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The association between weight change after gastric cancer surgery and type 2 diabetes risk: A nationwide cohort study

Yeongkeun Kwon[1,2,3], Jane Ha[4], Dohyang Kim[5], Jinseub Hwang[5], Shin-Hoo Park[1,2,3], Jin-Won Kwon[6]* & Sungsoo Park[1,2,3]*

[1]*Division of Foregut Surgery, Korea University College of Medicine, Seoul, South Korea;* [2]*Center for Obesity and Metabolic Diseases, Korea University Anam Hospital, Seoul, South Korea;* [3]*Gut & Metabolism Laboratory, Korea University College of Medicine, Seoul, South Korea;* [4]*Clinical and Translational Epidemiology Unit, Massachusetts General Hospital, Boston, MA, United States;* [5]*Department of Statistics, Daegu University, Gyeongsan, South Korea;* [6]*BK21 FOUR Community-Based Intelligent Novel Drug Discovery Education Unit, College of Pharmacy and Research Institute of Pharmaceutical Sciences, Kyungpook National University, Daegu, South Korea*

Abstract

Background Although gastric cancer patients generally experience drastic weight decrease post-gastrectomy, the impact of weight decrease on type 2 diabetes risk remains unclear. We investigated the type 2 diabetes risk after gastric cancer surgery according to postoperative weight decrease in gastric cancer survivors in South Korea, the country with the world's highest rate of gastric cancer survival.

Methods This retrospective nationwide cohort study included gastric cancer surgery recipients between 2004 and 2014 who survived for ≥5 years post-surgery. We included patients without a history of diabetes at the time of surgery and those who had not received adjuvant chemotherapy before or after the surgery. Postoperative weight loss was defined as the per cent body weight loss at 3 years post-surgery compared with the baseline. The type 2 diabetes risk was evaluated using Cox regression analyses for five groups of postoperative weight decrease.

Results In 5618 included gastric cancer surgery recipients (mean age, 55.7 [standard deviation, SD, 10.9] years; 21.9% female; mean body mass index, 23.7 [SD, 2.9] kg/m^2), 331 patients (5.9%) developed postoperative type 2 diabetes during follow-up duration of 8.1 years (median; interquartile range, 4.8 years; maximum, 15.2 years). Compared with those who gained weight post-surgery, patients with $\geq -15\%$ to $< -10\%$ of postoperative weight decrease (hazard ratio, 0.65; 95% confidence interval, 0.49–0.87; $P = 0.004$) had the lowest type 2 diabetes risk. A non-linear association occurred between postoperative weight decrease and the type 2 diabetes risk in gastrectomy recipients (Akaike's information criterion [AIC] for non-linear model, 5423.52; AIC for linear model, 5425.61).

Conclusions A U-shaped non-linear association occurred between the type 2 diabetes risk and postoperative weight decrease in gastric cancer survivors who underwent gastrectomy. The lowest type 2 diabetes risk occurred in patients with $\geq -15\%$ to $< -10\%$ of postoperative weight decrease at 3 years.

Keywords gastrectomy; gastric cancer; type 2 diabetes; weight loss

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**Correspondence to: Jin-Won Kwon, BK21 FOUR Community-Based Intelligent Novel Drug Discovery Education Unit, College of Pharmacy and Research Institute of Pharmaceutical Sciences, Kyungpook National University, 80, Daehakro, Bukgu, Daegu 41566, South Korea. Email: jwkwon@knu.ac.kr;*
Sungsoo Park, Center for Obesity and Metabolic Diseases, Korea University Anam Hospital, Division of Foregut Surgery, Korea University College of Medicine, 73, Goryeodae-ro, Seongbuk-gu, Seoul 02841, South Korea. Email: kugspss@korea.ac.kr
Yeongkeun Kwon and Jane Ha equally contributed to this work.

Introduction

The development of various types of cancer is associated with an increased risk of type 2 diabetes.[1] Gastric cancer patients have a 35% increased risk of developing type 2 diabetes,[1] which contributes to higher mortality in gastric cancer survivors.[2] Five-year survival rate of gastric cancer has drastically increased—from 12% in the 1950s to 28% in the 2010s in the United States[3] and from 44% in the early 1990s to 77% in the late 2010s in South Korea[4,5]—and gastric cancer survivor care has highlighted improvement in non-cancer mortality as well as cancer mortality. Gastric cancer survivors have a higher likelihood of dying from non-cancer causes compared with other cancers, and type 2 diabetes is one of the major non-cancer causes of death.[6] Therefore, guidance in lifestyle management (e.g., weight recommendation) after gastric cancer surgery to prevent type 2 diabetes is imperative in terms of gastric cancer survivor care.

