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Differential Impact of Subcutaneous and Visceral Fat on Bone Changes after Gastrectomy

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Background: Osteoporosis and fragility fractures are crucial musculoskeletal complications in long-term survivors of gastric cancer. However, the relationship between changes in body composition after gastrectomy and bone loss has not been investigated. Therefore, this study aimed to explore whether computed tomography (CT)-derived body composition parameters are associated with bone loss after gastrectomy in patients with gastric cancer.

Methods: We retrospectively reviewed medical records and abdomen CT scans of patients who underwent gastrectomy at Yonsei University Severance Hospital between 2009 and 2018. Patients with non-metastatic gastric adenocarcinoma and preoperative and postoperative non-contrast CT scans were analyzed. Section area of skeletal muscle (SMA), visceral fat (VFA), and subcutaneous fat (SFA) were assessed using semi-automatic segmentation software. Changes in trabecular bone attenuation of L1 mid-vertebra level (L1 Hounsfield units [HU]) were measured.

Results: Fifty-seven patients (mean age, 65.5±10.6; 70.2% males) were analyzed, and the median duration was 31 months. Forty-seven patients (82.5%) lost weight after gastrectomy. Baseline SMA and VFA did not differ between the bone loss and preserved groups; however, baseline SFA was significantly higher in the bone preserved group than in the bone loss group (P=0.020). In a multivariable linear regression model adjusted for confounding factors, one standard deviation higher VFA at baseline was associated with greater annualized L1 HU loss (%) (P=0.034). However, higher preoperative SFA was associated with protection against bone loss after gastrectomy (P=0.025).

Conclusion: Higher preoperative SFA exhibited a protective effect against bone loss after gastrectomy in patients with non-metastatic gastric cancer, whereas VFA exhibited a negative effect.

Keywords: Body composition; Subcutaneous fat; Gastrectomy; Stomach neoplasms

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INTRODUCTION

Gastric cancer is the fifth most frequently diagnosed cancer worldwide [1], with a 5-year survival rate of 77% overall and 90% in patients with early-stage gastric cancer. Osteoporosis and fragility fractures are crucial musculoskeletal complications in long-term survivors of gastric cancer. In a meta-analysis, the pooled prevalence of osteoporosis after gastrectomy was 36% [2]. The prevalence of osteoporosis after gastrectomy in men was 26%, which was higher than that of the general population, indicating clinical importance owing to the higher proportion of men with gastric cancer. The incidence of fracture after gastrectomy in a long-term observational study was 42.1 cases per 1,000 person-years [3], which is >2.5 times higher than that of a general Korean population aged >50 years [4]. Therefore, identifying patients at a higher risk of fracture after gastrectomy is crucial for early prevention.

Weight loss is a major contributor to bone loss [5,6]. Patients often lose 5% to 15% of body weight after gastrectomy [7], including loss of subcutaneous fat, visceral fat, and skeletal muscle [8]. In a prospective study, the amount of hip bone mineral density (BMD) loss after gastrectomy positively correlated to the magnitude of weight loss [9]. Given the unique metabolic characteristics of each body component [10-13], skeletal muscle and fat may exhibit a distinctive association with bone loss after gastrectomy. However, the relationship between changes in body composition after gastrectomy and bone loss has yet to be intensively investigated.

Abdomen computed tomography (CT) obtained during routine preoperative evaluation and postoperative follow-up of patients with gastric cancer provides an opportunity to analyze changes in CT-derived body composition after gastrectomy [14-16]. The present study aimed to explore whether CT-derived body composition parameters exhibit a distinctive association with bone loss after gastrectomy in patients with gastric cancer.

METHODS

Data source

We reviewed the medical records and images of 1,932 consecutive patients with histologically confirmed gastric adenocarcinoma who underwent gastrectomy at Yonsei University Severance Hospital in Seoul, Korea, between March 2009 and June 2018. The study protocol was approved by the International Review Board (IRB) of Yonsei University Health System, Severance Hospital (IRB No. 4-2023-1404). The IRB waived the requirement for informed consent owing to the retrospective design of this medical record review study. Data were obtained from Severance Hospital's Clinical Data Repository System, electronic medical record, radiographic storage, and communication system.

