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Negative Effects of Total Gastrectomy on Bone Tissue Metabolism and Volumetric Bone Mineral Density (vBMD) of Lumbar Spine in 1-Year Study in Men

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Abstract: Gastrectomy induces severe osteoporosis in humans but its quantitative scale within trabecular and cortical compartments was not estimated. The aim of the study was to determine changes of volumetric bone mineral density (vBMD) in lumbar vertebrae (L_1–L_4) and biochemical bone metabolism markers in serum of patients 1 year after total gastrectomy. The control group consisted of patients (N = 8) subjected to abdominal surgery due to cardiospasmus. Total gastrectomy was performed in the experimental group (N = 6).

Volumetric bone mineral density of trabecular and cortical bone of lumbar spine was measured before (baseline) and 1 year after the gastric surgery using the quantitative computed tomography method. Serum concentrations of insulin, insulin-like growth factor-1, tyroxine, interleukin-6, C-terminal telopeptides of type II collagen and bone formation, and resorption markers were determined at baseline and 1 year later, using ELISA, EIA, and IEMA methods.

Total gastrectomy induced significant decrease of vBMD values, up to 16.8% and 10.0%, within the trabecular and cortical bone compartments of lumbar spine ($P < 0.05$). These negative changes of vBMD were associated with significantly increased serum concentration of bone resorption markers such as deoxypyridinoline, pyridinoline, and C-terminal telopeptides of type I collagen, by 13.5%, 32.2%, and 121.5%, respectively ($P < 0.05$). Neither vBMD nor biochemical bone turnover markers and hormone concentrations were influenced in the control patients.

Dramatic bone loss during the first year in gastrectomized patients has proven dynamic osteoporosis progress indicating an importance of treatment interventions in these patients with emphasis on inhibition of intensive bone resorption processes.

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Abbreviations: BAP = bone-specific alkaline phosphatase, BMD = bone mineral density, Ca-HA = calcium hydroxyapatite, $Cb_{Ca\text{-}HA}$ = calcium hydroxyapatite density in the cortical bone, CICP = C-terminal propeptide of type I collagen, CTR group = control group, CTX-I = C-terminal telopeptides of type I collagen, CTX-II = C-terminal telopeptides of type II collagen, DEXA = dual-energy X-ray absorptiometry, DPD = deoxypyridinoline, EIA = enzyme immunoassay, ELISA = enzyme-linked immunosorbant assay, GHPA = gastric-hypothalamic-pituitary axis, GX group = gastrectomized (experimental) group, ICTP = carboxyterminal telopeptide of type I collagen, IEMA = immunoenzymometric assay, IGF-I = Insulin-like growth factor I, IL-6 = interleukin-6, NTX = collagen type I cross-linked N-telopeptide, OC = osteocalcin, PINP = procollagen type I N-terminal propeptide, PTH = parathyroid hormone, PYD = pyridinoline, QCT = quantitative computed tomography, $Tb_{Ca\text{-}HA}$ = calcium hydroxyapatite density in the trabecular bone, vBMD = volumetric bone mineral density.

INTRODUCTION

Gastric surgery is performed in humans, in cases of stomach damage due to various factors. The first stomach resection due to cancer was performed and described by Jules Emile Pean in 1879. Ludwik Rydygier performed gastroenterostomy for management of peptic ulcer disease 1 year later.[1] Theodor Billroth has performed gastroduodenostomy in a 43-year-old woman with pyloric cancer following partial gastrectomy and this procedure is known as the Billorth I operation. Billroth II operation, where gastrojejunal reconstruction was performed following partial gastrectomy, was introduced later.[2,3] Even though partial or total gastrectomy was introduced many years ago, the most common reasons are still the same and include gastric malignancy, advanced recurrent peptic ulcer disease, surgical treatment of morbid obesity (bariatric surgery), and fundal variceal bleeding.[4–6]

Human stomach has many important physiological functions that are lost when gastrectomy procedure is performed. Abnormal food transit, disturbed nutrition intake, abnormal digestion and absorption, disturbed protein and amino acid homeostasis, deficiencies of macro- and microelements and vitamins, as well as impaired hormone secretion and impaired gastric-hypothalamic-pituitary axis (GHPA) functions are the most important consequences of gastrectomy.[7–9] Total gastrectomy consists of surgical extirpation of the glandular part of the stomach followed by anastomosing the duodenum and the esophagus, and has negative impact on systemic functions and

homeostasis maintenance in the organism.[7] It was shown in experimental studies that total gastrectomy induces osteopenia in both humans and experimental animals, including the trabecular and cortical bone compartments.[10–14] Mechanically, gastrectomy-induced osteopenia affects load-carrying capacities of all regions of spine and their stability. Even though there have been previous studies on animals and humans, the mechanisms of postgastrectomy bone diseases have not yet been explained sufficiently and are still understood only partially.[8,15–17]

