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Bariatric Surgery on Type 2 Diabetes Mellitus Patients in Japan

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I Introduction

Amidst a worldwide epidemic of diabetes, the World Health Organization estimates that more than 220 million people have diabetes and an estimated 3.4 million people died from consequences of high blood sugar in 2004[1)]. In Japan, a 2009 report from the Ministry of Health, Labour and Welfare stated that there are approximately 8.9 million Japanese who are strongly suspected of having diabetes[2)]. Over time, diabetes can damage the heart, blood vessels, eyes, kidneys, and nerves. In particular, diabetes increases the risk of heart disease and stroke.

Obesity carries with it significant risks of diabetes[3)]. Improvement in obesity is attendant with improvements in this ailment[4)5)], and obese people consequently have been treated through pharmacotherapy, and intervention in life habits, including diet and exercise. Even with such treatment, however, it is very difficult to achieve satisfactory body weight loss. In the last few years many studies have been performed to compare intensive glucose control therapy with standard therapy. Most of the results show that body weight did not change with either intensive glucose control therapy or standard therapy[6)7)]. Additionally, in the case of the Veterans Affairs Diabetes Trial (VADT), body mass index (BMI) of the patients increased from 31.3 kg/m^2 to 33.8 kg/m^2 with intensive glucose control therapy in a median follow-up period of 5.6 years[8)]. Moreover, many patients who are initially successful at weight loss then go on to rebound[9)]. Thus, promoting weight loss without rebound is a major issue in treatment, especially in severely obese patients. Recently, there has been an increase in patients with a BMI＞35 undergoing bariatric surgery[9)]. Bariatric surgery generally consists of either gastric bypass, as typified by the Roux-en-Y Gastric Bypass (RYGB), or gastric binding, including vertical banded gastroplasty and laparoscopic adjustable gastric banding. The RYGB method creates a proximal pouch by segmentation of the stomach and the proximal pouch is drained with a Roux limb of proximal jejunum[10)]. Vertical banded gastroplasty features a small pouch based on the lesser curvature of the stomach and a mesh or plastic band around the outlet of the pouch to narrow the outlet to about 1 cm[10)]. Laparoscopic adjustable gastric banding is similar to vertical banding but uses an adjustable band, which is lined with an inflatable cuff joined to a small reservoir to allow adjustment of the pouch outflow and meal capacity[10)]. There has been a notable increase in studies describing the effect of bariatric surgery on type 2 diabetes patients[9)].

II Effect of Bariatric Surgery on Obesity and Diabetes

Although an average of 55.9 % loss in excess body weight was observed in bariatric surgery[9)], the extent of operation-induced weight loss varies depending on the surgical method[11)]. Gastric binding reduce the storage capacity of the stomach and as a result early satiety arises, leading to a decreased

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Table 1 Efficacy for improvement in diabetes-related outcomes for diabetic and glucose-intolerant patients[16]

	Total (n)	Gastric Binding (n)	Gastric Bypass (n)
Absolute Weight Loss (Kg)	-41.9 (266)	-26.0 (56)	-50.54 (129)
BMI Decrease (kg/m²)	-14.0 (306)	-9.1 (56)	-18.0 (166)
Excess Loss (%)	-57.3 (267)	-41.0 (83)	-65.7 (184)
Fasting Insulin (pmol/L)	-123.9 (160)	-49.5 (56)	-153.7 (90)
HbA1c (%)	-2.4 (171)	-1.2 (83)	-3.0 (88)
Fasting Glucose (mmol/L)	-4.0 (296)	-3.2 (56)	-3.4 (164)

BMI : body mass index

caloric intake[12]. RYGB also has this aspect but in addition it shortens the functional length of the small intestine and creates a short-bowel syndrome[13]. While loss in body weight from intervention in life habits is insufficient[3][14][15], it was 46.2 % for gastric binding and 59.5 % for gastric bypass, respectively, thus showing that bariatric surgery leads to more efficient weight-loss results[9]. However, although bariatric surgery generally leads to a great improvement in diabetes[16] (Table 1), there is a gradation of results depending on the procedure[17]. Additionally for type 2 diabetes patients, studies on gastric bypass have shown that improvements in fasting plasma glucose and insulin sensitivity are evident prior to weight loss[3][18][19]. These kinds of changes are not observed in gastric binding[9][20]. From these results, apart from improvements in insulin sensitivity induced through weight loss, gastric bypass is also thought to improve glucose metabolism.