Patients undergoing gastrectomy for cancer have distinct characteristics of glucose homeostasis. First, gastric cancer surgery recipients experience postoperative weight loss due to the combined effect of altered food intake, nutritional malabsorption and systemic endocrinologic changes due to altered foregut anatomy.[7,8] Postoperative weight decrease is pronounced until the first 6 months after the surgery, as the patients generally lose 5–15% of their baseline weight; subsequently, the body weight stabilizes or changes even after 12 months or more post-surgery.[9,10] In the general population, intentional weight loss was associated with a reduced risk of type 2 diabetes.[11] There is a paucity of literature investigating the impact of unintentional weight loss after gastric cancer surgery on the risk of type 2 diabetes in gastric cancer survivors.

Second, previous studies have underlined improvements in glycaemic control after gastric cancer surgery in type 2 diabetes patients. Approximately 25% of patients with comorbid type 2 diabetes undergoing gastric cancer surgery experience type 2 diabetes remission, defined as normoglycaemia without hypoglycaemic drugs, within 2 years post-surgery, more than half of whom did not develop type 2 diabetes for more than 4 years.[12] These beneficial effects of gastric cancer surgery on type 2 diabetes are considered attributable to modified foregut physiology following gastrectomy, resulting in reduced nutritional intake and absorption, weight loss, and alteration in gastric hormones related to glucose homeostasis.[13–15] Modifying the course of type 2 diabetes, even leading to remission, is characteristic of gastric cancer surgery and is distinctive from other gastrointestinal cancer surgeries.

Therefore, we investigated (1) the impact of weight decrease, following gastrectomy for gastric cancer, on the risk of type 2 diabetes, and (2) optimal postoperative weight goal to minimize the risk of type 2 diabetes in gastric cancer survivors undergoing gastrectomy. We used a nationwide population-based cohort in South Korea, the country with the world's highest rate of gastric cancer survival.[5]

Materials and methods

Data source and study population

The National Health Insurance Service (NHIS) is a single insurer managed by the Korean government. The NHIS manages a mandatory universal insurance system that covers the entire Korean population (97% via the health insurance system and 3% via medical aid). Therefore, the NHIS maintains representative population-based cohort data, including a claims database containing medical information of the entire Korean population based on insurance claims (e.g., patient demographics, disease diagnoses, medical treatments and procedures). The NHIS database was described extensively in a previous study.[16]

The NHIS provides biannual health check-ups for all insured Koreans aged ≥40 years. Among patients who underwent gastrectomy for cancer between 2004 and 2014, 47 032 who underwent health check-ups within 2 years pre-surgery and 4 years post-surgery were identified using the International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) codes for total gastrectomy (Q2533–Q2537, QA533, QA535 and QA536) or subtotal gastrectomy (Q0251–Q0259, Q2594, Q2595, Q2597, Q2598, QA595, QA597 and QA598), and gastric cancer (C16) (Supporting Information, *Figure S1*).

The following patients were excluded: those with pre-existing diabetes (*n* = 12 141; with ICD-10-CM codes [E11–E14] or antidiabetic medication) within 2 years prior to surgery; those who had fasting plasma glucose (FPG) level ≥ 125 mg/dL (*n* = 1301); those who died within 5 years post-surgery (*n* = 3430); those with a history of cancer other than gastric cancer (*n* = 12 442); those who received adjuvant chemotherapy 6 months before or after gastrectomy (*n* = 3946); those who developed type 2 diabetes within 3 years after gastrectomy (*n* = 7022); and those with any missing variables (*n* = 1132). Eventually, 5618 patients were enrolled and evaluated for type 2 diabetes development after surgery according to postoperative weight decrease. This study was approved by the institutional review board (No. 2019AN0156), which waived the requirement for informed consent because the customized database was released after de-identification and anonymization.

Weight decrease after gastrectomy for gastric cancer

We used postoperative weight measured at 3 years (±6 months) after gastrectomy for cancer, as it has been re-

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ported that body weight stabilizes ~2–3 years after gastric cancer surgery following drastic weight changes occurring within 1 year post-surgery.[9,10] The lowest weight was selected when it was measured more than once. Postoperative weight decrease (in percentage) was defined as [postoperative weight at 3 years (±6 months) − baseline weight]/baseline weight × 100.

Primary outcome

The primary outcome was the incidence of type 2 diabetes after 3-year weight decrease following gastrectomy for cancer. Type 2 diabetes was defined as a combination of antidiabetic medications use and ICD-10-CM codes E11–E14. Patients were followed up until the date of diagnosis of type 2 diabetes or until 31 December 2017 depending on which one occurred earlier.

Clinical variables

A standardized self-report questionnaire was used to obtain demographic and lifestyle data. Smoking status was categorized as never, former or current smoker. Individuals who consumed ≥30 and <30 g of alcohol per day were considered heavy and mild drinkers, respectively. Exercise was recorded as days of moderate-to-vigorous physical activity for more than 20–30 min/week (none, 1–4 times per week and ≥5 times per week). A low-income status was defined as a lower 30% level. The FPG was measured after an overnight fast. Blood pressure was measured after at least 10 min of rest in the sitting position and was repeated if the initial measurement was >120/80 mmHg. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in metres, and obesity was defined as BMI ≥ 25 kg/m^2 according to the Asia-Pacific criteria of the WHO guidelines.[17] Hospitals in which these health examinations were performed were certified by the NHIS and subjected to regular quality control. Baseline comorbidities (hypertension, dyslipidaemia, coronary artery disease, stroke, dementia and end-stage renal disease) were defined using the combinations of ICD-10-CM diagnosis, prescription codes or laboratory results. Detailed definitions of the comorbidities are presented in Supporting Information, *Table S1*.

