Original Article

Impact of Gastrectomy on High-Density Lipoprotein Cholesterol Elevation in Nonobese Patients During a 10-Year Follow-up

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***Aim*: The role of gastrectomy in glycemic control has been established in the current era of bariatric surgery for obesity. Gastrectomy in obese patients is associated with increased levels of high-density lipoprotein cholesterol (HDL-C). However, limited data on the effects of gastrectomy in nonobese patients are available. We herein investigated the long-term plasma lipid changes in nonobese patients who had undergone gastrectomy.**
***Methods*: Patients were enrolled as part of routine healthcare examinations from 1984 to 2003. Preoperative and postoperative data from patients who had undergone curative gastrectomy were analyzed for up to 10 years postoperatively. Three age- and sex-matched controls were assigned to each case.**
***Results*: Sixty-four nonobese patients without diabetes mellitus or a history of having taken lipid-lowering drugs who underwent curative gastrectomy during the study period were enrolled (60 subtotal gastrectomies, four total gastrectomies). The median follow-up period was 7.6 years. The mean body mass index was 9.6% lower one year after gastrectomy ($p < 0.01$), then plateaued with a slight recovery. Intriguingly, the preoperative HDL-C level was 21% higher one year after gastrectomy ($p < 0.01$), increased by another 30% six years after gastrectomy and remained at this level for the rest of the follow-up period. No significant changes in the HDL-C level were observed in the controls. The degree of HDL-C elevation was consistently significant, irrespective of the baseline triglyceride level, HDL-C level or body weight.**
***Conclusions*: Gastrectomy in nonobese patients was associated with consistent and distinct long-term HDL-C elevations and body mass index reductions.**

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Key words: High-density lipoprotein cholesterol (HDL-C), Gastrectomy, Nonobese population, Long-term effects

Introduction

There is great interest in raising the high-density lipoprotein cholesterol (HDL-C) level, because a low HDL-C level is a strong predictor of morbidity and mortality among patients with coronary heart disease[1]. In contrast to the low-density lipoprotein cholesterol (LDL-C) level, the level of which can be dramatically reduced with statins, only a modest HDL-C elevation can be achieved with statins or fibrates. Therefore, new techniques for elevating the HDL-C level have been eagerly anticipated. Low HDL-C levels predict the future occurrence of type 2 diabetes

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mellitus[2]. Elevated HDL-C levels, accompanied by low cholesterol ester transfer protein (CETP) activity, improve the glycemic control in patients with diabetes[3].

Bariatric surgery has recently become a feasible option for the treatment of morbid obesity, and increasing reports have demonstrated its beneficial effects on various comorbidities, including distinct elevations in the HDL-C level[4-7]. Bariatric surgery can dramatically resolve diabetes, often without a clear relationship to postoperative weight loss. The elevation in the HDL-C level following bariatric surgery can be partly accounted for by body weight reduction, but larger-than-expected increases in the HDL-C level may occur with lifestyle modification.

Based on the above-described findings of previous studies, we speculated that gastrectomy itself may lead to elevation in the HDL-C levels. However, few studies have reported the long-term influence of gastrectomy on the HDL-C levels in the nonobese population, because it is difficult to obtain epidemiological data on this topic.

Aim

The aim of this study was to compare the pre- and post-gastrectomy plasma lipid changes in nonobese patients with those of age- and sex-matched controls in a long-term follow-up, and to identify the factors that contribute to elevation of the HDL-C level after gastrectomy.

Methods

Study Design and Data Source

We conducted a case-control study using annual health check-up data collected from 1984 to 2013 at Hokuriku Central Hospital, Oyabe, Toyama, Japan. The cases were patients who had undergone curative gastrectomy for the treatment of any condition that had newly developed during the study period. The controls were age- and sex-matched to the cases; they had not undergone gastrectomy. The exclusion criteria were postoperative recurrence of gastric cancer, the development of other malignancies during the follow-up period, a history of gastrointestinal surgery, morbid obesity (body mass index [BMI] >30 kg/m^2), current administration of statins or other lipid-modifying drugs and current medical treatment for diabetes. All patients were enrolled from 1984 to 2003 and were followed for up to 10 years.

The Department of Health at Hokuriku Central Hospital provides annual health checkups for public school employees in adjacent areas and has examined approximately 6,300 patients every year since 1964. At the checkups, patients undergo comprehensive evaluations including a complete medical history, history of cigarette smoking and alcohol intake, physical examination, anthropometric measurements (height and body weight), and laboratory testing, including most routine blood analyses. These annual health checkups are mandatory for public school teachers in Japan; thus, this heath checkup record system provides an unparalleled resource for long-term follow-up studies. This study was approved by the institutional review board at Hokuriku Central Hospital, and signed informed consent was obtained from all participants.

Study Population

We identified 64 patients (cases) who underwent gastrectomy during the study period, and analyzed all of these cases' preoperative and postoperative data. Three age- and sex-matched controls were randomly selected in the same year for each of the 64 cases ($64\times3=192$ patients). The median follow-up duration was 7.6 years (range, 1-10 years), and the number of observations decreased over time, as shown in **Fig. 1A**. Patients (cases) who had undergone gastrectomy thus appear to have been prescribed acid-reducing drugs more frequently than the controls. Only cimetidine, a histamine H_2-receptor antagonist, reportedly increases the HDL-C levels[8]; however, no patients were prescribed cimetidine in this study.