Study participants

Among patients who underwent gastrectomy at Yonsei University Severance Hospital between 2009 and 2018, 299 with preoperative non-contrast abdomen CT scans were initially selected (Fig. 1). In order to analyze body composition parameters and L1 trabecular attenuation from CT images without confounding from intravenous contrast, we had to limit the participants with preoperative non-contrast CT scans only. Patients with metastat-

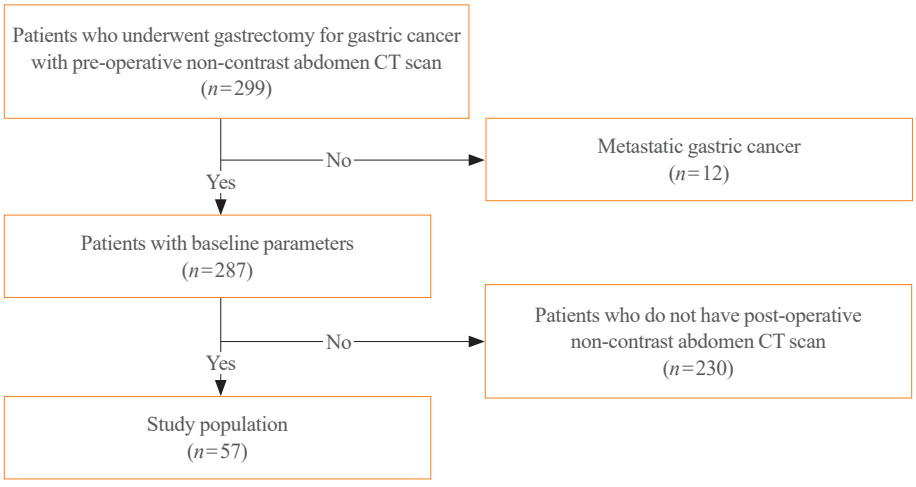

Fig. 1. Study flow. CT, computed tomography.

ic gastric cancer (n=12) and those without postoperative non-contrast abdomen CT scans (n=230) were excluded. The extent of lymphadenectomy and gastrectomy was determined according to Korean and Japanese guidelines [17,18]. The pathologic stage was determined according to the 8th edition of the American Joint Committee on Cancer staging system [19]. Clinicopathologic characteristics, including age, sex, body mass index (BMI), pathologic stage, partial or total gastrectomy, and adjuvant chemotherapy treatment were extracted from the database. Laboratory analyses were performed at the Department of Laboratory Medicine, Severance Hospital.

Body composition assessment

Anonymized preoperative and postoperative abdomen CT scans were analyzed using commercially available software for body composition assessment (MEDIP PRO v2.0.0.0, MEDICALIP Co. Ltd., Seoul, Korea). The software provides semi-automatic segmentation of body composition into seven classes. After segmentation, the software automatically detects waist ranges from the lower margin of the last rib to the upper margin of the iliac crest, consistent with the waist definition of the World Health Organization (WHO). Waist volume (cm^3) and section area (cm^2) of skeletal muscle (SMA), visceral fat (VFA), and subcutaneous fat (SFA) were automatically quantified. Compared with manual segmentation, automatic segmentation exhibited approximately 97% accuracy [20]. After automatic segmentation, an expert reviewer determined whether the segmentation masks for each body composition were generated properly. Then, each patient's preoperative and postoperative volumetric and WHO-defined waist sectional body composition indices were calculated.

Bone assessment

The CT attenuation of the L1 trabecular bone was manually measured, placing an ovoid region of interest in the anterior aspect of the L1 trabecular space. Mean attenuation was measured using Hounsfield units (HU), with lower values representing lower BMD. The efficiency of this manual measurement technique was proven by good interobserver agreement and reproducibility [21,22]. Changes in trabecular bone attenuation of L1 mid-vertebra level (L1 HU) were measured as the outcome. Because the duration between preoperative and postoperative CT scans varied among patients, annualized L1 HU percent change (%) was used as the study outcome. Bone loss and preserved groups were stratified by median (–2.27 HU/year) of annualized trabecular bone loss. For comparability with osteoporosis detected by dual-energy X-ray absorptiometry (DXA), we used <110 HU as corresponding threshold to detect osteoporosis by DXA T-score (>90% specificity in a previous study) [22]. Incident events for clinical vertebral and non-vertebral fractures during follow-up were ascertained by medical record review. We reviewed baseline and follow-up abdominal CT scans to find asymptomatic morphological vertebral fractures as possible.