Statistical analysis

Summary data were presented as frequencies with percentages for categorical variables and means with standard deviations (SDs) for continuous variables and compared between postoperative weight decrease quintiles using one-way analysis of variance (ANOVA) test for continuous variables and chi-square test for categorical variables. Patients were stratified into five categories based on their weight decrease (< −15%, ≥ −15% to < −10%, ≥ −10% to < −5%, ≥ −5% to <0%, and ≥0%), considering that the median postoperative weight change was −7.5%. The incidence rate of type 2 diabetes was calculated by dividing the number of incident type 2 diabetes cases by the total follow-up duration (person-years), and hazard ratios (HRs) and 95% confidence intervals (95% CIs) were estimated using multivariate Cox regression analyses for five groups of postoperative weight decrease. The Cox model was adjusted for age, sex, BMI, systolic blood pressure, FPG, smoking status, alcohol consumption, exercise, income status, surgical procedures (total or subtotal gastrectomy) and comorbidities (hypertension, dyslipidaemia, coronary artery disease, stroke, dementia and end-stage renal disease). Given the competing risks of type 2 diabetes and death in patients undergoing gastrectomy for cancer, a competing risk regression model was considered using the Fine and Gray method.[18] Sensitivity analysis, to avoid the potential effects of reverse causality, was performed after washout type 2 diabetes within 2 years following 3-year weight decrease after gastrectomy for cancer. Furthermore, we sought to explore the association between baseline BMI and type 2 diabetes after gastrectomy for cancer. Patients were stratified into the following categories based on their baseline BMI per definition of underweight, overweight and obesity applied for East Asians: <18.5 kg/m^2, ≥18.5 to <23 kg/m^2, ≥23 to <25 kg/m^2, ≥25 to <30 kg/m^2, and ≥30 kg/m^2.

Because of the possible non-linear association between postoperative weight decrease and the risk of type 2 diabetes identified from Cox regression analyses, we conducted restricted cubic spline regression using three knots placed at the 25th, 50th and 75th percentiles to develop HR curves with postoperative weight decrease as a continuous variable. Akaike's information criterion (AIC) was adopted to compare the linear or non-linear model's fit.[19] Subgroup analyses were performed to assess whether the association of postoperative weight decrease and type 2 diabetes after gastrectomy for cancer varied among different baseline BMIs (≥18.5 to <23 kg/m^2, ≥23 to <25 kg/m^2, and ≥25 kg/m^2), age groups (<65 and ≥65 years) and surgical procedures (subtotal and total gastrectomy). We also analysed the association between BMI after gastric cancer surgery and the risk of postoperative type 2 diabetes. Patients were stratified into five groups according to postoperative BMIs measured 3 years after surgery: <18.5 kg/m^2, ≥18.5 to <23 kg/m^2, ≥23 to <25 kg/m^2, and ≥25 kg/m^2. After identifying significantly low risk of type 2 diabetes in patients with normal BMI measured 3 years after surgery, we performed an additional sensitivity analysis with this population for the association between postoperative weight decrease and the risk of type 2 diabetes. The a priori level of statistical significance was set at $P < 0.05$. All analyses were two-tailed and were performed using SAS software Version 9.3 (SAS Institute Inc., Cary, NC, USA).

Results

Baseline characteristics

The mean age of the study population was 55.7 (SD, 10.9) years, 21.9% were female, the mean baseline BMI was 23.7 (SD, 2.9) kg/m^2, the mean baseline FPG level was 92.7 (SD, 11.5) mg/dL, and 86.1% of patients underwent subtotal gastrectomy for cancer. Baseline characteristics categorized by postoperative weight decrease are presented in *Table 1*. Patients with excessive postoperative weight decrease were more likely to have higher baseline BMI and higher blood pressure, to have never smoked, to not be heavy drinkers and to not perform moderate-to-vigorous exercise. Additionally, patients with excessive postoperative weight decrease were more likely to have undergone total gastrectomy and to have hypertension, dyslipidaemia and end-stage renal disease. The most excessive postoperative weight decrease category (≤ −15%) had the highest proportion of females, were more likely to be older and had the highest mean baseline FPG levels.

Type 2 diabetes risk after gastric cancer surgery according to postoperative weight decrease

There were 331 cases of type 2 diabetes (5.9%) during the follow-up period (median, 8.1 years; interquartile range, 4.8 years; maximum, 15.2 years). Compared with patients who gained weight at 3 years after gastrectomy for cancer (postoperative weight change ≥ 0%), those who had postoperative weight decrease of ≥ −15% to < −10% (HR, 0.68; 95% CI, 0.51–0.89; *P* = 0.005) and ≥ −10% to < −5% (HR, 0.65; 95% CI, 0.49–0.87; *P* = 0.004) had a significantly lower risk of type 2 diabetes after gastrectomy for cancer after full adjustment for covariates (*Table 2*). In the sensitivity analysis after washout incident type 2 diabetes within 2 years following 3-year weight decrease after gastrectomy for cancer, the significance of the original outcome was maintained (*Table S2*).

