Vagus Nerve Preservation Selectively Restores Visceral Fat Volume in Patients with Early Gastric Cancer who Underwent Gastrectomy

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Background. Body weight loss is a well-known complication after gastrectomy, and is mainly due to reduced fat volume. The effect of vagotomy on the postoperative fat volume was investigated in patients with early stage gastric cancer who underwent gastrectomy.

Methods. Subcutaneous fat area (SFA) and visceral fat area (VFA) were separately measured in a computed tomographic (CT) image at the level of the umbilicus using Fat Scan software. The changes in these two fat areas were determined by comparing CT images taken before and more than 6 mo after gastrectomy, and the ratio of postoperative to preoperative fat area was calculated in 77 patients.

Results. VFA was reduced significantly greater after total gastrectomy (TG) than distal gastrectomy (DG) ($P = 0.0003$). In 63 patients who underwent DG, the reduction in VFA, but not in SFA, was significantly less in vagus nerve-preserved than in vagus nerve-nonpreserved cases ($59.0\% \pm 24.2\%$ versus $74.9\% \pm 28.2\%$, $P = 0.027$). If compared in each case, VFA showed a significantly greater decrease than did SFA in vagus-nonpreserving, but not in vagus-preserving, gastrectomy ($68.2\% \pm 37.0\%$ versus $52.7\% \pm 25.2\%$, $P < 0.0001$; $76.3\% \pm 30.0\%$ versus $74.9\% \pm 28.2\%$, $P = 0.79$).

Conclusions. The vagus nerve has a function to locally regulate the amount of intra-abdominal fat tissue, and selective vagotomy in gastrectomy results in a preferential reduction of visceral fat in gastrectomy. Surgical denervation of vagus may be reconsidered as a reasonable treatment for excessive obesity.

Key Words: vagus nerve; gastrectomy; visceral fat; subcutaneous fat; obesity.

INTRODUCTION

Body weight loss is a common, but sometimes serious, problem for patients who undergo gastrectomy. Postoperative body weight loss could be explained by various mechanisms such as reduced food intake, appetite loss caused by the reduced reservoir or delayed gastric emptying [1, 2], diarrhea [3], and malabsorption possibly caused by reduced secretion of gastric acid [4], or pancreatic insufficiency [5, 6]. In addition, it has recently been suggested that alteration of the endocrine status, such as reduced gastrin [5] or ghrelin [7], and increased cholecystokinin [2, 5], might be involved in weight loss after gastrectomy. Previous studies have shown that the degree of body weight loss differs with the extent of gastrectomy, i.e., weight loss after conventional distal gastrectomy (DG) is significantly less than that after total gastrectomy (TG) [7, 8], while more than that after pylorus-preserving gastrectomy (PPG) [9, 10]. However, the mechanism of body weight loss after gastrectomy has not yet been fully clarified.

It has been shown that loss of adipose tissue is the main cause of postoperative weight loss after gastrectomy [8]. Recent studies have suggested that adipose tissue is an endocrine organ that can produce a variety of secretory peptides, named adipokines, and thus plays important roles in the pathophysiology of various disorders [11, 12]. In particular, it has been proposed that visceral, rather than subcutaneous, fat tissue is closely related to development of the metabolic syndrome [13, 14]. In general, men have more visceral fat than women, while
subcutaneous fat is more prominent in women than in men, suggesting that the volumes of these two adipose tissues are differently regulated in the body. However, the detailed mechanisms selectively controlling visceral fat are not understood.

In this study, we hypothesized that various surgical procedures in gastrectomy could affect the postoperative volume of each fat tissue, and investigated the changes in subcutaneous and visceral fat separately after various types of gastrectomy using Fat Scan software, which can separately calculate the area of subcutaneous (SFA) and visceral (VFA) fat from a fat density computed tomographic (CT) scan. Recent studies have shown that the metabolism of adipose tissue is controlled by autonomic nervous system and the visceral fat tissues were totally innervated by vagus nerve [15, 16]. In this study, therefore, we paid special attention to the effect of vagus nerve preservation, because vagotomy in gastrectomy might lead to loss of the parasympathetic anabolic effect on intra-abdominal adipose tissue.

