A Gender Comparison of Bone Metabolic Changes After Gastric Cancer Surgery: A Prospective Observational Study

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Abstract. *Background/Aim:* This study was designed to investigate gender-related differences in changes in bone metabolism after gastric cancer surgery. *Patients and Methods:* We prospectively recruited 47 patients (38 males and 9 females) who had early gastric cancer. The bone mineral density (BMD), serum levels of 1,25-dihydroxy vitamin D (1,25(OH)₂VD), 25-hydroxy vitamin D (25(OH)VD), and estradiol (E2) were measured before and after surgery. *Results:* BMD significantly decreased 12 months after surgery by median degrees of 3.4% and 3.9% in male and female patients, respectively ($p < 0.001$ and $p = 0.023$). There was no significant difference between both genders in the rate of change in BMD after surgery. The serum E2 level in male patients significantly increased by a median value of 22 pg/ml 12 months after gastrectomy ($p = 0.030$). Both the serum 25(OH)VD and 1,25(OH)₂VD levels remained nearly within the normal range throughout the observation period in both male and female patients. *Conclusion:* BMD significantly decreased within 12 months after gastrectomy in both male and female patients with gastric cancer, and there was no significant gender-related difference in the rate of change in BMD.

Recently, the survival rate of gastric cancer patients has improved because of early diagnosis, curative surgery, and adjuvant chemotherapy (1, 2). Accordingly, bone disorders that occur after gastrectomy for gastric cancer have drawn attention as sequelae, along with dumping syndrome and

anemia. Calcium and vitamin D deficiency caused by reduced food intake, reductions in gastric acid secretion, and inadequate mixing of biliary and pancreatic secretions due to rapid transit through the small intestine are considered to be causes of hyperparathyroidism followed by bone mineral loss and bone disorders (3-5). In particular, bone fractures impair patient's activities of daily living and quality of life. Furthermore, previous meta-analyses have reported a significant association between lower bone mineral density (BMD) and all-cause cardiovascular mortality (6, 7). A large retrospective study reported that fractures occurred on average 3.7 years postoperatively and the cumulative incidence of fractures increased up to a final of 40.6% (8).

However, the mechanisms of bone disorders after gastrectomy are not fully clear, and most previous studies investigating bone disorders after gastrectomy were retrospective or cross-sectional studies without BMD data before surgery (9-15). Hence, when BMD starts to decrease and the extent of the decline remain unclear. In addition, despite the fact that males and females have different bone metabolism due to differences in endocrinological factors, no study has estimated gender-related differences in the changes of BMD after gastric cancer surgery.

We previously recruited patients with early gastric cancer and reported prospective data on changes in male BMD before and after gastric cancer surgery (16). Female patients were also recruited at the same time. The purpose of the present study was to prospectively investigate gender-related differences changes in bone metabolism before and after gastrectomy in patients with gastric cancer.

Patients and Methods

Patients with advanced gastric cancer usually receive anticancer agents as adjuvant therapy after curative surgery (2, 17, 18), and some studies demonstrated that anticancer agents could reduce BMD (19, 20). Therefore, we recruited only patients with early gastric cancer. A total of 52 consecutive patients underwent gastrectomy for early gastric cancer from April 2009 through March 2015 in our

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Key Words: Gastric cancer, bone, gastrectomy.

Table I. Clinicopathological features of 47 patients.

Factor	Males	Females	p-Value
n	38	9	
Age (years)	68 (35~84)	63 (60~78)	0.43
BMI (kg/m ²)	23.4 (17.3~29.0)	21.4 (18.6~27.1)	0.69
ECOG PS			
0/1/2/3/4	38/0/0/0/0	9/0/0/0/0	
Type of surgery			
DG/TG/PG/	23/11/3/1	7/2/0/0	0.88
Partial resection			
Reconstruction			
BI/RY/EG/None	22/12/3/1	7/2/0/0	0.87
Depth of invasion			
pT1a/pT1b	16/22	4/5	1
Nodal involvement			
pN0/pN1	36/2	7/2	0.16
Tumor recurrence			
Yes/no	0/38	0/9	

Continuous variables are shown as the median (range). BMI: Body mass index; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; DG: distal gastrectomy; TG: total gastrectomy; PG: proximal gastrectomy; BI: Billroth-I reconstruction; RY: Roux-en-Y reconstruction; EG: esophagogastrectomy.

institution. We excluded patients with renal failure, liver failure, as well as patients receiving drug treatment with bisphosphonates or any other bone-active drugs, including vitamin D, before surgery or during the follow-up period. After excluding patients who met the exclusion criteria, 48 patients were enrolled. Only one patient was not followed up for 2 years because he had metachronous esophageal cancer immediately after gastric cancer surgery and was thus excluded. Therefore, a total of 47 patients were finally evaluated.

