scand*, 172(1962),497-503.

[7] M. Imawari, K. Kozawa, Y. Akanuma, et al, Serum 25-hydroxyvitamin D and vitamin D-binding protein levels and mineral metabolism after partial and total gastrectomy, *Gastroenterology*, 79(1980),255-258.

[8] T. Inoue, K. Kusida, S. Miyamoto, et al, Quantitative assessment of bone density on X-ray picture, *J Jpn Orthop Ass*, 57(1983), 1923-1936.

[9] D. Mellström, C. Johansson, O. Johnell, et al, Osteoporosis, metabolic aberrations, and increased risk for vertebral fractures after partial gastrectomy, *Calcif Tissue Int*, 53(1993),370-377.

[10] C. Miyaura, K. Toda, M. Inada, et al, Sex- and age-related response to aromatase deficiency in bone, *Biochem Biophys Res Commun*, 280(2001), 1062-1068.

[11] D.B. Morgan, G. Hunt, C.R. Paterson, The osteomalacia syndrome after stomach operations, *Quart J Med*, 39(1970),395-410.

- [12] A. Morishima, M.M. Grumbach, E.R. Simpson, et al, Aromatase deficiency in male and female siblings caused by a novel mutation and the physiological role of estrogens, *J Clin Endocrinol Metab*, 80(1995), 3689-3698.
- [13] L. Nilas, C. Christiansen, J. Christiansen, Regulation of vitamin D and calcium metabolism after gastrectomy, *Gut*, 26(1985),252-257.
- [14] Y. Rino, Clinical study of the relationship between a metabolic bone disorder and an amount of daily food intake, *Yokohama med J*, 47(1996), 25-29.
- [15] Y. Rino, T. Imada, Y. Yamamoto, et al, The efficacy of 1 α hydroxy vitamin D3 treatment of the metabolic bone disorder in patients who underwent gastrectomy for gastric cancer, *Hepatogastroenterology*, 47(2000),1498-1500.
- [16] C. Sarasin, Osteomalacia und hypochrome Anaemie nach Magenresektion, *Gastroenterologia*, 66(1941),182-197.
- [17] F.I. Tovey, M.L. Hall, P.J. Ell, et al, A review of postgastrectomy bone disease, *J Gastroenterol Hepatol*, 7(1992),639-645.
- [18] F.I. Tovey, M.L. Hall, P.J. Ell, et al, Postgastrectomy osteoporosis, *Br J Surg*, 78(1991),1335-1337.
- [19] T.T. Zittel, B. Zeeb, G.W. Maier, et al, High prevalence of bone disorders after gastrectomy, *Am J Surg*, 174(1997),431-438.

FIGURE LEGENDS

Fig. 1 Bone disorder and blood levels of estradiol

Blood levels of estradiol were 44.3 ± 14.7 pg/mL in the group not requiring treatment of bone disorder (normal, initial stage) ($n = 11$) and 58.2 ± 19.8 pg/mL in the group requiring treatment (Grade I, II or III) ($n = 6$). The values were higher in the group requiring treatment but the difference was not significant ($p=0.119$).

Table 1.

Characteristics	number	Mean±SD (range)
Sex male/female	17 / 0	
Age (years old)		
Mean±SD (range)		60.4±12.3 (35-80)
Duration after op (years)		
Mean±SD (range)		3.5±3.8 (0.2-13.8)
Surgical procedure	4 / 9 / 4	

TG RY/SG B1/SG B2

SD; standard deviation, op; operation, TG; total gastrectomy,
 RY; Roux-Y reconstruction, SG; subtotal gastrectomy,
 B1; Billroth-I reconstruction, B2; Billroth-II reconstruction

Table 2.

Bone atrophy					
Estradiol	Normal	Syoki	degree1	degree2	degree 3
Normal group (n=7)	5	1	0	0	1
High group (n=10)	5	0	3	0	2

SD; standard deviation, op; operation, TG; total gastrectomy,
 RY; Roux-Y reconstruction, SG; subtotal gastrectomy,
 B1; Billroth-I reconstruction, B2; Billroth-II reconstruction