PATIENTS AND METHODS

Measurement of Visceral Fat Area (VFA) and Subcutaneous Fat Area (SFA) in CT Scan

Visceral and subcutaneous fat volumes were evaluated by measurement of fat area determined in a single CT scan image at the level of the umbilicus (from L4 to L5), using Fat Scan software (N2 System; Osaka, Japan), as illustrated in Fig. 1. Several studies have revealed that VFA and SFA evaluated by this method are highly correlated with total visceral fat [17, 18]. Hence, in this study, we used the CT image at the umbilical level to measure VFA and SFA separately, using a previously reported technique [19]. As shown in Fig. 1, we examined VFA and SFA in the preoperative and postoperative periods, and compared the changes in these fat volumes after gastrectomy, by calculating the value of postoperative VFA (or SFA) divided by preoperative VFA (or SFA) in each subject separately. Preoperative CT images were taken just before surgery. Since fat volumes are considered to be dependent on food intake, we used CT images taken more than 6 mo (0.5–5.2 y) after gastrectomy. Since the ratios of postoperative body weight against preoperative values at the time of CT evaluation were mostly similar in these periods, the patients were supposed to be in a stable nutritional state.

Patients

We retrospectively analyzed 112 patients whose disease was pathologically diagnosed as stage I gastric cancer who underwent TG or DG between April 2001 and October 2007 at the Tokyo University Hospital. In this study, we focused on patients with early stage cancer, because fat volumes may be critically affected by the cancer volume in advanced-stage patients through causing diminished appetite and altered metabolism. Among the 112 patients, a postoperative CT scan image was unavailable in 30 patients, who were excluded from this study. Three patients who also had other intra-abdominal advanced malignant disease, one patient who developed unexpected recurrence, and another patient who developed postoperative severe stenosis that required reoperation 5 mo after the initial operation were also excluded, because these postoperative conditions may significantly affect fat volume in the postoperative period. Finally, 77 patients (56 men and 21 women) for whom a CT image of a slice at the umbilical level was available were enrolled in this study. None of the 77 patients had postoperative chemotherapy. This study was approved by the ethics committee of the University of Tokyo.

FIG. 1. Fat scan software can calculate VFA and SFA separately. Preoperative (A), (C) and postoperative (B), (D) fat density CT images at the level of the umbilicus in a patient with early stage gastric cancer who underwent DG. Red and pink areas of fat scan CT images (C), (D) indicate VFA and SFA, respectively. (Color version of figure is available online.)
Operative Procedures

In 14 cases, TG and bilateral truncal vagotomy were performed with D1 or D2 lymph node dissection and Roux-en-Y reconstruction. The spleen was resected in two cases, while the greater omentum was largely preserved in all cases. In other patients who underwent DG, 2/3 to 3/4 of the stomach was resected with D1 or D2 lymph node dissection, followed by Billroth-I or Roux-en-Y reconstruction. The omentum was also preserved in all cases. Among them, pylorus-preserving DG (PPG) was performed in 12 patients, in whom the hepatic and celiac branches of the vagus nerve were preserved except in one case with only hepatic branch preservation. The hepatic and celiac branches of the vagus were also preserved in 13 of 51 patients who underwent conventional DG. Among them, both the hepatic and celiac branches were fully preserved in 13 cases, and only the hepatic branch was preserved in another five cases. The longitudinal size of the tumor tended to be larger in patients who underwent TG, and D2 dissection was performed more frequently in patients who underwent DG without vagus nerve preservation. However, other factors did not show a significant difference among the four groups.

Statistical Methods

Statistical analyses were performed with commercially available software (JMP 7.0.1; SAS Institute, Cary, NC). Wilcoxon nonparametric analysis and \( \chi^2 \) test were used for comparisons between the two groups. Statistical significance was defined as \( P < 0.05 \).