This study was approved by the Institutional Review Board of Yokohama City University (Yokohama, Japan) and conducted according to the principles of the Declaration of Helsinki. Informed consent was obtained from all patients.

Bone densitometry. The BMD and T-score of the lumbar vertebrae (L2-L4) were measured by dual energy X-ray absorptiometry (DEXA) using a Hologic Discovery QDR system (Hologic Inc., Bedford, MA, USA). The T-score is the standard deviation from the mean BMD of young normal adults. A T-score between -1 and -2.5 indicates low bone mineral density (osteopenia), and a T-score below -2.5 is considered osteoporosis, as defined by the World Health Organization (WHO) (21). The National Osteoporosis Foundation (NOF) recommends that postmenopausal females and males aged 50 years or older who have low bone mineral density and certain risk factors and all patients with osteoporosis should consider receiving an osteoporosis treatment (22). The BMD and T-score were measured before and 1 and 2 years after surgery. The serum levels of 1,25-dihydroxy vitamin D [1,25(OH)₂VD], 25-hydroxy vitamin D [25(OH)VD], and estradiol (E2) were measured before surgery and every 3 months until 2 years after surgery. We also evaluated the clinicopathological and perioperative data of all patients.

We used the Wilcoxon signed-rank test to compare preoperative and postoperative continuous variables and the Mann-Whitney-U test to compare continuous variables between female and male patients.

Table II. Bone mineral density and bone metabolism-related markers of 47 patients.

Factor	Median (range) [Normal range]		p-Value
	Males	Females	
Preoperative lumbar spine BMD (g/cm ²)	0.93 (0.75~1.67)	0.91 (0.64~1.12)	0.19
Preoperative lumbar spine T score	-1.0 (-2.5~5.3)	-0.7 (-3.1~0.9)	0.52
Preoperative serum 1,25(OH) ₂ VD (pg/ml)	58.8 (31.9~93.1)	58.4 (24.4~83.3)	0.57
Preoperative serum 25(OH)VD (ng/ml)	[20.0~60.0]	[20.0~60.0]	0.071
Preoperative serum E2 (pg/ml)	29 (17~53)	24 (13~30)	
Preoperative serum E2 (pg/ml)	[10.0~55.0]	[10.0~55.0]	
Preoperative serum E2 (pg/ml)	20.5 (10~43)	10 (10~10)	<0.001
Preoperative serum E2 (pg/ml)	[20.0~60.0]	[less than 10]	
Calorie intake at discharge (kcal)	1150 (450~1900)	1000 (750~1250)	0.22

BMD: Bone mineral density; 1,25(OH)₂VD: 1,25 dihydroxyvitamin D; 25(OH)VD: 25 hydroxyvitamin D; E2: estradiol.

$p < 0.05$ was considered to indicate statistical significance. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphic user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics (23).

Results

Patient characteristics. Tables I and II give the patient characteristics according to each sex. We evaluated 38 male and 9 female patients. The median ages of the male and female patients were 68 years (range=35-84 years) and 63 years (range=60-78 years), respectively. The median body mass index (BMI) of male and female patients was 23.4 kg/m² (range=17.3-29.0 kg/m²) and 21.4 kg/m² (range=18.6-27.1 kg/m²), respectively. All patients had a good Eastern Cooperative Oncology Group Performance Status (ECOG-PS), and tumor was confined to the mucosa or submucosa. Distal gastrectomy (DG), total gastrectomy (TG), proximal gastrectomy (PG), and partial gastric resection were performed in 30 patients, 13 patients, 3 patients, and 1 patient, respectively. Billroth-I (BI), Roux-en-Y (RY), and esophagogastrectomy (EG) reconstruction were performed in 29 patients, 14 patients, and 3 patients, respectively. Only one patient underwent DG with RY reconstruction. There was no significant difference in the performed surgical procedures between the genders. All of the females were menopausal, and their serum E2 level was lower than 10.0 pg/ml. The preoperative serum E2 level was significantly

Figure 1. The percent changes from the baseline body weights in males (A) and females (B) are shown as boxplot. ○: outlier; X: mean value. The line graph shows the change in the mean value.

higher in males than in females [20.5 pg/ml (range=less than 10–43 pg/ml) vs. less than 10 pg/ml (all less than 10 pg/ml), $p < 0.001$]. No recurrence was found during follow-up.

