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## Bariatric Surgery on Obese Type 2 Diabetes Patients

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### 1. Introduction

Amidst a worldwide epidemic of diabetes, the World Health Organization estimates that 346 million people have diabetes and an estimated 3.4 million people died from consequences of high blood sugar in 2004<sup>1)</sup>. Over time, diabetes can damage the heart, blood vessels, eyes, kidneys, and nerves. Especially diabetes increases the risk of heart disease and stroke.

Obesity carries with it significant risks of diabetes. Improvement in obesity is attendant with improvements in this ailment<sup>2)3)</sup>, 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 have satisfactory body weight loss. In the last few years, many studies have performed to compare intensive glucose control therapy with standard therapy. Most of the results show that body weight did not change with both intensive glucose control therapy and standard therapy<sup>4)5)</sup>. Moreover, many patients who are initially successful at weight loss then go on to rebound<sup>6)</sup>. Thus, promoting weight loss 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 and there has been a notable increase in studies describing effect of bariatric surgery on type 2 diabetes patients<sup>6)</sup>.

### 2. Effect of bariatric surgery on obesity and diabetes

Although an average of 55.9% loss in excess body weight was observed in bariatric surgery<sup>6)</sup>, the extent of operation-induced weight loss varies depending on the surgical method<sup>7)</sup>. While loss in body weight from intervention in life habits is insufficient, 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<sup>6)</sup>. However, although bariatric surgery generally leads to a great improvement in diabetes<sup>8)</sup> (Table 1), there is a gradation of results depending on the procedure<sup>9)</sup>. 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<sup>10)11)</sup>. These kinds of changes are not observed in gastric binding<sup>6)12)</sup>. From these results, apart from improvements in insulin sensitivity induced through weight loss, gastric bypass is also thought to improve glucose metabolism.

	Total (n)	Gastric Binding (n)	Gastric Bypass (n)
Absolute Weight Loss (Kg)	-41.9 (266)	-26.0 (56)	-50.54 (129)
BMI Decrease (kg/m <sup>2</sup> )	-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			

Table 1. Efficacy for Improvement in Diabetes-Related Outcomes for Diabetic and Glucose-Intolerant Patients <sup>8)</sup>.

Incretin	Secretion	Function	Change after bariatric surgery
GLP-1	Distal ileum , Colon	Increase insulin release Slowing gastric emptying Controlling Glucagon secretion Induce satiety by working on the central nervous system	Increase
Ghrelin	Stomach	Stimulate appetite Increasing activity in the stomach Suppression of insulin secretion Increase growth hormone secretion	Decrease (Roux-en-Y Gastric Bypass)

Table 2. Summary of Intestin.

3. Effects of bariatric surgery on intestine hormone

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<sup>9)</sup>. GLP-1 acts on the beta cells to increase the level of cyclic AMP, leading to replenishment of the readily releasable pool of insulin granules during glucose-stimulated insulin secretion<sup>13)</sup>. Not only improving beta-cell function, GLP-1 is also involved in the proliferation and regeneration of pancreatic  $\beta$ -cells<sup>14)15)</sup>. Outside pancreatic effects, GLP-1 decreases dietary intake by slowing gastric emptying<sup>16)</sup>, controlling secretion of gastric acid<sup>17)</sup> and glucagon<sup>18)</sup>, and induce satiety by working on the central nervous system<sup>19)20)</sup>. 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<sup>21-24)</sup>. Studies show that the post-gastric bypass GLP-1 level is significantly higher when compared to the post-gastric binding GLP-1 level<sup>25) 26)</sup>. 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 related to the appetite, it is actually an appetite-stimulating hormone<sup>27-29)</sup>. It is likely that the appetite stimulating from ghrelin is due to its increasing activity in the stomach<sup>28)30)</sup> and suppressing of insulin secretion<sup>30)</sup>. Ghrelin levels increase in dietary restriction-induced weight loss and when there is a

negative energy balance, and conversely, decrease when eating or in the case of the obese<sup>31)32)</sup>. However in the case of the obese, ghrelin levels become unchanged even when eating, and therefore, ghrelin level is a potential factor in obesity<sup>33)</sup>. There are many reports demonstrating that fasting ghrelin levels decrease after Roux-en-Y Gastric Bypass compared to pre-operation<sup>34)35)</sup>. It has been reported that decrease in ghrelin levels occurs immediately following surgery and lasts for more than a year<sup>36) 37)</sup>. Through Roux-en-Y Gastric Bypass, food bypasses the distal stomach in which ghrelin is released, and this may account for the post-bypass decrease in ghrelin levels<sup>34)</sup>.

#### 4. Incretin-therapy on type 2 diabetes patients

Recently GLP-1 analog/receptor agonists and GLP-1 degradation inhibitors are in clinical use. The beneficial points of these antidiabetes agents are glucose-dependent insulinitropism which may be reduced the risk of hypoglycemia<sup>38)</sup>. Liraglutide is a GLP-1 analog with 97% sequence identity to human hormone. The mean reduction in HbA1c by liraglutide (1.8mg) was 1.14%<sup>39)</sup>. In addition to effective glucose lowering, liraglutide produced beneficial effects on body weight. The mean reduction in body weight after 16weeks treatment of 1.8mg liraglutide was 3.6kg and was sustained throughout the 52 week study<sup>39)</sup>. These results support the hypothesis that the bariatric surgery leads to a great improvement of diabetes not only by the reduction of the storage capacity of the stomach but also by the change in intestinal hormone.

#### 5. Clinical application of bariatric surgery in Asia

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 Asia? 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<sup>2</sup> and relatively young average age of 40.2 years old<sup>6)</sup>.

Obesity in the Asian 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)<sup>40)</sup>. The rate of obesity in diabetes is reported to be similar to that in the rest of the Japanese population<sup>41)</sup>, and at present bariatric surgery has only a limited application in Japan. To increase the application of bariatric surgery in Asia, 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 patients with a BMI > 35.

#### 6. Summary

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. Gastric bypass has been shown not only to decrease body weight but to have an effect on incretin (Table 2). Change in incretin, especially GLP-1, could support the improvement in body weight. GLP-1 also has beneficially affect on pancreatic  $\beta$ -cells function, proliferation and regeneration. Thus even if diabetes did not cure by bariatric surgery, change in incretin have beneficially effect on diabetes. Therefore to choose the operative procedure of bariatric surgery, especially on patients who have basic disease, it is necessary to think about dynamic state of incretin.

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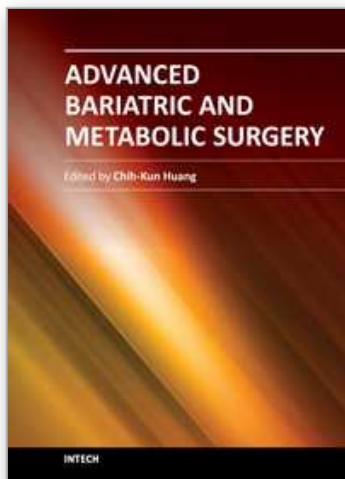
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Bariatric surgery has gained importance in the last 20 years because of the high prevalence of global obesity, and the vast understating of the physiological and pathological aspects of obesity and associated metabolic syndromes. This book has been written by a number of highly outstanding authors and pioneering bariatric surgeons from all over the world. The intended audience for this book includes all medical professionals involved in caring for bariatric patients. The chapters cover the choice of operation, preoperative preparation including psychological aspect, postoperative care and management of complication. It also extends to concept and result of metabolic surgery and scarless bariatric surgery.

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