RESULTS

Patient Characteristics

The demographic characteristics of the patients are shown in Table 1. TG and DG were performed in 14 and 63 patients with stage I gastric cancer, respectively. In the DG group, the pylorus was preserved in 12 patients, and the vagus nerve was preserved in 30 patients. In the 12 patients who underwent PPG, both the hepatic and celiac branches were fully preserved, except in one case with only hepatic branch preservation. The vagus nerve was also preserved in 18 of the 51 patients who underwent conventional DG. Among them, both the hepatic and celiac branches were fully preserved in 13 cases, and only the hepatic branch was preserved in another five cases. The longitudinal size of the tumor tended to be larger in patients who underwent TG, and D2 dissection was performed more frequently in patients who underwent DG without vagus nerve preservation. However, other factors did not show a significant difference among the four groups. In addition, the time to the CT scan examination was not different among the patients who underwent the different operative procedures.

VFA is Reduced Significantly more in Patients who Undergo TG than DG

Using Fat scan analysis, we first evaluated the postoperative changes in SFA and VFA in patients who underwent DG or TG. As shown in Fig. 2, postoperative SFA decreased to 74.2% ± 35.5% and 58.5% ± 26.8% of the preoperative values in patients who underwent DG and TG, respectively. The ratio of volume reduction was not
We next compared the changes of SFA and VFA between pylorus-preserving and non-preserving DG. As shown in Fig. 3B, however, both SFA and VFA in the postoperative state tended to be preserved in patients who underwent PPG. However, the ratio to preoperative fat volume was mostly similar for SFA and VFA, and the ratios were not significantly altered by the presence of the pylorus (SFA; 80.1% ± 33.3% versus 72.8% ± 36.2%, P = 0.43, VFA; 77.7% ± 29.7% versus 64.0% ± 26.1%, P = 0.13). Also, the ratio was not affected by the Billroth I or a Roux-Y reconstruction (Fig. 3C).

Interestingly, however, the reduction of VFA in vagus-preserving DG was significantly smaller than that in nonpreserving conventional DG (74.9% ± 28.2% versus 59.0% ± 24.2%, p = 0.027) (Fig. 3D). As for SFA, no difference was observed between vagus nerve-preserving and nonpreserving DG (76.3% ± 30.0% versus 72.4% ± 40.2%, P = 0.27). This finding suggests that the presence of the vagus nerve, but not the pylorus, may play a positive role in regulation of the visceral fat volume.

In order to confirm this, we also compared the change in VFA between pylorus-preserved and nonpreserved cases only in patients who underwent vagus nerve-preserved DG. As shown in Fig. 4, the ratio of postoperative VFA was mostly the same between pylorus-preserving- and pylorus-resected DG (77.7% ± 29.7% versus 73.0% ± 27.8%, P = 0.77).

Postoperative VFA Is Not Affected by Presence of Celiac Branch

Two vagus nerve branches, the hepatic branch and the celiac branch, have been shown to have different physiologic functions and thus appear to be important in gastrectomy. In our series of 30 patients who underwent vagus nerve-preserving gastrectomy, both branches were fully preserved in 24 cases, while the hepatic branch alone was preserved in the other six cases. We next compared the changes of SFA and VFA in these two groups. However, SFA and VFA were reduced to the same level irrespective of preservation of the celiac branch (SFA; 77.6% ± 29.0% versus 71.1% ± 36.2%, P = 0.90, VFA; 72.0% ± 25.8% versus 86.5% ± 36.5%, P = 0.42) (Fig. 5).