Data Collection and Study Variables

Using the "year of gastrectomy" as a reference point, the following data were collected for two years before gastrectomy (preoperative data) and up to 10 years after gastrectomy (postoperative data) for each individual case: age, sex, height, weight, BMI, type of gastrectomy (partial or subtotal), hemoglobin level, serum albumin level, total protein level, total cholesterol level, triglyceride level, HDL-C level, LDL-C level, γ-glutamyltranspeptidase (GGT) level, aspartate aminotransferase (AST) level, alanine aminotransferase (ALT) level and the glycosylated hemoglobin (HbA_{1c}) level. The HbA_{1c} level was estimated as the National Glycohemoglobin Standardization Program (NGSP) equivalent value (%), which was calculated by the following formula: HbA_{1c} (%) = HbA_{1c} (Japan Diabetes Society: JDS) (%) + 0.4%, considering the relational expression of HbA_{1c} (JDS) (%) measured by the previous Japanese standard substance and measurement methods and the HbA_{1c} (NGSP)[9].

Three controls were matched by preoperative age and sex to each case. The date for each visit were recorded once yearly for 10 years. All blood samples were drawn at 9:00 am following an overnight fast. All assays were conducted at the laboratory of Hokuriku Central Hospital. The hemoglobin levels were analyzed using an autoanalyzer (Sysmex SE-9000; Sysmex Corporation, Kobe, Japan). The HbA_{1c} level was measured by high-performance liquid chromatography (Automatic Glycohemoglobin Analyzer ADAMS A1c HA-8160; Arkray, Kyoto, Japan). The total cholesterol concentrations were determined with L-type CHO-M (Wako Pure Chemical Industries, Osaka, Japan), and the triglyceride concentrations were determined with Pureauto S TG-N (Sekisui Medical Co., Tokyo, Japan). The plasma levels of HDL-C were determined using Cholestest N HDL (Sekisui Medical Co.), as described previously. The concentration of LDL-C was estimated by the Friedewald equation when the triglyceride level was <400 mg/dL[10].

Statistical Analyses

Follow-up data were analyzed as the percent changes from the baseline year (Year 0). All variables were tested for normality using the Shapiro-Wilk method. The changes in the cases' data were compared with the changes in the age- and sex-matched controls' data at each follow-up year using the Student's *t*-test for parametric variables and the Wilcoxon signed-rank test for nonparametric variables. The χ^2 test was used for categorical variables. All reported *p*-values are two-sided. A correlation analysis was performed using Spearman's method to examine the baseline variables (non-normal distribution), and Pearson's method was used to examine relationships between longitudinal changes, because the relative changes from baseline were normally distributed. The JMP statistical software program version 10.0.1 for Windows (SAS Institute Inc., Cary, NC, USA) was used for all calculations, and differences were considered to be statistically significant for values of $p<0.05$. Correction for multiple comparisons was not taken into account because the comparisons were descriptive in nature.

Results

We identified 64 patients (cases) who underwent curative gastrectomy and had available pre- and postoperative data during the study period. Sixty cases underwent subtotal gastrectomy, and four underwent total gastrectomy. Fifty-nine cases had early gastric cancer, two had gastric submucosal tumors, and three had duodenal ulcers.

The baseline clinical characteristics of the cases and age- and sex-matched controls are summarized in **Table 1**. The mean preoperative age of all patients was 53.3±7.2 years, and 48 (75%) were men. The mean preoperative age of the controls was 53.2±6.9 years. There were no significant differences in the BMI, hemoglobin level, serum albumin level, total protein level, triglyceride level, HDL-C level, LDL-C level, GGT level, HbA_{1c} level or daily smoking or alcohol consumption between the two groups. Although all assessed values were within their reference ranges, the cases had slightly lower AST, ALT and total cholesterol levels ($p<0.05$) at the time of matching.

The mean percent changes in biochemical parameters for up to 10 years after baseline in both groups are shown in **Fig. 1**. The mean preoperative BMI among the cases was 22.8±3.0 kg/m^2. The BMI decreased maximally by one year after gastrectomy (mean ±SD: 20.5±1.1 kg/m^2, −9.6%±0.8%, $p<0.01$). After a slight recovery, the BMI among the cases plateaued at approximately −8.0% from baseline (**Fig. 1A**).

The mean serum HDL-C level among the cases was 54±14 mg/dL at baseline, and significantly increased one year after gastrectomy (64±2 mg/dL, +21%±5%), further increased to approximately +30% at six years (70±2 mg/dL, +30%±5%), and remained at this level for the rest of the follow-up period (**Fig. 1B**). The HDL-C levels of the cases were significantly higher than those of the controls throughout the follow-up period ($p<0.01$).

Regarding other lipid parameters, the mean preoperative triglyceride level among the cases was 120±61 mg/dL, and was significantly lower two to six years after gastrectomy compared to that among the controls (**Fig. 1C**). The mean preoperative LDL-C level among the cases was 128±33 mg/dL, and was significantly lower one to five years and seven years after gastrectomy than that among the controls (**Fig. 1D**). These changes in LDL-C were less distinctive than the changes in the HDL-C.