Thus, the aim of the study was to determine changes of volumetric bone mineral density (vBMD), separately in trabecular and cortical bone compartments in lumbar spine, as well as biochemical bone metabolism indices occurring in men 1 year after the total gastrectomy procedure.

METHODS

Experimental procedures used throughout this study were approved by The Local Ethics Committee of Medical University in Lublin, Poland—agreement number KE-0254/4/2008 on January 31, 2008.

Patients Qualified to the Study

Fourteen patients treated at the II Department of General and Gastroenterological Surgery and Surgical Oncology of the Alimentary Tract of Medical University in Lublin were qualified to the 1-year study and survived the whole follow-up period. Their characteristic is shown in Table 1. The control group consisted of 8 men (CTR group; $N = 8$) at mean age of 49.5 ± 4.9 years undergoing surgical operation due to cardiospasmus. Midline abdominal incision was used to cut the distal part esophageal muscle layer on the distance between 8 and 10 cm. In the next step, Nissen fundoplication was performed and a fold of the fundus was used to wrap lower part of the esophagus. Body mass index in the CTR group was similar at the beginning of the study (27.29 ± 1.00) and 1 year later (27.09 ± 1.11). The experimental group consisted of 6 men at mean age of 56.7 ± 4.5 years undergoing total gastrectomy procedure due to gastric cancer (GX group; $N = 6$). Midline abdominal incision was used to perform gastric resection and Roux-en-Y reconstruction. Following gastric resection, the anastomoses of distal part of esophagus and jejunum (end-to-side anastomosis), as well as duodenum and jejunum (end-to-side anastomosis), were executed. Body mass index in the GX group was similar at the beginning of the study (25.06 ± 1.29) and 1 year later (23.99 ± 1.23). The patients were diagnosed and operated on between February 2008 and January 2011. Baseline volumetric bone mineral density measurement of lumbar spine was performed and fasted overnight blood samples were collected (between 8:00 and 9:00 AM) for serum and plasma just before the oesophagus/gastric surgery in preoperative patients from both groups. One year from the baseline (1 year after the surgery), both control and experimental patients were subjected to measurement of lumbar spine vBMD and collection of fasted overnight blood samples (between 8:00 and 9:00 AM) for serum and plasma analysis. Blood samples were collected using standard venipuncture of the *cephalic vein* to avoid hemolysis. Immediately after centrifugation, serum samples were frozen and stored at -80°C for further biochemical analyses. Patients suffering from coexisting additional diseases to cardiospasmus or gastric cancer and impaired metabolic/hormonal homeostasis of the body were eliminated from the investigated participants at the initial stage of the study. Poor health status, death of patient, neoplastic disease recurrence, or metastasis were additional factors eliminating participants from the study.

TABLE 1. Characteristics of Control Patients (CTR Group) and Patients Subjected to Total Gastrectomy (GX Group)

	CTR Group	GX Group
Total number of patients (N)	8	6
Type of surgery	Abdominal surgery due to cardiospasmus	Total gastrectomy
Sex (male)	100%	100%
Mean age	49.5	56.7
Baseline BMI (kg/m^2)	27.29	25.06
Final BMI (kg/m^2)	27.09	23.99

Densitometry of Lumbar Spine

Volumetric bone mineral density of trabecular and cortical bone of 4 lumbar vertebrae (L_1–L_4) were determined using quantitative computed tomography (QCT) technique and Somatom Emotion–Siemens apparatus (Siemens, Erlangen, Germany) supplied with Somaris/5 VB10B software (Version B10/2004A). Volumetric bone mineral density was measured separately for the trabecular and the cortical bone of the vertebral body using 10-mm-thick, cross-sectional scans, placed at 50% of each vertebral body length. Both the trabecular and cortical vBMD were measured using Osteo CT application package (Software Version B10/2004A) and expressed quantitatively as calcium hydroxyapatite (Ca-HA) density in the trabecular ($Tb_{Ca\text{-}HA}$) and cortical bone ($Cb_{Ca\text{-}HA}$) compartments. Moreover, T-score and Z-score values were automatically determined for all the examined patients. All patients were scanned with the water- and bone-equivalent calibration phantom provided by the scanner producer and serving as a standard for such measurements.