Statistical analysis

Data were presented as mean±standard deviation, median (interquartile range), or as number (percentage). We tested normality of data using Shapiro-Wilk test and q-q plot. Serum alkaline phosphatase (ALP), creatinine, baseline SMA, VFA, SFA, and annual change in each body composition showed non-parametric distribution. Differences in clinical characteristics were analyzed using two-sample independent t test, Wilcoxon rank-sum test, and chi-square tests for continuous and categorical variables as appropriate. Changes of body composition parameters were analyzed using Wilcoxon signed-rank test. Multivariable linear regression models were built to predict the annualized change in trabecular bone L1 attenuation (HU). No evidence of multi-collinearity between covariates was observed using the variation inflation factor. Statistical significance threshold was set at two-sided P<0.05. All statistical analyses were performed using STATA version 14.4 (Stata Corp., College Station, TX, USA).

RESULTS

Baseline clinical characteristics

A total of 57 patients with both preoperative and postoperative non-contrast abdomen CT scans were included in the final analysis (mean age, 65.5±10.6 years; male patients, 70.2%) (Table 1). The median duration between preoperative and postoperative abdomen CT scans was 31 months. Thirty-four cases (61.4%) were diagnosed as stage 1. Men had higher baseline SMA (114.7 cm^2 vs. 88.7 cm^2), lower SFA (104.9 cm^2 vs. 156.1 cm^2), and higher trabecular L1 attenuation (136.8 cm^2 vs. 94.0 HU, P<0.05 for all) compared to women (Supplemental Table S1). During the follow-up period, one case of vertebral fracture and one case of non-vertebral fracture (femur neck fracture) occurred in the bone loss group, whereas two cases of vertebral fracture occurred in the bone preserved group.

Table 1. Preoperative Characteristics of the Study Population (n=57)

Variable	Value
Age, yr	65.5±10.6
Sex	
Male	40 (70.2)
Body mass index, kg/m^2	23.7±2.8
Surgical stage	
Stage 1	35 (61.4)
Stage 2	4 (7.0)
Stage 3	18 (31.6)
Operation	
Partial gastrectomy	44 (77.2)
Total gastrectomy	13 (22.8)
Postoperative chemotherapy	
Yes	23 (40.4)
No	34 (59.6)
Serum calcium, mg/dL	9.0±0.5
Serum phosphorus, mg/dL	3.5±0.7
Serum albumin, mg/dL	4.0±0.6
Serum alkaline phosphatase, IU/L	63.0 (52.0–73.0)
Serum creatinine, mg/dL	0.9 (0.8–1.3)
Skeletal muscle area, cm^2	107.1 (95.7–123.8)
Abdominal visceral fat area, cm^2	102.7 (68.0–142.7)
Subcutaneous fat area, cm^2	115.1 (90.8–146.2)
Trabecular bone L1 attenuation, HU	122.4 (94.0–147.5)

Values are expressed as mean±standard deviation, number (%), or median (interquartile range).
HU, Hounsfield units.

Comparison of body composition between the bone loss and preserved groups

Preoperative and postoperative values of the CT-derived body composition parameters were compared between the bone loss (n=28) and preserved (n=29) groups (Fig. 2). Bone loss group had older age than bone preserved group at baseline (69.2 years vs. 61.9 years, P=0.008). At baseline, proportion of individuals with low L1 HU (<110 HU) did not differ between bone preserved and loss groups (31% vs. 42%, P=0.355). However, at postoperative follow-up, bone loss group had significantly higher prevalence of low L1 HU (n=22/28, 79%) compared to bone preserved group (7/29, 24%; P<0.001). Patients lost SMA, VFA, and SFA after gastrectomy in both groups (all P<0.05). At baseline, SMA and VFA did not differ between the bone loss and preserved groups, whereas SFA was significantly higher in the bone preserved group than in the bone loss group (130.2 cm^2 vs. 101.8 cm^2, P=0.020) (Supplemental Table S2). Annualized changes of SMA and VFA in absolute value did not differ between two