Changes in SFA and VFA After Gastrectomy With or Without Vagus Preservation

Then, we compared the changes of SFA and VFA in the vagus-preserved and nonpreserved groups irrespective of the range of gastrectomy. As shown in Fig. 6, VFA was reduced to the same level as that of SFA in 30 patients who underwent vagus-preserving gastrectomy (76.3% ± 30.0% versus 74.9% ± 28.2%). In contrast, VFA was reduced to a significantly greater

Postoperative VFA is Significantly Affected by Preservation of Vagus Nerve, but Not by Nodal Dissection, Pylorus Preservation, or Reconstruction

Next, we examined the changes in SFA and VFA in 63 patients who underwent DG. Initially, we considered that the extent of nodal dissection might seriously affect the change in postoperative VFA, since nodal dissection is accompanied by the removal of visceral fat tissue. However, as shown in Fig. 3A, VFA decreased to 67.1% ± 27.6% in 47 patients who underwent D1 dissection, and to 65.0% ± 26.7% in 16 patients who underwent D2 dissection, and the change in VFA (P = 0.81) as well as in SFA (P = 0.84) did not show any significant difference according to the extent of lymph node dissection.

FIG. 2. Postoperative to preoperative VFA and SFA in 14 patients who underwent total gastrectomy (TG) and 63 who underwent distal (DG) gastrectomy. *P = 0.0003.

statistically significantly different between the DG and TG groups, although the change in TG tended to be larger. VFA was reduced to 66.5% ± 27.2% in the DG group, but was more greatly reduced to 37.8% ± 21.6% of the preoperative value in the TG group, and the difference was statistically significant (P = 0.0003). Adipose tissue is considered to be systemically controlled by the postoperative nutritional status. Since the postoperative nutritional state is significantly more impaired in patients who undergo TG than in those who undergo DG, it seems reasonable that patients who underwent TG showed a smaller fat area than those with DG. However, the difference in the reduction ratio between VFA and SFA in the TG group (P = 0.0006) suggests the existence of specific mechanisms to regulate the two different fat volumes.
degree than was SFA when the vagus nerve was resected with TG or DG (68.2% versus 52.7%, P < 0.0001).

Body Weight and Nutritional Status after Gastrectomy With or Without Vagus Preservation

Finally, we examined the changes of body weight and albumin, total cholesterol, and triglycerides levels in circulating blood after surgery and compared the ratio against preoperative values between vagus-preserved and resected patients. As shown in Table 2, the postoperative weight was higher in vagus-preserved than vagus-resected patients (P = 0.046). Albumin, total cholesterol, and triglycerides were also maintained at relatively high level in vagus-preserved group, however, the difference was not statistically significant. From these facts, it is supposed that the nutritional status may be related with the difference of the change of total body weight, but could not fully explain the biased reduction of VFA.

DISCUSSION

Weight loss is a well-known complication after gastrectomy, and is mainly due to reduced body fat [8]. However, the effects of various surgical procedures associated with gastrectomy on postoperative fat volumes are not well understood. In the present study, therefore, we examined the changes of VFA and SFA separately in gastrectomized patients using Fat Scan software, which is now widely used for the evaluation of visceral fat volume in the field of metabolic diseases [20–22]. In the early postoperative period, fat volumes are seriously affected by the metabolic abnormality caused by gastrectomy. Therefore, in this study, we compared CT images taken at 6 mo to 5.2 y after surgery, when the nutritional condition is expected to be fully recovered to a stable state. In fact, no significant correlation was observed between the ratio of postoperative to preoperative fat areas and the time when the postoperative CT scan was performed (data not shown).

We found that both VFA and SFA tended to be reduced more greatly after TG compared with DG,
although the difference was statistically significant only for VFA. Postoperative VFA as well as SFA also tended to be preserved in patients who underwent PPG compared with pylorus-resected DG, which basically agree with the results with previous studies [23, 10]. However, the ratio of SFA and VFA changes were mostly similar between PPG and DG. This fact suggests a possibility that the range of gastrectomy may systemically affect the postoperative nutritional status, but does not have a significant role in the specific regulation of intra-abdominal fat.