The mean preoperative levels of serum AST and ALT among the cases were 22.0±7.1 and 22.1±15.7 IU/L, respectively, and both values were significantly lower than those among the controls (**Table 1**). The serum AST level, but not the serum ALT level, increased after gastrectomy and was consistently higher (although usually still within the reference range) than that of the controls during the follow-up period (data not shown). The absolute value of serum AST was higher in the cases than in the controls at some time points, although most elevations were still within the reference range (31.4±3.3 vs. 24.3±1.4 IU/L, respectively; maximal difference at 10 years, $p<0.01$). The mean GGT level among the cases was 30.1

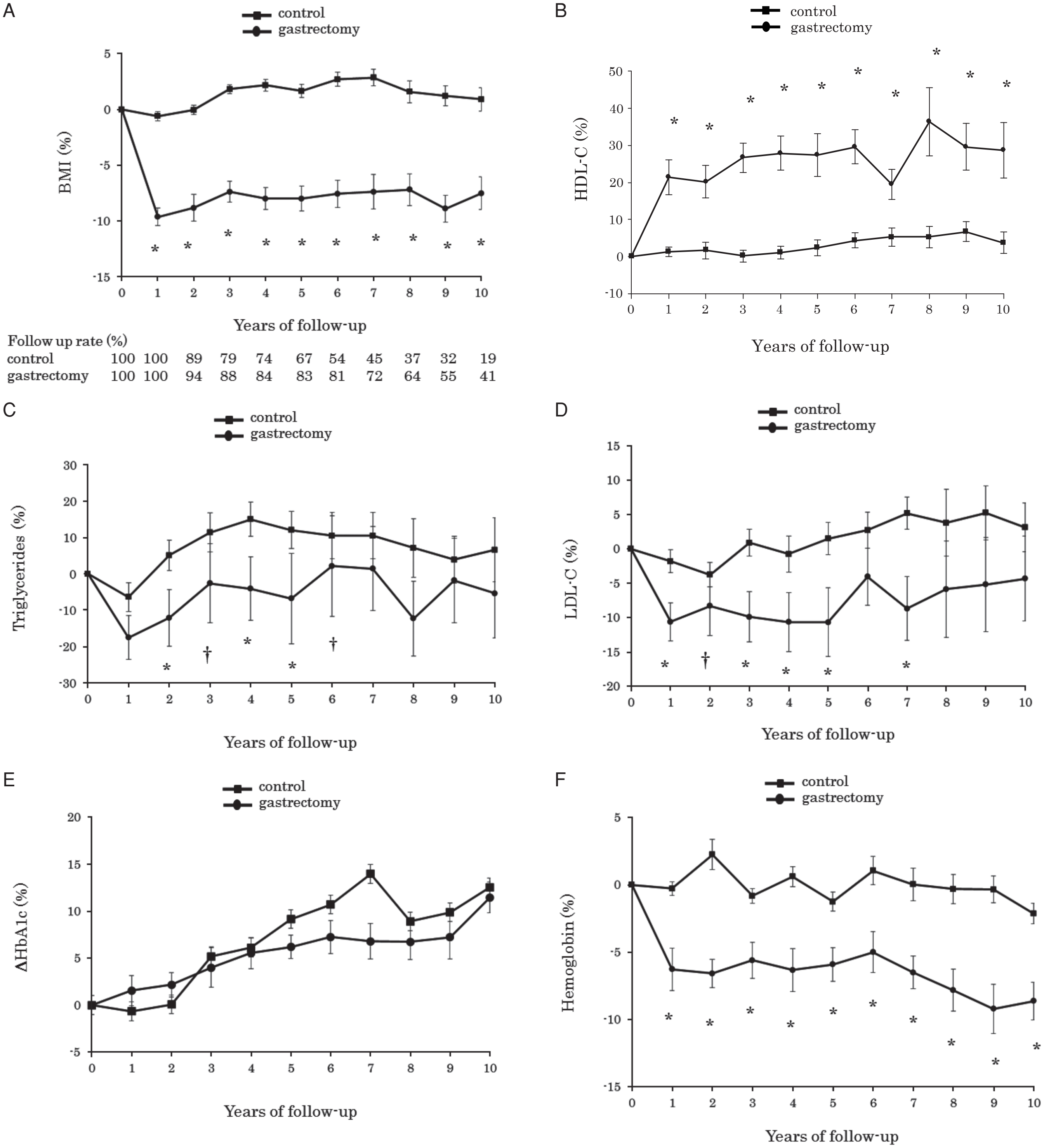


Fig. 1. The mean postoperative percent changes in parameters during the 10-year follow-up period in the control and gastrectomy groups

Panel A: BMI, B: HDL-C, C: triglycerides, D: LDL-C, E: HbA_{1c}, F: hemoglobin. The data are expressed as the means ± standard error. Asterisks denote $p < 0.01$ and daggers denote $p < 0.05$ for comparisons between the groups.