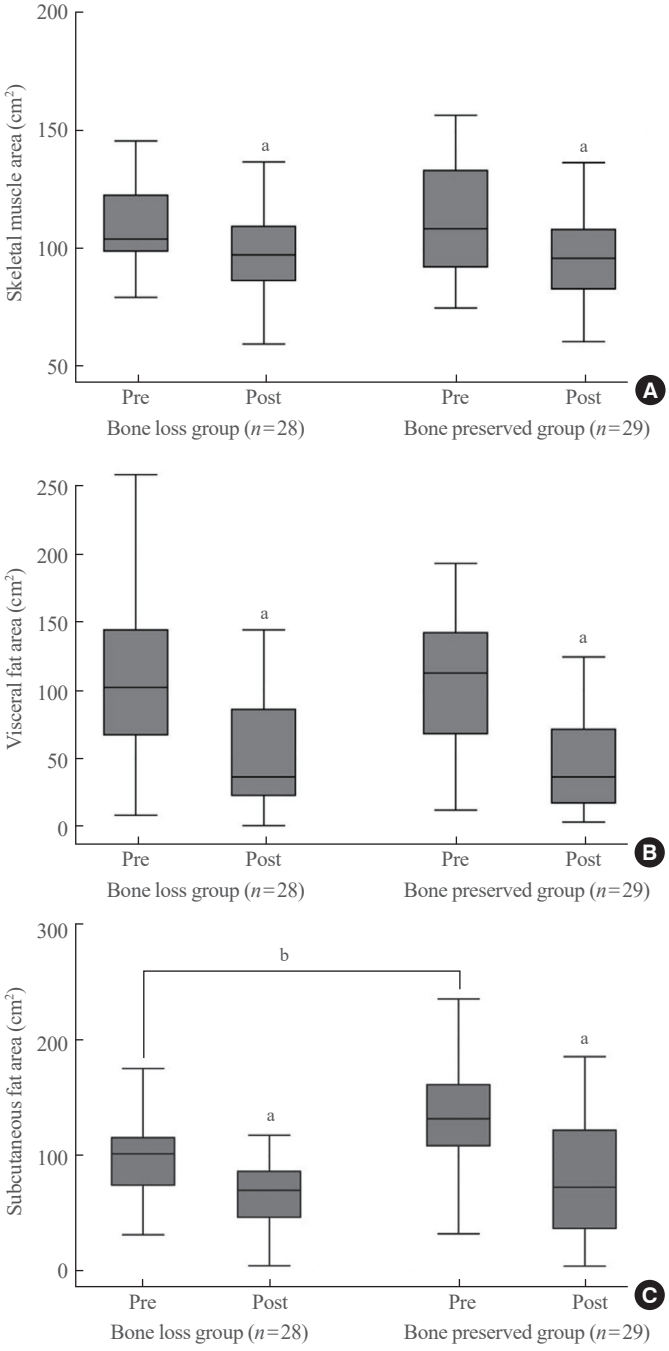

Fig. 2. Comparison of body composition including (A) skeletal muscle area, (B) visceral fat area, and (C) subcutaneous fat area between the bone loss and preserved groups. Bone loss and preserved groups are stratified by the median of annualized trabecular bone loss. Pre, preoperative; Post, postoperative. [a]P<0.05 vs. Pre value; [b]P=0.020.