Biochemical Analyses of Serum

Insulin concentration in serum was determined using Mercodia Insulin ELISA (Enzyme-Linked Immunosorbant Assay; Mercodia AB, Upsala, Sweden). Insulin-like growth factor I (IGF-I) was determined in serum using IGF-I ELISA kit and 2-site IEMA (Immunodiagnostic Systems Ltd, Boldon, Tyne & Wear, UK). Serum concentration of thyroxine was determined using the commercial ACTIVE T4 Enzyme Immunoassay (EIA) Kit (Diagnostic Systems Laboratories Inc, Webster, TX). Bone-specific alkaline phosphatase (BAP) concentration in serum was measured using Ostase BAP immunoenzymometric assay (IEMA; Immunodiagnostic Systems Ltd). Quantitative assessment of osteocalcin (OC) in serum was performed using MicroVue Osteocalcin EIA Kit (Quidel Corp, San Diego, CA). MicroVue CICP EIA Kit was used to measure C-terminal propeptide of type I collagen (CICP) concentration in serum (Quidel Corp). MicroVue Total DPD EIA Kit was used to evaluate serum deoxypyridinoline (DPD) concentration (Quidel Corp). For the quantitative determination of pyridinoline (PYD) crosslinks in serum, MicroVue Serum PYD EIA Kit was used (Quidel Corp). Assessment of degradation products of C-terminal telopeptides of type I collagen (CTX-I) in serum was performed using Serum CrossLaps ELISA (Immunodiagnostic Systems Ltd). Serum Pre-Clinical CartiLaps ELISA kit was used for quantitative determination of C-terminal telopeptides of type II collagen (CTX-II) in serum (Immunodiagnostic Systems Ltd). Serum concentration of

TABLE 2. Volumetric Bone Mineral Density (vBMD) of Trabecular and Cortical Bone of Lumbar Vertebrae in Control Patients (CTR Group) at the Baseline and 1 Year After the Surgical Procedure

Investigated Parameter	Baseline	1 Yr After Surgical Procedure	*P* Value
L_1 vertebra			
Calcium hydroxyapatite density in the trabecular bone (mg/mL)	117.2 ± 10.8	114.7 ± 11.0	$P = 0.341$
Calcium hydroxyapatite density in the cortical bone (mg/mL)	292.8 ± 19.9	290.5 ± 17.0	$P = 0.672$
L_2 vertebra			
Calcium hydroxyapatite density in the trabecular bone (mg/mL)	115.5 ± 11.2	111.7 ± 10.2	$P = 0.108$
Calcium hydroxyapatite density in the cortical bone (mg/mL)	317.1 ± 21.3	314.2 ± 21.6	$P = 0.708$
L_3 vertebra			
Calcium hydroxyapatite density in the trabecular bone (mg/mL)	111.2 ± 12.2	106.6 ± 12.0	$P = 0.116$
Calcium hydroxyapatite density in the cortical bone (mg/mL)	333.8 ± 21.1	340.3 ± 20.4	$P = 0.478$
L_4 vertebra			
Calcium hydroxyapatite density in the trabecular bone (mg/mL)	112.4 ± 12.8	107.6 ± 11.6	$P = 0.077$
Calcium hydroxyapatite density in the cortical bone (mg/mL)	354.3 ± 21.2	360.2 ± 20.6	$P = 0.495$
Average L_1–L_4 vertebrae			
Calcium hydroxyapatite density in the trabecular bone (mg/mL)	114.0 ± 11.7	110.2 ± 11.1	$P = 0.073$
Calcium hydroxyapatite density in the cortical bone (mg/mL)	325.2 ± 18.4	326.3 ± 18.5	$P = 0.828$
T-score (20 yr of age)	−2.29 ± 0.44	−2.44 ± 0.42	$P = 0.074$
Z-score	−0.39 ± 0.45	−0.60 ± 0.39	$P = 0.203$

Values are means ± SEM.

interleukin-6 (IL-6) was measured using Human IL-6 High Sensitivity ELISA kit (Diaclone, Besançon, France). Results of hormonal and biochemical bone and cartilage tissue metabolism markers in serum were obtained with the use of Benchmark Plus microplate spectrophotometer supplied with Microplate Manager Software Version 5.2.1 (Bio-Rad Laboratories Inc, Hercules, CA).