Table 1. The baseline clinical characteristics of the study subjects

	Gastrectomy group	Control group	*p* value
N	64	192	
Age (y)	53.3 ± 7.2	53.2 ± 6.9	0.99
Sex (male/female)	48/16	144/48	
Procedure (total gastrectomy/subtotal gastrectomy)	4/60	-	
Preoperative			
BMI (kg/m^2)	22.8 ± 3.0	23.4 ± 2.9	0.17
Hemoglobin (g/dL)	14.7 ± 1.2	14.8 ± 1.3	0.43
Total protein (g/dL)	7.1 ± 0.4	7.2 ± 0.4	0.20
Albumin (g/dL)	4.3 ± 0.3	4.4 ± 0.3	0.10
AST (IU/L)	22.0 ± 7.1	25.7 ± 10.7	0.012
ALT (IU/L)	22.1 ± 15.7	26.3 ± 12.7	0.032
GGT (IU/L)	30.1 ± 16.9	36.4 ± 33.2	0.18
Total cholesterol (mg/dL)	206 ± 34	216 ± 36	0.048
Triglycerides (mg/dL)	120 ± 61	129 ± 77	0.42
HDL-cholesterol (mg/dL)	54 ± 14	56 ± 14	0.35
LDL-cholesterol (mg/dL)	128 ± 33	134 ± 34	0.21
HbA1c (%)	5.5 ± 0.4	5.3 ± 0.7	0.10
Daily smoking (%)	29.7	28.6	0.87
Alcohol consumption (%)	53.1	51	0.77

The data are presented as the means ± standard deviation.

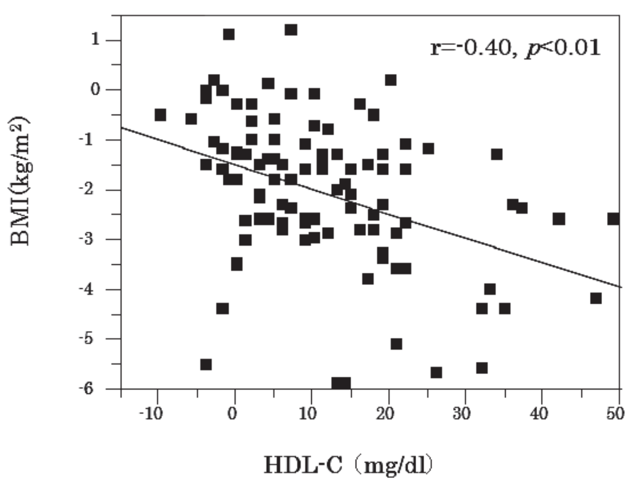


Fig. 2. The correlations between the mean postoperative absolute HDL-C level and the BMI one to three years after gastrectomy

± 16.9 IU/L and was significantly lower at two to seven years after gastrectomy compared to that in the controls (data not shown). The changes in the GGT level were not as clear as those reported in obese patients undergoing bariatric surgery because most of the patients in the present study showed normal GGT levels at baseline.

The mean preoperative HbA_{1c} level among the cases was 5.5% ± 0.4%. The HbA_{1c} level tended to increase slowly in both groups during the 10-year follow-up, and did not significantly differ between the two groups throughout the study period (**Fig. 1E**). No patients in this study had diabetes. Four cases (6.3%) and 12 controls (6.3%) exhibited significantly higher HbA_{1c} levels (>6.2%) at the end of this study than at baseline.

The mean preoperative hemoglobin and albumin levels were not significantly different between the two groups at baseline. The hemoglobin levels among the cases decreased by 5%, then by 10% biphasically during the follow-up period, as previously described following gastrectomy (**Fig. 1F**). The serum albumin level, which is another important nutritional parameter, and the total protein level showed no significant differences between the two groups throughout the study (data not shown).

A moderate correlation was observed between the degree of HDL-C elevation and the degree of BMI reduction ($r = -0.40$, $p < 0.01$) (**Fig. 2**). However, the degree of HDL-C elevation was not correlated with the degree of changes in the HbA_{1c}, the AST or the albumin levels (data not shown).

We also investigated whether the HDL-C elevation after gastrectomy depends on the preoperative HDL-C or triglyceride level. We defined a basal HDL-C level of <40 mg/dL as "low HDL-C" and a basal triglyceride level of >150 mg/dL as "high TG." The clinical characteristics of these subgroups are

Table 2. The baseline characteristics of patients who underwent gastrectomy with and without a low preoperative HDL-C level

	Normal HDL-C at baseline	Low HDL-C at baseline	*p* value
N	51	10	
Age (y)	53.2 ± 7.0	55.7 ± 7.6	0.32
Sex (male/female)	40/11	5/5	0.08
Procedure (total gastrectomy/subtotal gastrectomy)	49/2	9/1	0.46
Preoperative			
Body mass index (kg/m^2)	22.8 ± 3.1	22.9 ± 2.6	0.85
Hemoglobin (g/dl)	14.8 ± 1.3	14.3 ± 0.8	0.23
Total protein (g/dl)	7.1 ± 0.4	7.0 ± 0.4	0.81
Albumin (g/dl)	4.3 ± 0.3	4.3 ± 0.2	0.79
AST (IU/l)	22 ± 7.2	22.2 ± 7.7	0.94
ALT (IU/l)	22.6 ± 16.6	19.4 ± 12.9	0.56
GGT (IU/l)	30.9 ± 17.5	22.3 ± 12.8	0.25
Total cholesterol (mg/dl)	205 ± 34.4	211.4 ± 38	0.60
Triglycerides (mg/dl)	112.6 ± 59	161.9 ± 69.7	0.022
HDL cholesterol (mg/dL)	56.7 ± 13.3	41.1 ± 5.2	< 0.001
LDL cholesterol (mg/dl)	125.8 ± 32.9	137.9 ± 33.3	0.29
HbA1c (%)	5.6 ± 0.9	5.7 ± 0.4	0.80

The data are presented as the means ± standard deviation.