Table 2. Multivariable Regression Analysis of Annualized Change in Trabecular Bone L1 Attenuation (HU) after Gastrectomy (n=57)

Variable	Univariable		Model 1[c]		Model 2[d]		Model 3[e]	
	Beta coefficient (95% CI)	*P* value	Beta coefficient (95% CI)	*P* value	Beta coefficient (95% CI)	*P* value	Beta coefficient (95% CI)	*P* value
Age (/1 year increment)	–0.24 (–0.64 to 0.16)	0.239	0.08 (–0.49 to 0.65)	0.777	0.18 (–0.44 to 0.81)	0.556	–0.18 (–0.69 to 0.33)	0.486
Sex (women vs. men)	0.89 (–8.45 to 10.23)	0.849	–9.09 (–24.43 to 6.24)	0.239	–10.24 (–25.65 to 5.17)	0.188	–1.71 (–13.80 to 10.38)	0.777
BMI (/1 kg/m^2 increment)	0.75 (–0.78 to 2.28)	0.331	–0.25 (–3.12 to 2.61)	0.861	–0.01 (–2.97 to 2.95)	0.995	1.20 (–0.66 to 3.06)	0.199
Preoperative SMA[a]	0.72 (–3.83 to 5.27)	0.752	2.94 (–6.99 to 12.87)	0.555	3.32 (–7.35 to 13.99)	0.534		
Preoperative VFA[a]	–1.27 (–5.46 to 2.92)	0.546	–6.17 (–12.57 to 0.24)	0.059	–7.03 (–13.49 to –0.56)	0.034		
Preoperative SFA[a]	4.29 (–0.06 to 8.64)	0.053	9.51 (1.39 to 17.64)	0.023	9.65 (1.28 to 18.02)	0.025		
Cancer stage (stage III vs. I, II)	2.91 (–6.11 to 11.94)	0.520			1.20 (–10.23 to 12.62)	0.834	3.21 (–9.20 to 15.62)	0.605
ALP (log-transformed)	–15.43 (–31.57 to 0.70)	0.060			–18.92 (–36.35 to –1.50)	0.034	–16.60 (–35.24 to 2.05)	0.080
Operation (partial vs. total)	–2.30 (–8.81 to 4.22)	0.483			–2.65 (–9.38 to 4.08)	0.432	–2.18 (–9.90 to 5.55)	0.573
Chemotherapy (no vs. yes)	–0.10 (–7.36 to 7.17)	0.979			–0.71 (–10.14 to 8.72)	0.880	–2.75 (–12.60 to 7.11)	0.577
Δ Change in SMA[b]	–0.01 (–0.80 to 0.78)	0.982					0.04 (–0.99 to 1.07)	0.933
Δ Change in VFA[b]	0.03 (–0.18 to 0.23)	0.801					0.10 (–0.24 to 0.45)	0.546
Δ Change in SFA[b]	–0.04 (–0.22 to 0.15)	0.695					–0.03 (–0.35 to 0.28)	0.833

HU, Hounsfield units; CI, confidence interval; BMI, body mass index; SMA, skeletal muscle area; VFA, visceral fat area; SFA, subcutaneous fat area; ALP, alkaline phosphatase.
[a]Standardized value, per 1 standard deviation increase; [b]Change of body composition area (cm^2) from baseline after gastrectomy, annualized value; [c]Model 1 was adjusted for age, sex, preoperative SMA, preoperative VFA, and preoperative SFA; [d]Model 2 was adjusted for age, sex, preoperative SMA, preoperative VFA, preoperative SFA, cancer stage, ALP, surgery type, and chemotherapy; [e]Model 3 was adjusted for age, sex, cancer stage, ALP, surgery type, chemotherapy, and annualized changes in SMA, VFA, and SFA.

groups but greater annualized loss in SFA was observed in bone preseved group (–20.9 cm^2 vs. –8.3 cm^2, P=0.025).