Table 1 Baseline characteristics

Variables	Weight decrease after gastric cancer surgery (%) < −15% (*n* = 886)	≥ −15% to < −10% (*n* = 1389)	≥ −10% to < −5% (*n* = 1544)	≥ −5% to <0% (*n* = 1103)	≥0% (*n* = 696)	*P* value
Age (years), mean (SD)	56.2 (11.6)	55.9 (10.6)	55.2 (10.4)	55.5 (10.9)	55.7 (11.2)	0.235
Female sex, *n* (%)	250 (28.2)	295 (21.2)	308 (20.0)	224 (20.3)	154 (22.1)	<0.0001
BMI, kg/m^2, mean (SD)	25.0 (3.0)	24.1 (2.5)	23.6 (2.6)	23.0 (2.7)	22.0 (2.9)	<0.0001
BMI ≥ 25 kg/m^2, *n* (%)	427 (48.2)	485 (34.9)	472 (30.6)	268 (24.3)	112 (16.1)	<0.0001
Systolic blood pressure, mmHg, mean (SD)	126.2 (15.1)	125.5 (15.7)	124.4 (14.9)	124.0 (15.0)	121.5 (16.0)	<0.0001
Diastolic blood pressure, mmHg, mean (SD)	78.8 (9.8)	78.6 (10.4)	78.1 (10.0)	77.5 (10.0)	76.0 (10.6)	<0.0001
FPG, mg/dL, mean (SD)	93.4 (11.7)	92.8 (11.1)	92.9 (11.6)	92.5 (11.7)	91.3 (11.1)	0.007
FPG (100–125 mg/dL), *n* (%)	261 (29.5)	357 (25.7)	424 (27.5)	299 (27.1)	155 (22.3)	0.019
Smoking status, *n* (%)						
Never	479 (54.1)	679 (48.9)	696 (45.1)	475 (43.1)	293 (42.1)	<0.0001
Former	196 (22.1)	329 (23.7)	314 (20.3)	181 (16.4)	69 (9.9)	
Current	211 (23.8)	381 (27.4)	534 (34.6)	447 (40.5)	334 (48.0)	
Alcohol consumption, *n* (%)						
Non-user	519 (58.6)	739 (53.2)	775 (50.2)	556 (50.4)	334 (48.0)	<0.0001
Mild drinker	292 (33.0)	487 (35.1)	583 (37.8)	390 (35.4)	251 (36.1)	
Heavy drinker	75 (8.5)	163 (11.7)	186 (12.1)	157 (14.2)	111 (16.0)	
Moderate-to-vigorous exercise, *n* (%)						
None	519 (58.6)	739 (53.2)	775 (50.2)	556 (50.4)	334 (48.0)	<0.0001
1–4 times per week	292 (33.0)	487 (35.1)	583 (37.8)	390 (35.4)	251 (36.1)	
≥5 times per week	75 (8.5)	163 (11.7)	186 (12.1)	157 (14.2)	111 (16.0)	
Low income, *n* (%)	106 (12.0)	169 (12.2)	182 (11.8)	130 (11.8)	91 (13.1)	0.926
Surgical procedures, *n* (%)						
Total gastrectomy	245 (27.7)	229 (16.5)	183 (11.9)	76 (6.9)	48 (6.9)	<0.0001
Subtotal gastrectomy	641 (72.4)	1160 (83.5)	1361 (88.2)	1027 (93.1)	648 (93.1)	
Comorbidities, *n* (%)						
Hypertension	251 (28.3)	343 (24.7)	367 (23.8)	259 (23.5)	152 (21.8)	0.029
Dyslipidaemia	244 (27.5)	333 (24.0)	352 (22.8)	249 (22.6)	152 (21.8)	0.039
Coronary artery disease	19 (2.1)	28 (2.0)	30 (1.9)	29 (2.6)	13 (1.9)	0.753
Stroke	45 (5.1)	63 (4.5)	62 (4.0)	35 (3.2)	24 (3.5)	0.195
Dementia	6 (0.7)	6 (0.4)	3 (0.2)	3 (0.3)	4 (0.6)	0.348
End-stage renal disease	8 (0.9)	7 (0.5)	2 (0.1)	2 (0.2)	2 (0.3)	0.026

Note: Postoperative weight decrease was defined as the per cent body weight loss at 3 years post-surgery compared with the baseline. Abbreviations: BMI, body mass index; FPG, fasting plasma glucose; SD, standard deviation.