Table 3. The baseline characteristics of patients who underwent gastrectomy with and without preoperative triglyceride elevation

	Normal TG in Baseline	High TG in Baseline	*p* value
N	46	18	
Age (y)	53.6 ± 7.9	52.6 ± 5.2	0.61
Sex (male/female)	34/12	14/4	0.75
Procedure (total gastrectomy/subtotal gastrectomy)	44/2	16/2	0.34
Preoperative			
Body mass index (kg/m^2)	22.2 ± 2.3	24.4 ± 3.8	0.009
Hemoglobin (g/dl)	14.6 ± 1.3	15.2 ± 0.8	0.07
Total protein (g/dl)	7.1 ± 0.4	7.1 ± 0.5	0.57
Albumin (g/dl)	4.3 ± 0.3	4.4 ± 0.3	0.38
AST (IU/l)	22.4 ± 8.0	21.0 ± 4.1	0.48
ALT (IU/l)	21.9 ± 18.3	22.4 ± 5.8	0.91
GGT (IU/l)	28.2 ± 16.2	34.6 ± 17.6	0.22
Total cholesterol (mg/dl)	197.5 ± 30.8	225.8 ± 32.4	0.002
Triglycerides (mg/dl)	88.2 ± 30.6	201.6 ± 40.7	< 0.001
HDL cholesterol (mg/dl)	56.3 ± 14.4	48.9 ± 9.1	0.04
LDL cholesterol (mg/dl)	124.1 ± 32.8	136.6 ± 30.6	0.18
HbA1c (%)	5.7 ± 1.1	5.5 ± 0.3	0.49

The data are presented as the means ± standard deviation.

shown in **Tables 2** and **3**. Patients with low HDL-C levels at baseline had significantly higher preoperative triglyceride levels than did the patients with normal HDL-C levels at baseline (**Table 2**). Patients with high triglyceride levels at baseline had significantly lower preoperative HDL-C levels than did patients with normal triglyceride levels at baseline (**Table 3**).

We found that the degree of HDL-C elevation one year after gastrectomy in the "low HDL-C" group was significantly greater than that in the "normal HDL-C" group, and that the degree of HDL-C elevation from baseline was consistently significant, irrespective of the baseline HDL-C level (**Fig. 3A**). We also found that the degree of HDL-C elevation five and nine years after gastrectomy in the"high TG" group was significantly greater than that in the "nor-

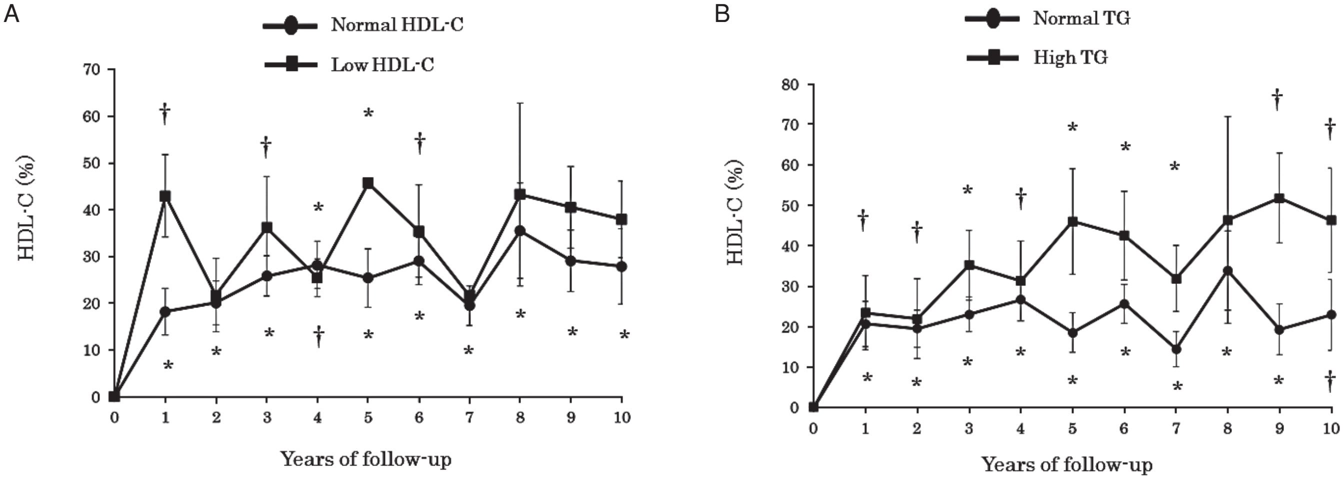
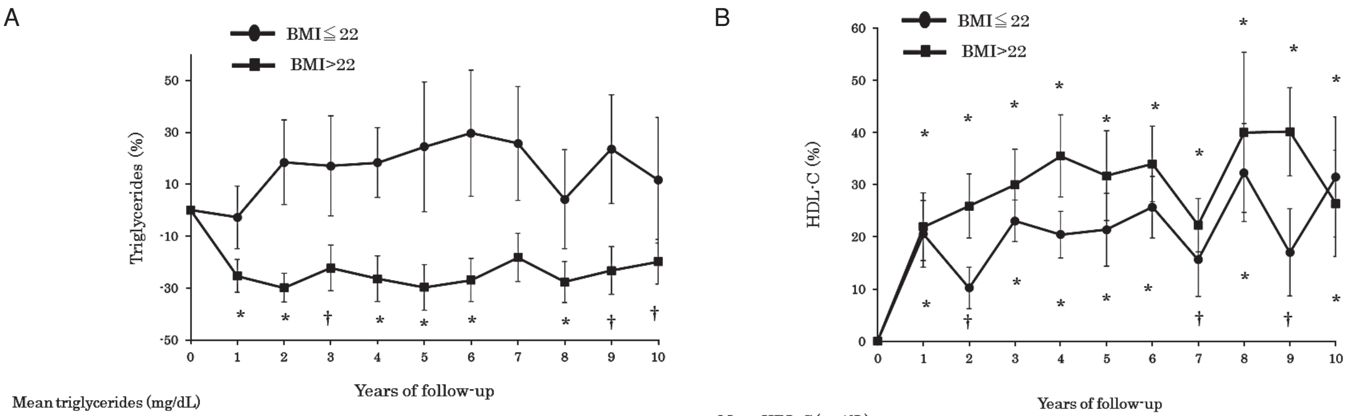