In contrast, the reduction of VFA was significantly greater in patients who underwent conventional DG than that in vagus nerve-preserving DG, although similar changes in SFA were observed. It is unlikely that the difference was caused by nodal dissection because the reduction of VFA did not show any significant difference between the groups with D1 and D2 dissection. However, when we compared the change of VFA and SFA in each patient, the reduction rate of VFA was significantly greater than that of SFA only when the vagus nerve was resected in conventional TG or DG, whereas VFA remained at the same level as that of SFA in patients who underwent vagus nerve-preserved gastrectomy. These findings strongly suggest that the vagus nerve is selectively involved in the maintenance of visceral fat, and raises the possibility that the biased decrease of VFA in TG may also be caused by bilateral

<table>
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<th>Vagus nerve status</th>
<th>% Preoperative values (n)</th>
<th>Resected</th>
<th>Preserved</th>
<th>P value</th>
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<tr>
<td>Weight</td>
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<td>89.0% ± 7.8%</td>
<td>92.8% ± 7.2%</td>
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<tr>
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<td>100.0% ± 8.8%</td>
<td>0.43</td>
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<tr>
<td>Total cholesterol</td>
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<td>92.3% ± 19.5%</td>
<td>98.2% ± 9.8%</td>
<td>0.36</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>33</td>
<td>94.7% ± 50.5%</td>
<td>132.2% ± 102.2%</td>
<td>0.16</td>
</tr>
</tbody>
</table>

Blood data were obtained at the same day of the CT scan examination, and P value was examined by Wilcoxon nonparametric analysis.
truncal vagotomy associated with gastrectomy, although other local factors might also be involved.

It is well known that in an energy-saving catabolic state of the body, the sympathetic nervous system predominates, whereas in an energy-saving anabolic state, the parasympathetic nervous system prevails [24, 25]. Anatomical and physiologic studies have demonstrated innervation of adipose tissue by sympathetic nerves, which accelerate lypolysis of adipocytes [15, 26]. More recently, Kreier et al. reported that the intra-abdominal and subcutaneous fat pads are innervated by separate parasympathetic neurons [16]. These findings clearly suggest that the autonomic nervous system locally controls the metabolism and energy expenditure of adipose tissue toward a catabolic or anabolic state. The vagus nerve is a major parasympathetic nerve distributed to the intra-abdominal organs and fat tissue. Since parasympathetic nerves function to save energy in an anabolic state, our results that preservation of the vagus nerve results in the preservation of visceral fat volume after gastrectomy seem to be reasonable. In fact, Kreier et al. demonstrated that selective denervation of the vagus nerve caused a reduction of insulin-mediated free fatty acid uptake and increased hormone-sensitive lipase in adipose tissue in the rat [16], which is totally consistent with our data in humans.

The vagus nerve consists of ventral and dorsal vagi that run in the anterior and posterior wall of the abdominal esophagus, respectively. In vagus-preserving DG, hepatic branches derived from the ventral vagus are preserved in all cases, while the celiac branch derived from the dorsal vagus is sometimes difficult to identify and is resected with the left gastric artery in the course of nodal dissection [27]. Previous studies showed that the hepatic branch contains both afferent and efferent nerve fibers and controls the metabolic function of the liver [24, 28], while the celiac branch has been shown to be related to motor activity and secretion in the gastrointestinal tract [27, 29]. In our data, the changes in VFA and SFA were not significantly affected by the presence of the celiac branch, although the number of cases is too small to draw a conclusion. However, since these two vagus branches are considered to have closely interrelated functions in metabolism in intra-abdominal organs, including visceral fat, further investigation in a larger number of gastrectomized patients may bring some interesting findings on the definite function of the hepatic and celiac branches.

In summary, our data strongly suggest that the vagal system locally controls fat metabolism in the intra-abdominal area. In fact, truncal vagotomy was first proposed for the treatment of severe obesity in 1978 [30]. Recently, it was shown that intermittent intra-abdominal vagal blocking with an implantable medical device successfully reduced weight in 31 overweight patients [31]. Together with these clinical observations, our data support the hypothesis that selective denervation of the vagus nerve may lead to excessive weight loss and thus might be a reasonable strategy as surgical treatment for pathologic obesity.

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