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Table 2 Type 2 diabetes risk after gastric cancer surgery according to postoperative weight decrease, and baseline body mass index

Categories	Total (*n*)	Event (%)	Person-years	Incidence rate	Adjusted hazard ratios (95% confidence intervals)	*P* value
Postoperative weight decrease (%)						
≥0	696	50 (7.2)	5815	8.60	[Reference]	
≥ −5 to <0	1103	84 (7.6)	9140	9.19	0.90 (0.69–1.18)	0.483
≥ −10 to < −5	1544	73 (4.7)	12 653	5.77	0.68 (0.51–0.89)	0.005
≥ −15 to < −10	1389	62 (4.5)	11 465	5.41	0.65 (0.49–0.87)	0.004
< −15	886	62 (7.0)	7275	8.52	0.89 (0.66–1.20)	0.451
Baseline body mass index (kg/m^2)						
<18.5	131	5 (3.8)	1053	4.75	1.32 (0.84–2.06)	0.221
≥18.5 to <23	2158	116 (5.4)	17 693	6.56	[Reference]	
≥23 to <25	1565	88 (5.6)	13 083	6.73	0.91 (0.74–1.12)	0.382
≥25 to <30	1650	112 (6.8)	13 620	8.22	0.97 (0.79–1.19)	0.804
≥30	114	10 (8.8)	900	11.11	1.06 (0.60–1.86)	0.838

Note: Postoperative weight decrease was defined as the per cent body weight loss at 3 years post-surgery compared with the baseline.

Type 2 diabetes risk after gastric cancer surgery according to baseline weight status

When the adjusted risk of type 2 diabetes was evaluated according to baseline BMI quintiles, no baseline BMI interval was significantly associated with the risk of type 2 diabetes after gastrectomy for cancer, compared with normal weight (BMI ≥ 18.5 to <23 kg/m^2) (*Table 2*).

Non-linear association between weight decrease following gastric cancer surgery and type 2 diabetes risk

Given that (1) the HR of type 2 diabetes development after gastric cancer surgery was lowest in patients with postoperative weight decrease of ≥ −15% to < −10% and (2) HR increased with excessive (< −15%) or small postoperative weight decrease (≥ −10%), a cubic spline plot was generated to visualize the association between postoperative weight decrease and type 2 diabetes risk, and a characteristic U-shaped association was observed (*Figure 1*). The non-linear model was superior to that of the linear model (AIC for non-linear model, 5423.52; AIC for linear model, 5425.61). Type 2 diabetes risk after gastric cancer surgery was higher for both with excessive postoperative weight decrease and with small weight decrease with the nadir of the U-shaped curve around postoperative weight decrease of −15%.

Subgroup analyses

A non-linear association was observed across all subgroups according to baseline BMI, and no significant interaction was identified (*Figure 1*); significant effect modification and variations in the shapes of the cubic spline plot were observed in subgroups of ≥65 years ($P < 0.0001$) and total gastrectomy recipients ($P < 0.0001$) (*Figure 2*). The protective effect of postoperative weight decrease of ≥ −10% to < −5% on type 2 diabetes risk was pronounced in subtotal gastrectomy recipients. However, a significant association between type 2 diabetes risk and postoperative weight decrease was not observed in total gastrectomy recipients.

Effects of postoperative body mass index on the risk of type 2 diabetes after gastric cancer surgery

When patients were stratified according to their postoperative BMI measured 3 years after gastric cancer surgery, we observed that those with normal BMI (≥18.5 to <23 kg/m^2) had the lowest risk of incident type 2 diabetes after surgery (HR, 0.73, compared with patients with postoperative BMI lower than 18.5 kg/m^2; 95% CI, 0.57–0.94; P = 0.016) (*Table S3*). Furthermore, in the sensitivity analysis of patients with normal BMI 3 years after gastric cancer surgery, we consistently observed the lowest risk of type 2 diabetes in patients with postoperative weight decrease of ≥ −15% to < −10% (HR, 0.64; 95% CI, 0.41–0.96; *Table S4*) and a non-linear association between the postoperative weight decrease and the risk of type 2 diabetes following gastric cancer surgery (*Figure S2*).

Discussion

Cancer survivor care requires cancer-specific strategies considering the effects of diverse treatment modalities across different cancers in cancer survivors.[20] The foregut is known to be responsible for nutrient absorption and glucose metabolism,[21] and surgical modification of foregut anatomy induces metabolic changes in patients with gastric cancer.[12,15] In particular, weight trends after gastrectomy for gastric cancer follow a characteristic course; unintentional weight loss is induced by decrease in nutritional intake and anatomical modification of the foregut even after 12 months or more post-surgery.[9,10,22] In this study, we observed a non-