Fig. 3. The results of the subanalyses in the gastrectomy group

A: The mean postoperative percent changes in the serum HDL-C levels during the 10-year follow-up period in the "normal HDL-C" and "low HDL-C" groups. B: The mean postoperative percent changes in the serum HDL-C levels during the 10-year follow-up period in the "normal TG" and "high TG" groups. Asterisks denote $p<0.01$ and daggers denote $p<0.05$ for comparisons with the baseline.



Mean triglycerides (mg/dL)

	0	1	2	3	4	5	6	7	8	9	10
BMI≦22	101	77	87	81	82	92	108	87	96	81	96
BMI>22	136	91	97	100	89	88	78	98	83	92	90

Mean HDL-C (mg/dL)

	0	1	2	3	4	5	6	7	8	9	10
BMI≦22	57	64	68	69	70	75	73	73	73	71	72
BMI>22	52	64	62	66	69	66	73	63	67	70	64

Fig. 4. The results of the subanalyses in the gastrectomy group

A: The mean postoperative percent changes in the serum triglyceride levels during the 10-year follow-up period in patients with a BMI ≤ 22 or >22 kg/m^2. B: The mean postoperative percent changes in the serum HDL-C levels during the 10-year follow-up period in patients with a BMI ≤ 22 or >22 kg/m^2. Asterisks denote $p<0.01$ and daggers denote $p<0.05$ for comparisons with the baseline.

mal TG" group, and that the degree of HDL-C elevation from baseline was consistently significant, irrespective of the baseline triglyceride level (**Fig. 3B**).

Next, we investigated whether the baseline BMI influences the degree of HDL-C elevation associated with gastrectomy. The Japan Society for the Study of Obesity originally defined an "ideal body weight" as a BMI of 22 kg/m^2 [11]. We found that the triglyceride levels in patients with a BMI of >22 kg/m^2 were significantly lower than the baseline level throughout the follow-up period year, except for seven years after gastrectomy, but no statistically significant changes were observed in patients with a BMI of ≤ 22 kg/m^2 (**Fig. 4A**). The HDL-C levels were significantly higher than those at baseline in all patients throughout the follow-up period, regardless of whether the BMI was >22 or ≤ 22 kg/m^2 (**Fig. 4B**).

Finally, we investigated whether the degree of elevation in the HDL-C level after gastrectomy was affected by sex. The HDL-C levels were significantly higher than the baseline level throughout the post-gastrectomy follow-up period in men, and at one,

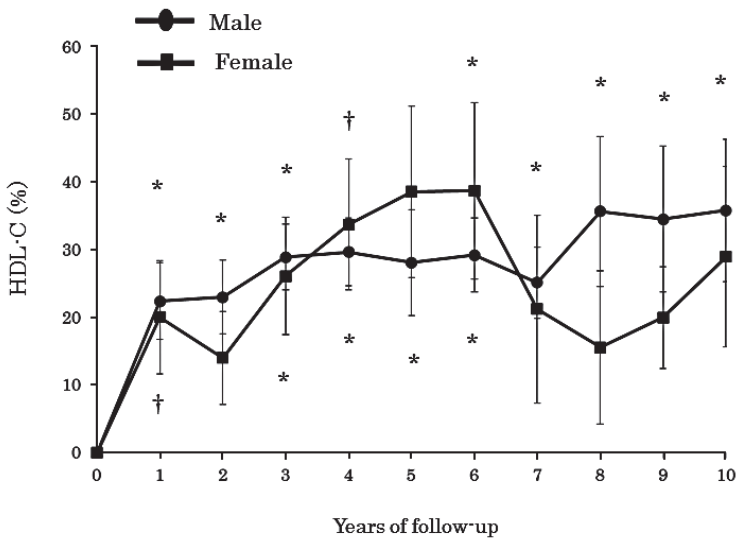


Fig. 5. The results of the subanalyses in the gastrectomy group

The mean postoperative percent changes in the serum HDL-C levels during the 10-year follow-up period in men and women. Asterisks denote $p<0.01$ and daggers denote $p<0.05$ for comparisons with the baseline.

