Surgery for Diabetes at Lower BMI: Some Caution

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Many thousands of years ago, our ancestors were hunter–gatherers and performed arduous labor. They hunted animals and also ate some fibrous roots, berries, and nuts—a diet high in protein with some complex carbohydrates [1–3]. This coincides with a diet with a low glycemic index [4, 5]. These meals were irregular and sometimes infrequent, and when there was a “kill”, the entire clan would share the meal. Through natural selection, early man developed “thrifty” genes for times of famine [6].

However, in the past 8,000 years, farming of indigenous wild grains commenced. Frequent high carbohydrate meals with a higher glycemic index became available, with frequent stimulation of insulin secretion from the pancreas. High plasma insulin levels and insulin resistance developed, with impaired glucose tolerance. This progressed to the modern era where fast foods (containing particularly high levels of simple sugars), affluence, and a sedentary lifestyle have led to an “obesity pandemic”. The so-called metabolic syndrome, with insulin resistance, type 2 diabetes, hypertension, dyslipidemia, atherosclerosis, and coronary artery disease, and fatty liver are now prevalent [7]. The prior thrifty genes now contribute to obesity.

We now have the increasing incidence of type 2 diabetes. The impaired glucose handling is associated with elevated plasma insulin and a down-regulation of insulin receptors [8]. The high levels of circulating insulin inhibit lipolysis and promote lipogenesis.

Immediately following all types of bariatric operations, there is rapid improvement in glucose handling, before there is significant weight loss and often before the patient is even discharged from hospital [9, 10]. After the old jejuno-ileal bypass, the oral glucose tolerance and insulin tolerance curves were markedly flattened—glucose bypassed its absorptive area in the intestine [11]. Shortly after gastric restrictive or gastric bypass operations with gastric channel and stomal edema, the patient is only able to consume 575±146 kcal/day at time of discharge from hospital [12–14] and there is rapid up-regulation of insulin receptors [15, 16] located on cell membranes in muscle and adipose tissue.

Later, the improved glucose metabolism after gastric restrictive [17] and bypass [18] procedures is associated with the weight loss, and is greater after gastric bypass operations, which are followed by a more rapid and greater decrease in fat mass [9].

Originally, bypass of hormones in the foregut was postulated as the reason for the improved glucose processing [19, 20]. More recently, stimulation of incretins (intestinal hormones that stimulate insulin secretion) in the distal small bowel due to expedited nutrient delivery, have been confirmed to be elevated [21]. The most interest has been in glucagon-like peptide-1 (GLP-1) secreted into the bloodstream by the L-cells of the hindgut [22, 23]. GLP-1 (7-36) amide has been found to stimulate postprandial
Insulin secretion from the beta cells and increase beta-cell mass (as well as delay emptying of the intact stomach) [21]. GLP-1 has been associated with dramatic improvement of diabetes mellitus in those operations that bypass the proximal intestine [24].

This has led to a GLP-1 frenzy, with a move by bariatric surgeons currently to treat diabetes in patients with lower BMIs (even below the obesity range) with a bariatric operation that includes bypass of the proximal intestine—i.e., the gastric bypass, duodenal switch, or the original biliopancreatic diversion [25–27]. The sleeve gastrectomy has also been found to result in accelerated gastric emptying for GLP-1 elevation [28]. Additionally, those bariatric operations that remove the fundus of the stomach have the benefit of removing the major site of the orexigenic hormone ghrelin (growth hormone releasing hormone)—i.e., removing a stimulus to appetite [29]. Ileal transposition to the proximal jejunum has been suggested to increase GLP-1 secretion in normal-weight patients, as a treatment for type 2 diabetes [30, 31].