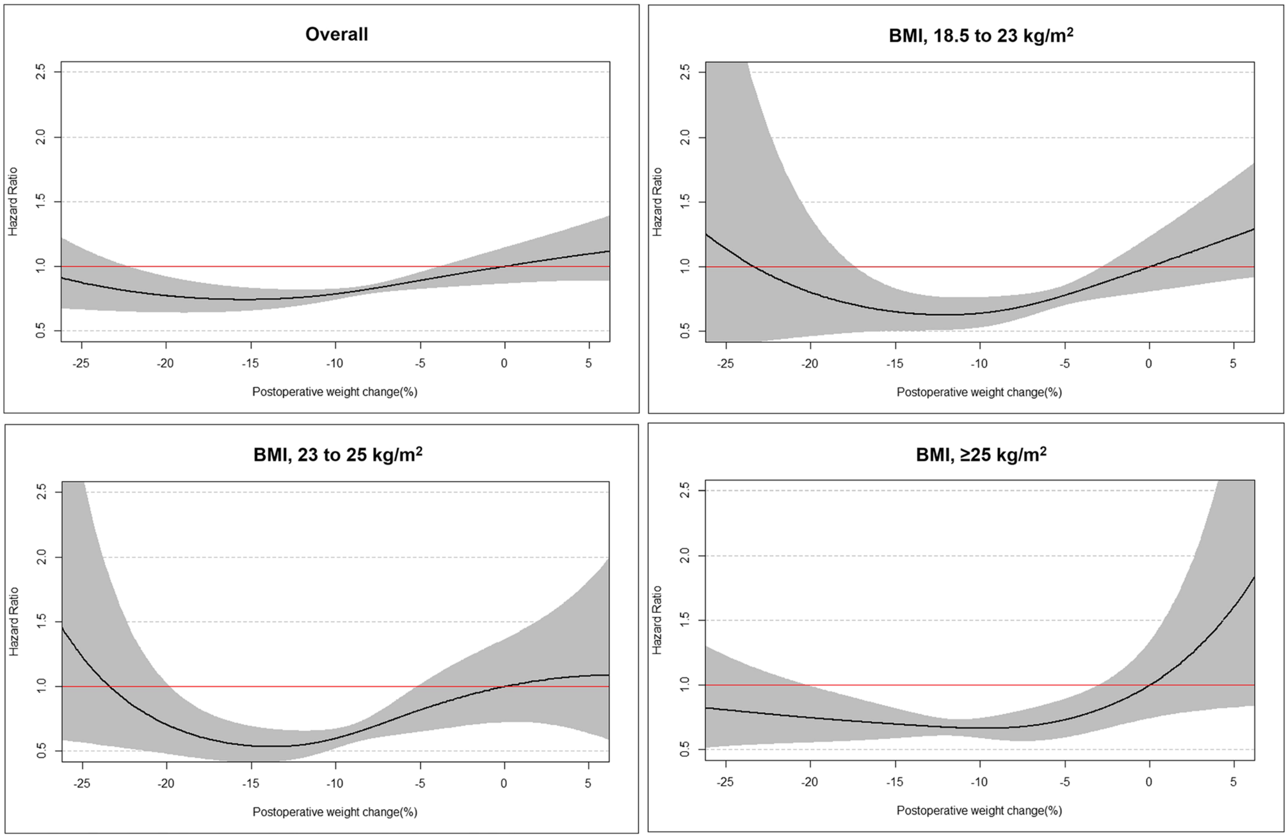

Figure 1 Cubic spline plot presenting the association between weight decrease following gastric cancer surgery and postoperative type 2 diabetes risk in gastric cancer survivors. Shaded areas represent 95% confidence intervals. BMI, body mass index.

linear U-shaped association between postoperative weight decrease and type 2 diabetes risk after gastrectomy for gastric cancer and identified that postoperative weight decrease of approximately −15% to −10% maximizes the preventive effect of type 2 diabetes. This association was maintained in the subgroup analysis according to the baseline BMI. This study (1) is the first to identify that weight decrease following gastric cancer surgery affects type 2 diabetes risk and (2) suggests the need for a type 2 diabetes prevention strategy customized for gastric cancer survivors by providing optimal weight decrease intervals.

We identified that the optimal weight decrease following gastrectomy for the prevention of type 2 diabetes in gastric cancer survivors is −15% to −10%. This finding not only provides evidence of the beneficial effects of postoperative weight decrease following gastric cancer surgery but also leads to a change in attitudes regarding weight decrease during postoperative management for patients and their healthcare professionals. Earlier, with the concept of cancer-related cachexia, involuntary weight decrease in cancer patients was perceived as a malnutrition condition that affects survival and quality of life and needed to be corrected.[23] Several studies have reported postoperative weight decrease as a risk factor for poor outcomes in patients undergoing gastric cancer surgery.[24,25] However, two subjects should be considered separately: (1) improving gastric cancer-related outcomes and (2) preventing chronic diseases in gastric cancer survivors. Considering that chemotherapy is administered to 94.4% of patients with stage II or III gastric cancer in Korea,[26] >95% of the investigated study population was thought to be constituted of patients with stage I gastric cancer, which shows a 5-year survival rate of >90% in South Korea. Our results regarding the optimal weight decrease interval for prevention of type 2 diabetes were investigated in gastric cancer survivors (and highly expected to be in early stages of cancer), which should be differentiated from the previous studies that investigated cancer-related outcomes in heterogeneous patients, including those with advanced stages of gastric cancer.