Table 4. The lipid parameters three to five years before gastrectomy and at baseline

	Three to five years before baseline $n=44$	Baseline without a diagnosis of gastric disease $n=64$	p value
Total cholesterol (mg/dl)	205.0 ± 5.7	205.5 ± 4.2	0.91
Triglycerides (mg/dl)	131.1 ± 14.4	120.1 ± 7.7	0.45
HDL cholesterol (mg/dl)	54.0 ± 2.4	54.1 ± 1.7	0.97
LDL cholesterol (mg/dl)	127.2 ± 6	127.8 ± 4.2	0.96

The data are presented as the means ± standard deviation.

three, four and six years post-gastrectomy in women. No significant changes were observed between men and women throughout the follow-up period (**Fig. 5**).

The pre-baseline serum lipid levels were available for most patients, and no differences in lipid levels were observed between three and five years pre-baseline and at the baseline in this study (**Table 4**). The presence of advanced cancer may decrease the HDL-C level before the diagnosis of the cancer. However, all cases in our study were cured with gastrectomy, presumably because all had undergone mandatory periodic health checkups that included gastric endoscopy, which facilitated the early detection of gastric cancer.

Discussion

We found that gastrectomy in nonobese patients caused a distinct elevation in the HDL-C level, and that this elevation persisted for 10 years compared with the findings in age- and sex-matched controls. The increases in the HDL-C level showed a significant negative correlation with the decreases in the BMI, although the patients in this study were not obese and did not have diabetes. The HDL-C elevations were consistently significant, irrespective of the baseline triglyceride level, baseline HDL-C level or baseline body weight. Our results indicate, for the first time, that weight reduction in association with gastrectomy may cause long-term HDL-C elevations, even in the non-obese population.

Our study showed a 2.8-mg/dL HDL-C increase for every 1-kg decrease in body weight after gastrectomy (15-mg/dL increase in HDL-C with a 5.4-kg body weight reduction; BMI decreased from 22.8 to 20.8 kg/m^2). Although a low HDL-C level is a common feature of metabolic syndrome, the increases in HDL-C levels associated with lifestyle modifications that promote weight reduction are reported to be relatively small. The results of a meta-analysis of 70 studies showed that the BMI decreased from 34.8 to 27.8 kg/m^2 with dietary management; and there was a 0.35-mg/dL HDL-C increase for every 1-kg decrease in body weight in that study[12]. The rate of increase in the HDL-C level was almost 10 times higher in the present study than in that study. In another study, a marked increase in the HDL-C level occurred 12 months after gastric bypass and sleeve gastrectomy (28.5% and 28.4%, respectively) in association with body weight reduction (−29.4 and −25.1 kg, respectively)[13].

The amelioration of insulin resistance does not adequately explain the HDL-C elevation in this study. The HbA_{1c} level in the two groups remained substantially unchanged during the follow-up period despite the decreased hemoglobin levels in the gastrectomy group. One reason for this finding is that patients with diabetes were not included in this study. The presence of anemia after gastrectomy may affect the HbA_{1c} level, and the hemoglobin level was significantly lower in the patients who underwent gastrectomy at all follow-up points. The anemia could have concealed the exacerbation of preexisting diabetes, but this cannot explain the HDL-C elevation in this study.

We showed that neither a low baseline HDL-C level nor a high baseline triglyceride level is a determinant of the HDL-C elevation after gastrectomy. Laws and Reaven showed that a high triglyceride level and low HDL-C level are strong indicators of insulin resistance[14], and are frequently correlated with each other. Insulin resistance may not a relevant feature in the present population, because most post-gastrectomy patients in this study had triglyceride levels, HbA_{1c} levels and BMIs within the reference ranges. The baseline HDL-C and triglyceride levels are reportedly highly predictive of the increase in HDL-C induced by statins[15]. However, in the present study, the baseline HDL-C and triglyceride levels were not predictive of the increase in the HDL-C level after gastrectomy.

It is considered that gastrectomy is a major factor leading to the HDL-C elevation, because it was the main intervention in this study. Reports of the effects of bariatric surgery on morbid obesity can provide important information with regard to this finding. Weight loss following bariatric surgery always produces substantial decreases in the fasting triglyceride levels, and an increase in the HDL-C level has been seen in most studies. Observational studies have reported 40-63% decreases in the serum triglyceride level, 20-39% increases in the HDL-C level and 19-31% decreases in the LDL-C level after Roux-en-Y gastric bypass[16-18]. Schauer *et al.* recently reported a markedly higher HDL-C level after bariatric surgery than after medical therapy alone[13].