Statistical Analysis

Statistical analysis of raw data was performed using Statistica software (version 6.0). All data are presented as means ± SEM. The comparison of 1-year changes of the investigated variables within each group (1 year after the surgery versus baseline) was performed using paired Student *t* test for dependent variables. *P* value ≤ 0.05 was considered statistically significant for all comparisons.

RESULTS

Volumetric Bone Mineral Density of Lumbar Spine

Results of vBMD, T-score, and Z-score measurements in the control group of patients are shown in Table 2. Calcium hydroxyapatite density in the trabecular bone in lumbar spine of the control patients was not significantly changed during 1 year since the abdominal surgery when measured separately for each lumbar vertebra ($P > 0.05$). Calcium hydroxyapatite density in the cortical bone in lumbar spine was not changed significantly after 1-year follow-up when assessed separately for each lumbar vertebra ($P > 0.05$). The average values (L_1–L_4) of $Tb_{Ca\text{-}HA}$ and $Cb_{Ca\text{-}HA}$ were not changed significantly during 1-year study in the patients from the CTR group ($P > 0.05$). Moreover, T-score and Z-score values were not changed after 1 year since the abdominal surgery in the CTR group of patients ($P > 0.05$).

Results of vBMD, T-score, and Z-score measurements in the group of patients subjected to the total gastrectomy are shown in Table 3. Calcium hydroxyapatite density in the trabecular bone in lumbar spine of the patients subjected to the total gastrectomy procedure was significantly decreased after 1 year of the follow-up in all lumbar vertebrae by 16.8%, 15.9%, 15.6%, and 11.8% for L_1, L_2, L_3, and L_4, respectively (all $P < 0.01$). Calcium hydroxyapatite density in the cortical bone in lumbar spine of the gastrectomized patients was significantly decreased, by 10.0% and 9.0%, after 1 year since the gastric surgery when measured separately for L_1 and L_2 (both $P < 0.05$). The average value (L_1–L_4) of $Tb_{Ca\text{-}HA}$ was significantly decreased by 15.1% 1 year after the total gastrectomy in the GX group when compared with the baseline value ($P = 0.004$). Similar tendency was observed for the average value (L_1–L_4) of $Cb_{Ca\text{-}HA}$ which was decreased by 7.2% ($P = 0.071$). Furthermore, T-score and Z-score values were significantly decreased after 1 year since the total gastrectomy in the GX group of patients when compared with the baseline values (both $P < 0.01$).

Analysis of Hormones and Biochemical Bone Metabolism Markers in Serum

Results of biochemical analyses of serum in patients from the CTR group are presented in Table 4. Serum concentrations of insulin, thyroxine, IL-6, IGF-1, BAP, OC, CICP, DPD, PYD, CTX-I, and CTX-II were not changed after 1 year of the study in the control patients when compared with the baseline values (all $P > 0.05$). Results of biochemical analyses of serum in patients from the GX group are presented in Table 5. Serum concentrations of DPD, PYD, and CTX-I were significantly increased by 13.5%, 32.2%, and 121.5% 1 year after the total gastrectomy in the GX group of patients when compared with the baseline values, respectively (all $P < 0.05$).

DISCUSSION

Prevalence of postgastrectomy osteoporosis and bone fractures in patients is commonplace. Studies in Korea have

TABLE 3. Volumetric Bone Mineral Density of Trabecular and Cortical Bone of Lumbar Vertebrae in Patients Subjected to Total Gastrectomy (GX Group) at the Baseline and 1 Year After the Surgical Procedure