Association between body composition and bone density changes after gastrectomy

Forty-seven patients (82.5%) lost weight after gastrectomy (median –3.7%), and the median of BMI change was –3.5% (percent change from baseline, annualized value; weight change –3.7%) (Supplemental Table S3). The magnitude of annualized percentage loss in VFA was highest (–22.5%), followed by SFA (–14.0%) and SMA (–3.4%). In the multivariable linear regression models adjusted for age, sex, preoperative SMA, SFA, cancer stage, ALP, and surgery and chemotherapy types, one standard deviation higher VFA at baseline was associated with greater annualized L1 HU loss (%) (adjusted beta coefficient, –7.03; 95% confidence interval [CI], –13.49 to –0.56; P=0.034) (model 2; Table 2). However, higher preoperative SFA was associated with protection against bone loss after gastrectomy (adjusted beta coefficient, 9.65 per one standard deviation increment in baseline SFA; 95% CI, 1.28 to 18.02; P=0.025). Preoperative SMA did not show a significant association with bone loss after gastrectomy after adjusting for covariates (adjusted beta coefficient, 3.32; 95% CI, –7.35 to 13.99; P=0.534). The annual percentage changes in SFA, VFA, and SMA were not associated with bone loss in univariate and multivariable models (model 3; Table 2). Elevated ALP level was associated with more significant bone loss (adjusted beta coefficient, –18.92; 95% CI, –36.35 to –1.50; P=0.034), although the association attenuated in model 3 (P=0.080). ALP at the time of follow-up CT was available in 55 of 57 study participants (96%). ALP level was increased by 47.3% (median 25 IU/L in absolute value) in overall, without statistical difference between bone loss and preserved groups (33.9% and 50.9%, P=0.515). Changes in ALP level (%) was not an independent predictor of bone loss in univariate model (beta coefficient 0.01 per 1% increment; 95% CI, 0.00 to 0.03; P=0.165) and when entered into multivariable model instead of baseline ALP level (model 2; beta coefficient 0.00 per 1% increment; 95% CI, –0.01 to 0.02; P=0.615).

DISCUSSION

In the present study, preoperative baseline fat area was a significant predictor of bone loss after gastrectomy, with subcutaneous fat being a protective factor and visceral fat being a negative

factor. This association remained robust after adjusting for age, sex, cancer stage, ALP, and surgery and adjuvant chemotherapy types. The preoperative SMA and changes in body composition area after gastrectomy did not show any association with bone loss. The amount of bone loss was greater when the baseline serum ALP level was elevated. The results of the present study showed that baseline fat area is associated with bone loss rather than changes in body composition area.

In this study, subcutaneous fat exhibited a protective effect against bone loss, whereas excess of visceral fat was detrimental to changes of bone density, which aligned well with previous studies suggesting the distinctive impact of fat on bone mass [11,13]. Hormones and inflammatory cytokines secreted by adipose tissue could mediate the distinctive impact of fat depots on bone remodeling [23]. Adiponectin, known to have a protective effect against osteoporosis, is expressed in lower quantities in visceral fat tissue than in subcutaneous fat tissue [24]. Leptin, known for its role in appetite regulation, promotes osteoblast differentiation and has a bone-protective effect, with higher secretion observed in subcutaneous fat [25]. In contrast, visceral fat is associated with insulin resistance and inflammatory markers, such as tumor necrosis factor-alpha and interleukin-6, which affect bone health negatively [26]. Bariatric surgery, especially Roux-en-Y gastric bypass (RYGB), was associated with bone loss at weight-bearing sites in previous studies. In a high-resolution peripheral quantitative computed tomography (HRpQCT) and DXA study of 22 women underwent bariatric surgery, bone loss at the total hip and femoral neck measured by DXA 12 months postoperatively was predicted by the degree of weight loss. HRpQCT at distal radius and tibia showed stable trabecular parameters but impaired cortical parameters particularly at the tibia, which was only predicted by parathyroid hormone increase after bariatric surgery [27]. This study suggests the impact of skeletal unloading and secondary hyperparathyroidism on hip bone loss and cortical bone impairment. In another study with 10-year follow-up of individuals after gastric bypass surgery or adjustable gastric banding (AGB), substantial deficits in cortical and trabecular microarchitecture were observed only in RYGB but not in AGB group compared to nonsurgical age, sex, and current BMI-matched controls, with lower than expected hip and peripheral BMD for the new weight setpoint in RYGB, suggesting pathophysiologic processes other than skeletal unloading or secondary hyperparathyrodism [27]. In line with these findings, we observed deterioration of trabecular bone attenuation at lumbar spine in relatively short term period in patients underwent gastrectomy, and the magnitude of loss was predicted by amount of fat depot at baseline [28]. Whether the difference in fat depot would have impact on cortical bone loss in gastrectomy for cancer treatment or bariatric surgery setting need to be explored further.