Prospective studies have shown that the serum total cholesterol level decreases prior to the diagnosis of malignant disease[19-21]. In the present study, there were no significant differences between the three- and five-year pre-baseline and baseline HDL-C levels, and no difference was seen in the HDL-C levels between the cases and controls. The presence of advanced cancer may decrease the serum HDL-C level before the diagnosis of the cancer; however, all cases in our study were cured by gastrectomy, presumably because they had undergone the mandatory periodic health checkups that included gastric fiberscopy. The effect of latent gastric cancer on the lipid levels therefore seemed to be relatively small in this study.

A recent review of many studies found that the association between low baseline HDL-C levels and cancer risk is shared among many types of cancer, and is linked to obesity and inflammation[22]. Previous studies focusing on HDL-C showed that the serum HDL-C levels were lower in patients with than without gastrointestinal cancer[23-25]. Tamura *et al.* reported that lymphatic invasion and vascular invasion were significantly more severe in patients with low HDL-C levels than in those with normal HDL-C levels, and that the serum HDL-C level may be a clinical prognostic factor in patients with gastric cancer[26]. There was no significant difference in the baseline HDL-C levels between the cases and controls in the present study. All patients in our study were cured with gastrectomy; therefore, none of the cases had unresectable cancer. Additionally, their baseline serum HDL-C levels were not low prior to the diagnosis of gastric cancer. Therefore, we speculate that latent gastric cancer has limited effects on the HDL-C level.

Only patients with a BMI of >22 kg/m^2 in our study exhibited a decline in the triglyceride level after gastrectomy. However, the HDL-C levels increased after gastrectomy regardless of the baseline BMI. Our results indicate that a low adiposity level is not a determinant of HDL-C elevation.

In women, menopause is associated with dyslipidemia, characterized by an increased very-low-density lipoprotein triglyceride level and a decreased HDL-C level[27]. In the present study, the HDL-C level increased after gastrectomy regardless of sex. All women in this study were postmenopausal with the exception of one who was 44 years old at baseline. Therefore, menopause also seemed to have a small impact in this study.

Craig *et al.* showed that smokers had significantly lower serum concentrations of HDL-C (−5.7%) than did nonsmokers[28], and that alcohol consumption is associated with high triglyceride and HDL-C concentrations in the general population[29]. Our study showed no significant differences in the daily smoking or alcohol consumption levels at baseline between the two groups. During the follow-up period, nine subjects (14.1%) quit smoking after gastrectomy and 17 controls (8.9%) quit smoking within three years from baseline; there was no significant difference between the two groups. With respect to alcohol consumption, one control, but no cases quit drinking. Therefore, smoking and alcohol consumption seemed to have only a limited effect on the HDL-C levels in this study.

Exercise training increases the serum HDL-C level by 5-10% while lowering the CETP level[30, 31]. Inflammation also affects the HDL-C level, and a reduced HDL-C level is correlated with an elevated serum CRP level. Thus, elevated inflammatory activity due to conditions such as cancer and metabolic syndrome[22, 32] may lead to reduced HDL-C and increased serum CRP levels. The patients' exercise histories and serum CRP levels were not available in the present study, which represents a limitation of this work.

HDL metabolism is complex, and is regulated by many factors. Lipoprotein lipase, hepatic lipase, endothelial lipase, lecithin cholesterol acyltransferase, and CETP all modify HDL metabolism[33]. Some studies have shown that the fasting lipoprotein lipase activity is increased in the abdominal and gluteal subcutaneous adipose tissue after weight loss[34, 35]. CETP is a plasma glycoprotein that facilitates the transfer of cholesteryl esters from HDL-C to apolipoprotein B-containing lipoproteins[36]. Inhibition of CETP is a proposed strategy to raise the HDL-C levels[37]. In obese rats lacking CETP, sleeve gastrectomy did not increase the plasma HDL-C levels compared to those of control rats[38]. Doğan *et al*. reported that the increase in the level of large HDL particles after laparoscopic sleeve gastrectomy in obese patients was accompanied by a decrease in the CETP level[39]. Asztalos *et al*. reported that CETP activity continually decreased throughout a 12-month follow-up period, and that the HDL-C level increased after Roux-en-Y gastric bypass surgery in obese patients[40]. Alcohol-induced HDL-C elevation is a well-known condition that is reportedly accompanied by lower CETP activity[41, 42]. The present study showed no significant differences in the level of alcohol consumption at baseline or during the follow-up between the two groups. It is possible that the body weight reduction after gastrectomy can decrease both the CETP expression and activity in nonobese patients, and this may lead to the increase in HDL-C.

Unexpectedly, a slight but statistically significant elevation in the AST level occurred after gastrectomy in this study. One explanation for this finding is ineffective hematopoiesis after gastrectomy. This may explain the lack of an association between the changes in the AST and ALT levels (ALT is more specific to hepatocytes).

Conclusion

In this long-term study, gastrectomy was associated with a distinct elevation in the HDL-C level with BMI reduction, even in nonobese patients. Resolution of insulin resistance is not likely to be the main cause of the HDL-C level elevation in such patients. The HDL-C level elevation was consistently significant irrespective of the baseline triglyceride level, baseline HDL-C level or baseline body weight in these patients.

Conflicts of Interest

None.

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