Investigated Parameter	Baseline	1 Yr After Surgical Procedure	*P* Value
L_1 vertebra			
Calcium hydroxyapatite density in the trabecular bone (mg/mL)	93.5 ± 5.2	77.8 ± 5.1*	$P = 0.006$
Calcium hydroxyapatite density in the cortical bone (mg/mL)	259.6 ± 16.6	233.7 ± 20.1*	$P = 0.039$
L_2 vertebra			
Calcium hydroxyapatite density in the trabecular bone (mg/mL)	91.1 ± 6.1	76.6 ± 5.1*	$P = 0.003$
Calcium hydroxyapatite density in the cortical bone (mg/mL)	287.1 ± 13.9	261.3 ± 15.3*	$P = 0.020$
L_3 vertebra			
Calcium hydroxyapatite density in the trabecular bone (mg/mL)	88.9 ± 7.5	74.9 ± 6.3*	$P = 0.008$
Calcium hydroxyapatite density in the cortical bone (mg/mL)	293.8 ± 21.5	276.1 ± 20.2	$P = 0.139$
L_4 vertebra			
Calcium hydroxyapatite density in the trabecular bone (mg/mL)	90.0 ± 5.6	79.4 ± 5.7*	$P = 0.005$
Calcium hydroxyapatite density in the cortical bone (mg/mL)	294.2 ± 17.8	282.6 ± 16.3	$P = 0.490$
Average L_1–L_4 vertebrae			
Calcium hydroxyapatite density in the trabecular bone (mg/mL)	90.9 ± 5.9	77.2 ± 5.4*	$P = 0.004$
Calcium hydroxyapatite density in the cortical bone (mg/mL)	283.7 ± 14.3	263.4 ± 16.3	$P = 0.071$
T-score (20 yr of age)	−3.16 ± 0.22	−3.68 ± 0.20*	$P = 0.004$
Z-score	−0.80 ± 0.18	−1.24 ± 0.22*	$P = 0.008$

Values are means ± SEM.
* Statistically significant differences versus baseline for $P < 0.05$ by paired Student *t* test.

revealed osteoporosis incidence in 39.6% gastric cancer patients older than 50 years of age following gastrectomy procedure. Osteoporosis incidence in lumbar spine of gastric cancer patients was present in 29.8% of men and in 54.5% of women, while the osteoporosis rate of the femoral neck was less frequent and reached 11.9% in men and 26.3% in women. It was shown in Korean population that the incidence of postgastrectomy osteoporosis is significantly higher than the general rate of ostoporosis in lumbar spine in patients over 50 years of age assessed on 6.5% men and 40.1% women.[18,19] It was shown that surgical resection of different anatomic parts of the stomach may have various consequences for patients with regard to their quality of life, postoperative disorders, and osteoporosis rate.[7] Experimental studies on animals have also shown that total gastrectomy causes severe effects in several regions of skeleton, including trabecular and cortical bone compartments in rats.[13,14] Both gastrectomy and fundectomy are the most effective in inducing osteoporosis, while the antrectomy has a less negative effect on bones.[12]

In this study, the effects of total gastrectomy procedure on volumetric bone mineral density and hormonal and biochemical bone metabolism indices were evaluated in male patients. For the first time, the scale of the gastrectomy-induced negative effects on bone tissue metabolism rate and vBMD of lumbar spine in terms of trabecular and cortical bone compartments properties were assessed quantitatively after the period of 1 year since the operation. The advantage of this study lies also in the inclusion of control group of patients undergoing abdominal surgery procedure due to cardiospasmus. Such an experimental design has allowed for monitoring and comparison of the bone

TABLE 4. Serum Concentrations of Hormones and Biochemical Bone Metabolism Markers in Control Patients (CTR Group) at the Baseline and 1 Yr After the Surgical Procedure

Investigated Parameter	Baseline	1 Yr After Surgical Procedure	*P* Value
Insulin (μg/L)	0.69 ± 0.19	0.32 ± 0.04	$P = 0.083$
Insulin-like growth factor I (μg/L)	106.4 ± 15.3	109.4 ± 12.6	$P = 0.880$
Thyroxine (μg/dL)	9.93 ± 2.03	6.95 ± 1.79	$P = 0.406$
Bone-specific alkaline phosphatase (μg/L)	17.50 ± 1.89	18.79 ± 1.67	$P = 0.618$
Osteocalcin (ng/mL)	5.83 ± 0.79	6.35 ± 0.91	$P = 0.670$
C-terminal propeptide of type I collagen (ng/mL)	7.24 ± 0.54	8.65 ± 0.80	$P = 0.167$
Deoxypyridinoline (nmol/L)	6.39 ± 0.28	5.87 ± 0.13	$P = 0.124$
Pyridinoline (nmol/L)	11.03 ± 0.41	10.46 ± 0.62	$P = 0.464$
C-terminal telopeptides of type I collagen (ng/mL)	0.401 ± 0.056	0.521 ± 0.036	$P = 0.093$
C-terminal telopeptides of type II collagen (pg/mL)	22.34 ± 6.77	8.70 ± 2.84	$P = 0.198$
Interleukin-6 (pg/mL)	53.0 ± 12.9	49.5 ± 4.3	$P = 0.846$

Values are means ± SEM.