We found a specific interval of weight decrease that minimizes the risk of type 2 diabetes after gastric cancer surgery, which is distinct from previous studies on the association between the risk of type 2 diabetes and surgical or non-surgical weight loss interventions.[11,27] It is widely known that intentional weight loss has protective effects against incident type 2 diabetes. A study from the Diabetes Prevention Program Research Group showed that lifestyle modification targeting at least a 7% weight decrease reduced the risk of type 2 diabetes by 58% (95% CI, 4–66%).[11] Bariatric surgery, which is

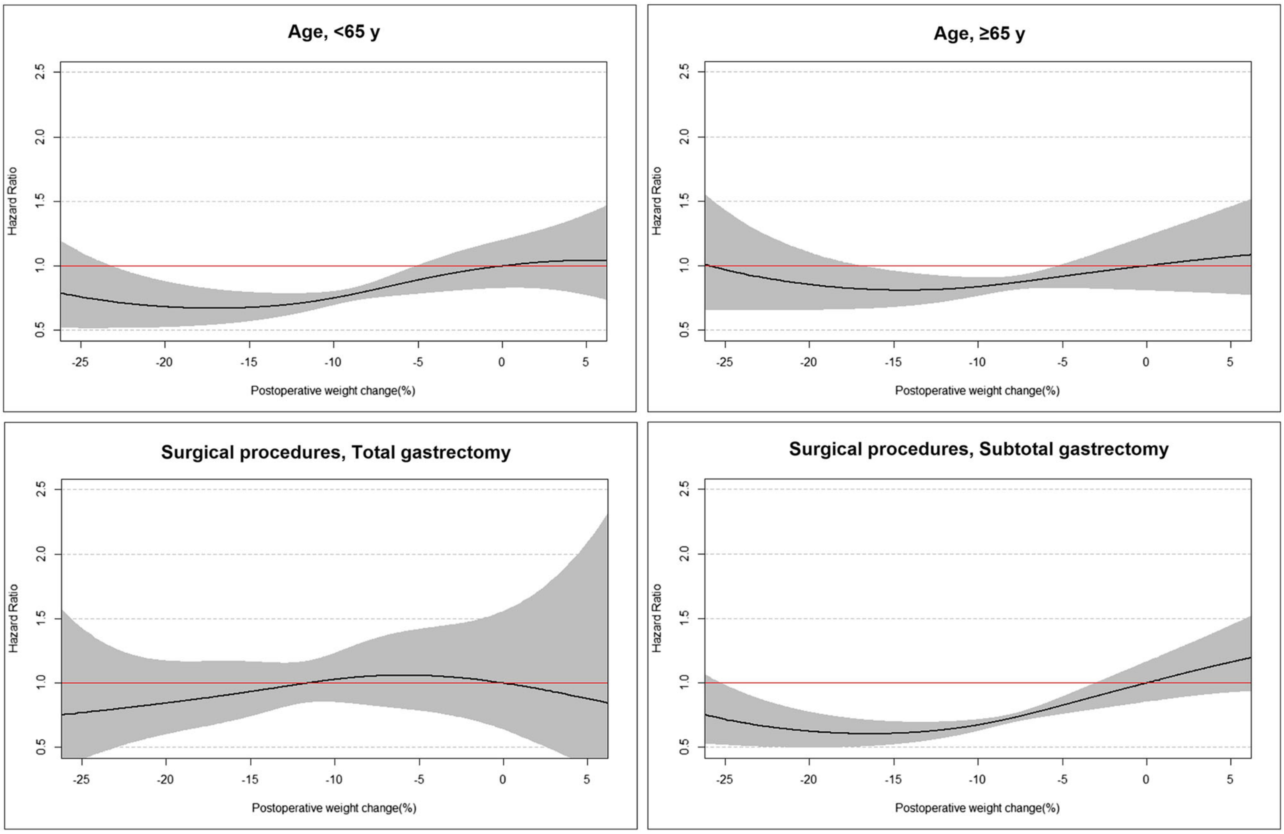

Figure 2 Subgroup analyses according to age and surgical procedures: The association between weight decrease following gastric cancer surgery and postoperative type 2 diabetes risk in gastric cancer survivors. Shaded areas represent 95% confidence intervals.

the most widely performed surgical weight loss intervention, has also been proven to reduce type 2 diabetes risk.[27] However, these studies cannot be directly applied to weight management in gastric cancer survivors to prevent type 2 diabetes, as we found that the optimal postoperative weight decrease is between −15% and −10%, and cannot explain the non-linear association between weight decrease after gastric cancer surgery and the risk of type 2 diabetes, which was characteristic in our research.

We highlighted the significance of postoperative weight change rather than one-point weight status measured before or after surgery as a predictor of type 2 diabetes. Baseline BMI has been discussed as a predictor of the remission and relapse of type 2 diabetes in patients undergoing gastric cancer surgery.[12,22] However, unlike the higher likelihood of type 2 diabetes remission in patients with higher BMI following gastric cancer surgery, we observed the protective effect of normal BMI on type 2 diabetes (*Table S3*). Furthermore, in a sensitivity analysis of patients with normal BMI after gastric cancer surgery, we found a U-shaped non-linear association between the postoperative weight change and the risk of type 2 diabetes (*Table S4* and *Figure S2*). We propose that a one-point body weight measurement cannot fully explain the risk of incident type 2 diabetes after gastric cancer surgery, and postoperative weight change needs to be considered.