In the present study, elevated preoperative baseline serum ALP level was significantly associated with greater bone loss after gastrectomy, consistent with the findings of previous studies [29]. Serum ALP level tends to increase in the presence of calcium and vitamin D deficiency, and this increment worsens after gastrectomy, persisting even 1 year postoperatively [30-32]. Furthermore, ALP includes bone-specific ALP (BAP). Given that BAP serves as a marker for bone turnover and formation, elevated ALP could be a negative factor for BMD. A study indicated that BAP serves as a surrogate marker for bone metastasis in patients with gastric cancer [33]. In addition, elevated pre-treatment serum ALP levels have been associated with shorter disease-free survival and tumor burden in patients with gastric cancer [34]. Therefore, serum ALP is a clinically important marker in patients with gastric cancer.

Considering that this study was not powered to detect fracture outcomes, we used L1 HU as a proxy for bone density. Several studies suggested that L1 HU measured from routine clinical CT could be used for the opportunistic screening for osteoporosis based on the ease and utility of simple region-of-interest attenuation measurement. In a study of 1,867 adults undergoing CT and DXA, area under the receiver-operating characteristics curve (AUROC) was 0.83 to discriminate osteoporosis from osteopenia and normal BMD, with 90% specificity threshold of <110 HU and 90% sensitivity threshold of >160 HU [22]. L1 HU showed modest to good positive correlation with DXA T-score in lumbar spine (ranged from 0.65 to 0.73) in individuals without degenerative deformities [22]. In a matched case-control study of patients with hip fracture and controls, odds for hip fracture reduced by 17% per 10-HU increase in L1 HU, with modest discriminatory ability of AUROC 0.70 [35]. Older adults with vertebral fracture had lower L1 HU compared to those without (70 HU vs. 101 HU; AUROC 0.77), with 100 HU as 90% sensitivity threshold [36]. A recent study of 9,223 adults showed that automated measurement of L1 HU was associated with higher risk of incident fracture during median 8.8 years of follow-up, showing AUROC 0.71 for 2-year fracture which was similar to that of the Fracture Risk Assessment Tool (FRAX) score (0.72) [37]. Taken together, L1 HU may serve as imaging marker for bone health at least in population level, although individual level utility or value as monitoring marker need to be further investigated [38].

One strength of the present study is that, to the best of our knowledge, it is the first to indicate longitudinal changes in bone density before and after gastrectomy, according to the changes in body composition. Another strength is that changes in body composition were analyzed using routine CT scans of patients with gastric cancer followed up for 31 months. This study also has some limitations. First is the exclusion of patients without postoperative non-contrast abdominal CT scans, which led to a small sample size. Second, owing to the retrospective study design, other factors that could affect bone loss (such as serum vitamin D status, history of calcium and cholecalciferol, or other anti-osteoporotic medications, parathyroid hormone, nutritional status, and concurrent medications) could not be collected. Bone turnover markers other than ALP such as c-telopeptide or procollagen type 1 N-terminal propeptide were not available in this study. Third, given the absence of DXA-measured BMD values, we evaluated bone loss using only L1 trabecular bone attenuation, and a direct comparison with DXA-measured BMD was not performed. Finally, results regarding total hip and femoral neck bone density were not obtainable owing to the focus on abdominal CT scans in this study.

In conclusion, higher preoperative SFA exhibits a protective effect against bone loss after gastrectomy in patients with non-metastatic gastric cancer, whereas VFA exhibits a negative effect. Further research is required to investigate whether individuals identified to be at a high risk of bone loss according to body composition experienced a higher incidence of fractures and whether treatments such as bisphosphonates contribute to the prevention of fractures in this population.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTIONS

Conception or design: S.S., N.H. Acquisition, analysis, or interpretation of data: S.C., S.S., S.L., N.H. Drafting the work or revising: S.C., S.S., Y.R., H.I.K., N.H. Final approval of the manuscript: N.H.

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