Changes in body weight. The body weights of male and female patients significantly decreased by 11.3% (range of change=–24.64 to –2.86%, $p < 0.001$) and 7.6% (range of change=–15.87 to –0.49, $p = 0.009$), respectively, 3 months after surgery (Figure 1). There was no significant difference in the rate of change in body weight between male and female patients 3 months after surgery.

Changes in bone mineral density, vitamin D, and estradiol. DEXA showed that BMD 12 months after surgery decreased significantly by a median of 3.4% and 3.9% (range of change=–8.1% to 2.5%, $p = 0.023$), in both male and female patients (range of change=–14.3% to 2.4%, $p < 0.001$) respectively. There was no significant difference between male and female patients in the rate of change in BMD 12 months after surgery. Although BMD further decreased during the second postoperative year in both genders [males: median change –1.6% (range of change=–7.0% to 7.9%), females: median value of –0.8% (range of change=–4.7 to 3.9%)], the rates of change in BMD were less than in the first year (Figure 2). The number of patients with a T score of ≤ -1 (“low bone mass” or osteoporosis) at 12 months was

27 of 47 (57.5%). The serum 25(OH)VD level decreased 24 months after surgery by a median of 5 ng/ml (range of change=–25 to 5 ng/ml) in male patients and by a median of 5 ng/ml (range of change=–9 to 7 ng/ml) in female patients ($p < 0.001$ and $p = 0.11$, respectively). There was no significant difference between male and female patients in the rate of change in the serum 25(OH)VD level 24 months after surgery (Figure 3). Meanwhile, the serum 1,25(OH)₂VD levels after gastrectomy increased by a median of 13.4 pg/ml (range of change=–2.0 to 24.3 pg/ml) 24 months after surgery in female patients, and by a median of 2.4 pg/ml (range of change=–34.6 to 37.3 pg/ml) 24 months after surgery in male patients ($p = 0.016$ and $p = 0.94$, respectively). There was a significant difference between female and male patients in the rate of change in serum 1,25(OH)₂VD levels 24 months after surgery (+13.35 pg/ml vs. +2.4 pg/ml, $p = 0.028$). However, both the serum 25(OH)VD and 1,25(OH)₂VD levels remained within the nearly normal range throughout the observation period in both male and female patients (Figure 4). The serum E2 level in male patients significantly increased by a median value of 22 pg/ml (range of change=–14 to 22 pg/ml) 12 months after gastrectomy ($p = 0.030$). Although not significantly, the serum E2 level in some female patients also increased after gastrectomy despite the fact that all of the female patients were menopausal (Figure 5).

Figure 2. The percent changes from the baseline body mineral density in males (A) and females (B) are shown as boxplot. ○: outlier; X: mean value. The line graph shows the change in the mean value.

Figure 3. Serum 25-hydroxy vitamin D (25(OH)VD) levels in males (A) and females (B) before and after surgery are shown as boxplot. Shaded areas show the normal range of the serum 25(OH)VD level. ○: outlier; X: mean value. The line graph shows the change in the mean value.

Discussion

In this study, we prospectively assessed the changes and gender-related differences in bone metabolism after gastric cancer surgery. Indeed, we demonstrated that BMD

considerably decreased during the first postoperative year in both male and female patients with gastric cancer, and further decreased during the second postoperative year. There was no significant difference in the rate of change in BMD between male and female patients. Furthermore, both

Figure 4. Serum 1,25-dihydroxy vitamin D (1,25(OH)₂VD) levels in males (A) and females (B) before and after surgery. Shaded areas show the normal range of the serum 1,25-dihydroxy vitamin D (1,25(OH)₂VD) level. ○: outlier; X: mean value. The line graph shows the change in the mean value.

the serum 25(OH)VD and 1,25(OH)₂VD levels remained within the nearly normal range for 2 years after surgery in both male and female patients in this study.