**Slow Onset Type 1 Diabetes (Latent Autoimmune Diabetes in the Adult)**

A number of the papers submitted to *Obesity Surgery* regarding treatment of diabetes in adults with lower BMIs, by a gastric bypass or BPD, have had to be rejected because of lack of essential documentation. These patients had been automatically assumed to be type 2 diabetes by their surgeons and team; the presence of adult onset of type 1 diabetes had not been considered in these patients. Latent Autoimmune Diabetes in the Adult (LADA) has been reported to make up 10% of diabetics with onset at age 30 and onward. Autoimmune Diabetes in the Adult (LADA) has been overlooked this feature, and/or have not provided long-term follow-up regarding late insulin dependency [25–27, 31].

LADA may be diagnosed by auto-antibodies to: islet cells, glutamic acid decarboxylase, and/or insulin. Plasma insulin levels in these individuals are low (unlike often found in type 2 diabetics). Thus, the C-peptide level is very low, as the pancreas eventually has no beta-cell activity [32, 33].

C-Peptide: when proinsulin is released from the pancreas into the blood in response to a rise in glucose, the proinsulin is split into insulin and C-peptide (connecting peptide)—one C-peptide for each insulin molecule. Patients with LADA (slow type 1 diabetes) have autoimmune destruction of pancreatic beta cells and over time are unable to produce insulin, so that their C-peptide levels become very low (often <0.25 ng/ml, with no response to meal- or glucagon-stimulation).

In type 2 diabetes, C-peptide levels are above normal or normal. However, with the insulin resistance and associated lipogenesis and lipotoxicity of type 2 diabetes, cells become “starved” for glucose, signaling a compensatory increase in insulin production, which can eventually lead to beta-cell apoptosis, unless treated with diet and hypoglycemic agents.

Early LADA may respond to stimulation by GLP-1. However, as beta cells are progressively destroyed, these individuals must be placed on insulin injections and must maintain dietary consistency. If they undergo a gastric restrictive operation which occasionally can have stomal edema (e.g., after NSAIDs or other irritating drugs), or more importantly, if they undergo a malabsorptive bariatric operation, in which hypertonic sugary liquids precipitate rapid transit, it becomes difficult to standardize their insulin requirements. Thus, although a bariatric operation may provide early satisfactory results in these individuals, it can eventually lead to problems in tight diabetic control.

These “slow” type 1 diabetics do not have hyperinsulinemia and an associated metabolic syndrome. Their diabetic control is monitored by HbA1c determinations. Longstanding elevated plasma glucose in LADA (reflected by elevated HbA1c) will lead to diabetic complications. On the other hand, episodes of hypoglycemia from excess injected insulin can be problematic.

Thus, it is important to differentiate between types 1 and 2 diabetes in the adult when bariatric surgery is being considered, particularly in patients whose BMI is below that of severe obesity. Published papers appear to have overlooked this feature, and/or have not provided long-term follow-up regarding late insulin dependency [25–27, 31].

**GLP-1**

GLP-1 has an insulinoergic effect on the beta cells and its significance has even been compared to the discovery of
insulin. However, in the situation of no endogenous insulin, diabetes is certainly present, whereas with no GLP-1, diabetes does not seem to occur. In patients with marked Crohn’s disease and major resections when I worked under Dr. Leon Ginzburg in New York and when I followed my own regional enteritis patients and bowel resections from the 1960s to 1990s, extensive ileo-colic (hindgut) resections were not followed by diabetes. Also, in the late 1960s, when I locally pioneered intravenous hyperalimentation (TPN) and many patients were referred with massive small bowel and right colon resections due to mesenteric vascular occlusion or antithrombin III deficiency, the development of diabetes postoperatively was not a feature. This requires investigation.

GLP-1 Mimetic

The GLP-1 mimetic, exenatide, has been synthesized (Byetta®, Amlyn Pharmaceuticals and Lilly, injected as 10 μg S.C. b.i.d.) [36, 37]. In type 2 diabetics with a lower BMI, the oral GLP-1 mimetic may be tried first (with surveillance), as a potential test before bariatric surgery, or as treatment to produce a GLP-1 effect on the pancreas, to determine individual effect [23].

References