TABLE 5. Serum Concentrations of Hormones and Biochemical Bone Metabolism Markers in Patients Subjected to Total Gastrectomy (GX Group) at the Baseline and 1 Yr After the Surgical Procedure

Investigated Parameter	Baseline	1 Yr After Surgical Procedure	*P* Value
Insulin (μg/L)	2.36 ± 0.69	1.99 ± 0.78	$P = 0.755$
Insulin-like growth factor I (μg/L)	70.0 ± 13.2	70.5 ± 9.5	$P = 0.979$
Thyroxine (μg/dL)	9.78 ± 3.15	11.97 ± 4.34	$P = 0.761$
Bone-specific alkaline phosphatase (μg/L)	21.76 ± 3.40	24.76 ± 3.43	$P = 0.583$
Osteocalcin (ng/mL)	6.03 ± 0.89	8.34 ± 0.93	$P = 0.135$
C-terminal propeptide of type I collagen (ng/mL)	10.46 ± 1.81	9.64 ± 0.86	$P = 0.718$
Deoxypyridinoline (nmol/L)	6.20 ± 0.18	7.04 ± 0.23*	$P = 0.024$
Pyridinoline (nmol/L)	11.69 ± 11.07	15.45 ± 0.78*	$P = 0.027$
C-terminal telopeptides of type I collagen (ng/mL)	0.488 ± 0.098	1.081 ± 0.116*	$P = 0.005$
C-terminal telopeptides of type II collagen (pg/mL)	288 ± 212	248 ± 198	$P = 0.907$
Interleukin-6 (pg/mL)	41.5 ± 11.6	61.6 ± 4.3	$P = 0.261$

Values are means ± SEM.
* Statistically significant differences versus baseline for $P < 0.05$ by paired Student *t* test.

metabolism changes occurring in both the gastrectomized and control group of patients. In the current study, it was shown that the most dramatic changes of vBMD occur in the trabecular bone compartments on all 4 levels of lumbar spine where the 1-year bone loss was assessed between 11.8% and 16.8%. Less negative consequences of total gastrectomy on vBMD to these observed in the trabecular bone were found in the compact bone compartments of the lumbar spine. It was revealed that significant changes of vBMD (−9.0% to −10.0% decrease) after 1 year since the gastrectomy have occurred in L_1 and L_2; however, similar tendencies were observed for L_3 (−4.0%) and L_4 (−6.0%) or for whole lumbar spine segment (−7.2%). As contrary to the gastrectomized group of patients, neither the trabecular bone nor the cortical bone compartments of lumbar vertebrae in the controls were characterized by the decreased values of vBMD during this 1-year period. The results of vBMD evaluation in the GX group of patients have proved dynamic osteoporosis progress during the first year since the gastric resection, indicating an importance for treatment intervention in gastrectomized patients during this critical period of bone tissue metabolism acceleration. An additional evidence of these findings is provided by the results of T-score and Z-score analysis. It was shown that in the gastrectomized patients, T-score and Z-score values have decreased significantly from −3.16 and −0.80 to −3.68 and −1.24, respectively. Such negative changes of vBMD were not observed in the control group of patients where both these parameters have remained unaffected. As opposite to the results obtained in the current studies, earlier investigations on Korean population have revealed different rates of mean bone loss in lumbar spine (−5.7%), total hip (−5.4%), femoral neck (−6.6%), and trochanter (−8.7%) during 1 year after gastrectomy, which was expressed as the percentage change from the baseline.[20] The difference in the scale of bone tissue loss within lumbar spine observed in the previous and the current studies may result from different densitometric techniques. As opposed to the current study, where vBMD was evaluated separately for trabecular and cortical bone compartments with the use of quantitative computed tomography, the previous trial on Korean patients was performed with the use of dual-energy X-ray absorptiometry (DEXA) technique. In contrast to the DEXA method, which enables areal determination of the bone mineral density (expressed in g/cm^2), QCT allows volumetric analysis of trabecular and cortical bone density (expressed in g/cm^3) independently of one another. Another advantage of QCT method for the determination of vBMD, in comparison with the DEXA method, is the fact that with the use of this method, vBMD can be easily measured without errors resulting from surrounding soft tissues and possible osteoarthritic changes such as osteophytes.[21,22] The observed discrepancy in bone loss rate during 1 year after the gastrectomy in both studies may also result from ethnic divergences between Caucasian and Asian populations in terms of physiological differences in bone metabolism rate and skeletal system characteristics. Moreover, the previous study was performed on both men and women and sex-related effects on bone loss rate cannot be excluded.[20] In other DEXA-based studies in postgastrectomy patients (USA population), bone loss expressed as a decrease of bone mineral density (BMD) has reached in lumbar spine −14.1%, total hip −9.0%, and distal radius −9.9%. However, BMD measurements in that study were performed in men between 60 and 92 years of life with mean age of 71.5 years. Thus, a difference of nearly 15 years in age of the patients included to both the follow-ups may have consequences for BMD assessments.[23] In studies with obese women (mean age, 40.4 years) subjected to laparoscopic sleeve gastrectomy, BMD values measured 6 months after the operation by the DEXA method in spine, femoral neck, and total hip were significantly decreased by 1.3%, 7.2%, and 5.7%, respectively, when compared with the baseline values collected before the gastric surgery. Analogous results were obtained in those studies comparing T-sore and Z-score values before and half year after the sleeve gastrectomy.[24] It is worth underlining that the decrease in trabecular and cortical bone density is 2% to 4% and 1% to 2% per year, respectively, during the rapid phase of postmenopausal bone loss. Furthermore, age-related bone loss rate in humans was assessed on 0.5% to 0.75% per year that corresponds to the insignificant changes of vBMD observed in the control group of patients enrolled to the current study.[20] The results obtained in the current study are in accordance with other studies on animals in which gastrectomy was shown to induce osteopenia in femur and lumbar vertebrae of female rats at a degree similar or greater than that by ovariectomy.[14] The amount of bone loss after gastrectomy is comparable to that which occurs after solid organ and bone marrow