Previous cross-sectional studies showed that the BMD of the lumbar spine in normal adult males decreased gradually by about 5% in 10 years (24, 25). A previous large, longitudinal, multiethnic cohort study reported that the rate of spinal bone loss was about 2% per year in postmenopausal females (26), and a Japanese prospective study reported that the rate of spinal bone loss was 0.85% per year in Japanese postmenopausal females (27). As compared with these reports, bone loss in patients after gastrectomy in our study (3.4% in males and 3.9% in females) was considerably higher, and gastrectomy appeared to be a stronger risk factor than menopause, especially in Japanese postmenopausal females. The only previous prospective study that included patients who had received adjuvant chemotherapy and had a follow-up period of only 12 months, showed a similar rate of BMD decrease (−5.7%/year) to that in our study (20). Thus, it was suggested that it is necessary to start BMD follow-up immediately after gastric cancer surgery in order to detect bone loss.

We demonstrated that the body weights of both male and female patients significantly decreased 3 months after

surgery and remained nearly flat after that. It is interesting that this study also showed that BMD decreased during the first postoperative year and the rates of change in BMD during the second postoperative year were less than those during the first year, which were similar to the changes in the patients' body weights. We previously showed that reduced oral intake after gastrectomy gradually recovered and became stable from 6 months after surgery onward with a range from 82% to 91% of healthy individuals' food consumption (28). Other previous studies also showed that food intake decreased during the first postoperative year and improved subsequently (29, 30). This study and previous studies have suggested that reduced food consumption during the early postgastrectomy period might affect the BMD, and especially in females, the effect of the rapid decrease in food intake on BMD decline is greater than the effect of menopause.

Vitamin D, which is absorbed and produced in the small intestine and in the skin, is hydroxylated in the liver and kidney. The serum 25(OH)VD level reflects the body's store of vitamin D, and 1,25(OH)₂VD is the biologically active form of vitamin D, which has important functions in calcium and bone metabolism. This study prospectively showed that the serum levels of both 25(OH)VD and 1, 25(OH)₂VD

Figure 5. Serum estradiol (E2) levels in males (A) and females (B) before and after surgery. ○: outlier; X: mean value. The line graph shows the change in the mean value.

remained within the nearly normal range in both genders throughout the observation period. Pharmacologic treatment for bone disorders occurring after gastric cancer surgery has not been established. The results of this study suggest that only vitamin D supplementation might be insufficient and other drugs such as anti-bone resorbing agents might be needed to improve bone loss after gastric cancer surgery. Our previous study showed that alendronate administration significantly increased BMD in patients after gastrectomy whereas administration of only active vitamin D3 agent did not (31). A prospective study in patients with vitamin D-resistant osteopenia after gastrectomy showed that alendronate administration improved clinical symptoms and BMD of the lumbar spine (32). The results of the present study support these previous studies.

E2 is an estrogen steroid hormone and the major female sex hormone. E2 prevents bone loss by inhibiting osteoclast bone resorption and promoting osteoblast osteogenesis (33). Previous studies reported that estrogen was essential for the maintenance of bone mass not only in females but also in males (33-38). In previous studies, we showed that the serum E2 level increased after gastrectomy, especially in patients who had progressive bone disorders (15, 39). In the present study, male patients after gastrectomy showed a significantly elevated serum E2 level and some menopausal female patients also showed a slightly, but not significantly elevated serum E2 level. Our findings suggested that

elevation of the serum E2 level might be a feedback reaction to inhibit bone loss.

Our study had several limitations. First, the sample size in this study was so small that we could not perform multivariate risk factor analysis to evaluate bone loss. A second limitation was that bone metabolic markers such as bone specific alkaline phosphatase (BAP), tartrate-resistant acid phosphatase (TRACP), type 1 collagen cross-linked N-telopeptide (NTX), type 1 collagen C-terminal telopeptide (CTX), parathormone (PTH), and calcium were not measured. If they could be evaluated, pathological mechanisms and risk factors for bone loss after gastric cancer surgery might become clear. Third, our study was short-term and had a small number of subjects. Given these limitations, we suggest that it is important to investigate changes in BMD and bone metabolic markers after gastric cancer surgery and thereby, identify risk factors for bone loss in a large, long-term prospective study to establish a strategy for the prevention and treatment of bone metabolic disorders occurring after gastric cancer surgery.

Conclusion

This study showed that the BMD decreased significantly within 12 months after gastrectomy in both male and female patients with gastric cancer. There was no significant gender-related difference in the rate of change in BMD.

Conflicts of Interest

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Authors' Contributions

YA, YR, TA, KK, MN, HT, TO and NY conceived and coordinated the study, collected patient data, and participated in the statistical analysis; YA, YR, TA, NO, SK, and MM participated in preparing and drafting the manuscript; all Authors read and approved the final manuscript. YA and YR contributed equally to this article.

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