This study highlighted the protective effect of weight decrease after gastric cancer surgery on incident type 2 diabetes in gastric cancer survivors, whereas a large portion of the mechanism remains unclear. A recent study observed that an increase in small bowel glucose utilization and white adipose tissue glycolysis, observed after gastric cancer surgery, was correlated with greater weight loss.[15] This may explain the lower risk of type 2 diabetes in the group of patients who achieved postoperative weight decrease after gastric cancer surgery compared with those who did not. However, this cannot explain the increase in the risk of type 2 diabetes observed on the left side of the nadir of the U-shaped curve. Thus, further studies of the effects of gastrointestinal hormones on type 2 diabetes after gastric cancer surgery are warranted. Changes in gastrointestinal hormones after foregut surgery affect body weight, satiety and insulin resistance,[28,29] and duodenal mucosal resurfacing is performed to treat type 2 diabetes, appreciating such roles of the foregut in metabolism.[30]

An increase in the risk of type 2 diabetes with excessive weight decrease might be related to malnutrition and sarcopenia, as a decrease in skeletal muscle contributes to insulin resistance, which is well known to predispose patients to type 2 diabetes.[31] Moreover, patients with excessive postoperative weight decrease might have been predisposed to type 2 diabetes with metabolic syndrome components (high baseline BMI, overweight patients, impaired fasting glucose and high prevalence of hypertension and dyslipidaemia [*Table 1*]). This finding suggests a novel hypothesis that baseline metabolic status may characterize excessive weight decrease and increased risk of type 2 diabetes after gastric cancer surgery, as shown on the left side of the U-shaped curve.

The non-linear model showed heterogeneity between subgroups according to surgical procedures, and the protective effect of postoperative weight decrease on incident type 2 diabetes after gastric cancer surgery was not observed in patients undergoing total gastrectomy (*Figure 2*). Greater weight loss after gastric cancer surgery in total gastrectomy recipients[9] and a greater decrease in ghrelin, a hormone that controls insulin sensitivity, after total gastrectomy[32,33] have been reported in previous observational studies. Gastric peptides, including gastric inhibitory polypeptide and glucagon-like peptide-1, which regulate insulin sensitivity,[34] could also contribute to the interaction of the extent of surgery and the association between weight loss and the risk of type 2 diabetes. However, these are insufficient to explain why total gastrectomy recipients did not have protective effects of weight decrease post-surgery for incident type 2 diabetes. We suggest that postoperative weight management for these populations needs to be performed per type 2 diabetes preventive strategy developed for the general population.

Some limitations of this study need to be acknowledged. First, there might be some cancer-related confounding factors that may affect weight status. We tried to minimize the effects of chemotherapy or cachexia by excluding patients who died within 5 years post-surgery and who received chemotherapy. However, excluding patients who had received adjuvant chemotherapy could potentially limit the generalizability of our findings. Further research is warranted to evaluate the association between weight change and the risk of incident diabetes in patients with advanced gastric cancer. Second, the limitations of using claims data, including possible coding errors, misdiagnoses or misclassification, require consideration. For example, when including patients with type 2 diabetes using diagnosis codes and medication prescription records, there is a concern of underestimation of incident type 2 diabetes cases by excluding those who did not receive antidiabetic drugs after diagnosis. Third, although all available variables were used, unavailable potential confounders might not be adjusted due to the retrospective design of the study (e.g., waist circumference and family history of type 2 diabetes). Fourth, reconstruction methods after gastrectomy for cancer were not considered in the analysis because of the unavailability of the variables. However, the extent of gastrectomy is known to play a more dominant role in metabolic effects and postoperative weight decrease than do reconstruction methods.[9,35] Fifth, concern remains regarding reverse causation. We performed a sensitivity analysis after washout type 2 diabetes within 2 years following 3-year weight decrease after gastrectomy for cancer, and the significance of the main outcome was maintained.

This study presented a non-linear U-shaped association between postoperative weight decrease and type 2 diabetes risk in gastric cancer survivors undergoing gastrectomy; this association remained in subgroup analyses according to baseline BMI. Our findings suggest that the optimal postoperative weight decrease for incident type 2 diabetes after gastrectomy for cancer is $>$10% to $\leq$15% of the baseline weight. A significant prophylactic effect of postoperative weight decrease on incident type 2 diabetes was not observed in total gastrectomy recipients. These results may provide evidence and insights for establishing lifestyle guidelines for gastric cancer survivors to prevent type 2 diabetes.

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The authors of this manuscript certify that they comply with the ethical guidelines for authorship and publishing in the *Journal of Cachexia, Sarcopenia and Muscle*.[36]

Conflict of interest

None declared.

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Online supplementary material

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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