transplantation.[25] In studies on gastric bypass surgery for morbid obesity, the rates of bone loss of 3.3% at lumbar spine and 7.8% at the total hip after 9 months following gastric surgery were seen.[26] The results obtained in this study are also in accordance with the previous investigations on pigs, where the values of vBMD measured for the trabecular and cortical bone compartments of humerus were decreased by 13.3% and 11.8%, respectively after 7 months since the fundectomy. Furthermore, the results obtained in pigs have shown that the fundectomy decreased the calcium hydroxyapatite density in the trabecular and the cortical bone compartments by 38.7% and 44.7%, respectively. However, the difference between the previous and the current study with adult patients is that the experiment on pigs was performed on growing animals at very intensive period of skeletal development.[8]

Biochemical analyses of serum in the GX group of patients after 1 year since the total gastrectomy have revealed significantly increased levels of all the evaluated bone resorption markers such as deoxypyridinoline, pyridinoline, and C-terminal telopeptides of type I collagen by 13.5%, 32.2%, and 121.5%, respectively, when compared with the baseline values. The biochemical marker of cartilage degradation (C-terminal telopeptide of type II collagen) in these patients was not influenced significantly within the period of 1 year since the total gastrectomy. Noteworthy is the fact that the concentration of CTX-II in gastric cancer patients was nearly 13 and 29 times higher at the beginning and the termination of the study when compared with the values measured in serum of the control patients, respectively. It suggests that the neoplastic disease course may be associated with intensive degradation of cartilage tissue. However, this issue needs further studies to be better explained. In the GX group of patients, all the evaluated bone formation markers (BAP, OC, and CICP) in serum were on similar levels at the baseline and 1 year later, indicating lack of effects of the gastrectomy procedure on bone formation rate. Furthermore, long-term effects of the gastrectomy on serum concentration of insulin, IGF-I, tyroxine, and IL-6 in the GX group of patients were not observed in this study, suggesting that all these factors do not participate in the mechanisms responsible for gastrectomy-induced osteoporosis in humans. Results of the biochemical analyses of serum in the control group of patients have shown that neither the hormones nor biochemical bone metabolism indices were influenced by abdominal surgery due to cardiospasmus. The results of biochemical analyses performed in the current study are in accordance with the results reported by Baek and colleagues in which bone formation markers were evaluated. It was shown that serum concentrations of carboxyterminal telopeptide of type I collagen (ICTP) and OC were not significantly different after 1 year from the gastrectomy for gastric adenocarcinoma. However, ICTP was found to be increased in patients at 1, 3, and 6 months since the gastrectomy in comparison to pregastrectomy measurements. Osteocalcin was increased in those patients only 6 months after the gastrectomy when compared with the baseline values.[20] In other studies in humans, it was shown that serum concentrations of osteocalcin and BAP activity were found to be significantly increased in gastrectomized patients (total gastrectomy 5–20 years prior to the measurements) in comparison to age- and sex-matched controls. These effects were combined with elevated serum parathyroid hormone (PTH) level, decreased serum calcium concentration, and osteoporosis occurrence.[11] Similar findings were reported by Glatzle et al. in studies on humans in which total gastrectomy induced increased serum BAP, alkaline phosphatase, and PTH concentrations associated with osteopenia and osteoporosis in lumbar spine.[27] The results of the IGF-I evaluation in the current study are in accordance with other reports where BMD and IGF-I were compared a year after Roux-en-Y gastric bypass and sleeve gastrectomy in women. It was shown in those studies that the applied operation technique has no effects on BMD of femoral neck and lumbar spine and IGF-I concentration in serum. Moreover, no differences of serum concentrations of IFG-I before operation and a year after the bariatric surgery were observed in women with both normal and low (≤ -1 SD) BMD.[28] Contrary to the current findings, results obtained in growing fundectomized pigs have revealed that severe osteopenia in humerus and lumbar spine was associated with significantly decreased serum concentration of IGF-I by 54.6% in comparison with sham-operated, sex-, and age-matched controls. Moreover, the performed fundectomy in pigs decreased serum ghrelin and growth hormone concentrations by 74.4% and 90.6%, respectively, indicating disturbed GHPA function as the causative factor for severe osteopenia development in growing animals.[8]