Ⅲ Effects of Bariatric Surgery on Intestinal Hormones

One hypothesis to explain this phenomenon is the influence of gastrointestinal hormones. Glucagon-like peptide-1 (GLP-1), an intestinal hormone secreted from the distal ileum and colon in response to nutrient ingestion[17], increases c-AMP in pancreatic β-cells and is involved in glucose-dependent insulin release[20][21]. GLP-1 decreases dietary intake by slowing gastric emptying[9][22], controlling secretion of gastric acid[23] and glucagon[24], and inducing satiety by working on the central nervous system[25]-[27]. GLP-1 is also involved in the proliferation and regeneration of pancreatic β-cells[28][29]. There have been numerous studies detailing a post-operative increase in GLP-1 secretion from gastric bypass, and this increase occurs prior to post-gastric bypass weight loss[30]-[33]. Studies show that the post-gastric bypass GLP-1 level is significantly higher when compared to the post-gastric binding GLP-1 level[34][35]. There are also studies showing that the GLP-1 level is significantly higher in post-gastric bypass groups than in groups reducing their weight through diet and/or medication[36][37]. Because there is no statistical difference in post-operative body weight based on surgical methods according to these studies, it seems that the change in body weight is not the primary factor modulating GLP-1 in gastric bypass. Based on the food stimulation-induced secretion from the distal ileum, some groups think that increases in GLP-1 secretion after the gastric bypass can be attributed to the phenomenon whereby the post-operative gut forms in such a way that dense foods pass rapidly into the distal intestine[37]-[40]. As no improvement occurs in fasting plasma glucose in cases in which food is made to pass via both the duodenum and the stomach-small intestine shunt, an alternative hypothesis is that food passing via the proximal intestine exerts a negative influence on glucose metabolism[41][42]. When considering the effect of GLP-1, it is possible that the increase in endogenous GLP-1 secretion plays an important role in the improvement of glucose metabolism by the gastric bypass surgery.

Although ghrelin is similar to GLP-1 in that it is

Table 2 Complications from bariatric surgery[59]

	RYGB (Studies/Patients)	VBG (Studies/Patients)	AGB (Studies/Patients)
% Early or time-unspecified mortality Rate	1.0 (15/907)	0.2 (11/401)	0.4 (6/268)
GI Symptoms			
% All	16.9 (34/7374)	17.5 (21/1692)	7.0 (17/3400)
% Reflux	10.9 (3/727)	2.2 (7/823)	4.7 (4/485)
% Vomiting	15.7 (8/1324)	18.4 (10/1177)	2.5 (4/562)
% Nutritional and electrolyte abnormalities	16.9 (10/2088)	2.5 (4/397)	NR
% Anatomic or Stromal Stenosis	4.6 (30/5645)	6.0 (14/1456)	NR
% Bleeding	2.0 (19/5026)	0.7 (6/1027)	0.3 (6/2844)
% Reoperation	1.6 (9/4356)	11.3 (7/520)	7.7 (11/2140)

RYGB : Roux-en-Y Gastric Bypass, VBG : Vertical Banded Gastroplasty, AGB : Adjustable Gastric Band, NR : not reported

related to the appetite, it is actually an appetite-stimulating hormone[43)–45)]. It is likely that the appetite stimulation from ghrelin is due to its increasing activity in the stomach[44)46)] and suppression of insulin secretion[46)]. Ghrelin levels increase in dietary restriction-induced weight loss and when there is a negative energy balance[47)], and conversely, decrease when eating or in the case of the obese[48)]. However in the case of the obese, ghrelin levels become unchanged even when eating, and therefore, ghrelin level is a potential factor in obesity[49)]. There are many reports of postprandial, post-RYGB ghrelin levels and ghrelin levels decreasing in times of fasting compared to pre-operation[50)51)], lean[51)52)], normal body weight[53)54)], obese[51)–55)], and post-surgery in other types of bariatric surgery[35)54)56)]. However, there are also studies showing that postprandial, post-RYGB ghrelin levels are comparable to those of lean and post-surgery patients in other kinds of bariatric surgery[57)58)]. It has been reported that a decrease in ghrelin levels occurs immediately following surgery and lasts for more than a year[54)58)]. Through RYGB, food bypasses the distal stomach in which ghrelin is released, and this may account for the post-bypass decrease in ghrelin levels[50)]. This explanation would suggest the possibility that appetite cannot be suppressed in bariatric surgery that does not bypass the distal stomach.

Ⅳ Adverse Effects of Bariatric Surgery

There are some complications from bariatric surgery that occur solely from its nature as surgery. In addition to the post-operative short-term mortality rates (deaths within 30 days post-surgery) of 0.2 % in the case of VBG and 1.0 % in the case of the potentially more effective RYGB[59)], complications other than death have been reported as follows : GI symptoms in 16.9 % of RYGB cases and 17.5 % of VBG cases, and nutritional and electrolyte abnormalities in 16.9 % for RYGB and 2.5 % for VBG (Table 2)[59)].

Ⅴ Clinical Application of Bariatric Surgery in Japan

As previously stated, there are reports that bariatric surgery leads to dramatic improvement in type 2 diabetes compared to pharmacotherapy and lifestyle intervention-based treatment. Will bariatric surgery replace conventional medication and/or life style intervention-based treatment in Japan? At present, however, most of these reports are not necessarily targeting regular subjects, given the subjects' extremely high average BMI of 47.9 kg/m^2 and relatively young average age of 40.2 years old.

Obesity in the Japanese population is much less than in Western populations. The Ministry of Health, Labour and Welfare, Japan reported that

only 3.7 % of the population is obese (BMI＞30)[60]. The rate of obesity in diabetes is reported to be similar to that in the rest of the Japanese population[61], and at present bariatric surgery has only a limited application in Japan.

Ⅵ Summary

In this review, we outlined the endocrinological and clinical effects of bariatric surgery in obese and diabetic patients. Recently, in certain countries, there has been an increase in obese patients undergoing bariatric surgery which leads to more efficient weight-loss results. Bariatric surgery is an effective treatment option for severely obese patients for whom weight loss has been problematic with conventional pharmacotherapy and/or life style intervention-based treatment. At present, however, there is a need for a high-evidence level cohort study based on previous research that varies by age and obesity level in order to further the discussion on whether bariatric surgery should be given precedence over conventional medication and life style intervention-based treatment in Japan.

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