In previous studies focused on evaluation of bone resorption markers in patients subjected to gastrectomy, it was shown that urine concentration of DPD increases as the consequence of the gastrointestinal surgery that corresponds to the results obtained in the current follow-up. However, contrary to our measurements, in the previous studies DPD in urine of patients was evaluated 1 and 14 days after the surgery.[29] In other study on humans, the comparison of plasma concentration of CTX-I in gastrectomized patients (mean age 41.2 years and mean time between gastric surgery and study 6.7 years) and healthy controls has revealed its significantly higher concentration as the consequence of total gastrectomy procedure, while the bone formation marker–procollagen type I N-terminal propeptide (PINP), ghrelin, and growth hormone concentrations were similar in both groups of patients.[30] The data reported by Huda et al. and the results obtained in the current study together with previous experiments on pigs indicate the difference in pathogenesis of gasterectomy-induced osteopenia/osteoporosis in growing and matured organism. While disturbances of the function of the GHPA in growing mammals contribute significantly to the osteopenia/osteoporosis development, the observed unchanged serum concentrations of ghrelin, growth hormone, and IGF-I in gastrectomized patients indicate lack of participation of the GHPA in pathomechanisms responsible for postgastrectomy osteopenia and osteoporosis.[8,30] In another long-term study on biochemical bone metabolism markers in obese individuals undergoing laparoscopic sleeve gastrectomy, it was reported that serum level of a bone resorption marker, collagen type I cross-linked N-telopeptide (NTX), was significantly increased 2 years after the surgery in comparison with preoperative values. Contrary to NTX, serum concentrations of BAP, calcium, PTH, and 25-hydroxyvitamin D were not different from baseline values after 1, 2, and 3 years from the laparoscopic sleeve gastrectomy.[31] Moreover, urine NTX concentration was found to be increased by 123% after 12 months since the gastric surgery in morbidly obese women between 18 and 55 years of age subjected to laparoscopic sleeve gastrectomy and Roux-en-Y gastric bypass.[32]

CONCLUSIONS

In conclusion, this study has shown that total gastrectomy induced significant bone loss in patients during the first year after the operation, which was expressed by significantly decreased values of vBMD up to 16.8% and 10.0% within

the trabecular and cortical bone compartments of lumbar spine. These negative changes of vBMD were associated with significantly accelerated bone tissue resorption. Neither vBMD nor the biochemical bone resorption and formation markers were influenced in control group of patients. Dramatic bone loss in the GX group has proven dynamic osteoporosis progress during the first year from the gastric resection indicating an importance for treatment intervention in these patients during this critical period with emphasis on inhibition of bone resorption processes. Lack of effect of gastrectomy on serum IGF-I concentration indicates different pathomechanisms of osteoporosis development in adult patients than disturbances of the GHPA function reported previously in growing animals.

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