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Review

Changes in Insulin Resistance Following Bariatric Surgery: Role of Caloric Restriction and Weight Loss

Andrew A. Gumbs, MD[1]; Irvin M. Modlin, MD, PhD[1]; Garth H. Ballantyne, MD[2]

Departments of Surgery, [1]Yale University School of Medicine, New Haven, CT, and [2]Hackensack University Medical Center, Hackensack, NJ, USA

The prevalence of type 2 diabetes mellitus (T2DM) and obesity in the western world is steadily increasing. Bariatric surgery is an effective treatment of T2DM in obese patients. The mechanism by which weight loss surgery improves glucose metabolism and insulin resistance remains controversial. In this review, we propose that two mechanisms participate in the improvement of glucose metabolism and insulin resistance observed following weight loss and bariatric surgery: caloric restriction and weight loss. Nutrients modulate insulin secretion through the entero-insular axis. Fat mass participates in glucose metabolism through the release of adipocytokines. T2DM improves after restrictive and bypass procedures, and combinations of restrictive and bypass procedures in morbidly obese patients. Restrictive procedures decrease caloric and nutrient intake, decreasing the stimulation of the entero-insular axis. Gastric bypass (GBP) operations may also affect the entero-insular axis by diverting nutrients away from the proximal GI tract and delivering incompletely digested nutrients to the distal GI tract. GBP and biliopancreatic diversion combine both restrictive and bypass mechanisms. All procedures lead to weight loss and decrease in the fat mass. Decrease in fat mass significantly affects circulating levels of adipocytokines, which favorably impact insulin resistance. The data reviewed here suggest that all forms of weight loss surgery lead to caloric restriction, weight loss, decrease in fat mass and improvement in T2DM. This suggests that improvements in glucose metabolism and insulin resistance following bariatric surgery result in the short-term from decreased stimulation of the entero-insular axis by decreased caloric intake and in the long-term by decreased fat mass and resulting changes in release of adipocytokines. Observed changes in glucose metabolism and insulin resistance following bariatric surgery do not require the posit of novel regulatory mechanisms.

Key words: Diabetes, insulin resistance, obesity, morbid obesity, weight loss, bariatric surgery

Reprint requests to: Garth H. Ballantyne, MD, Professor of Surgery, Hackensack University Medical Center, 20 Prospect Avenue, Suite 901, Hackensack, NJ 07601, USA. Fax: 1-201-996-3222; e-mail: ghb@lapsurgery.com

Introduction

The prevalence of obesity is steadily increasing worldwide and is associated with some of the most common diseases affecting the developed world: type 2 diabetes mellitus (T2DM), coronary artery disease, hypertension and cancer. Obesity now affects over 34 million Americans of which almost one-third are classified as morbidly obese, defined as a body mass index (BMI) ≥40 kg/m^2.[1] Indications for surgery now include morbidly obese patients or patients with a BMI >35 with co-morbidities.[2] Although the initial impetus driving the development of bariatric operations was for weight loss in the obese, another important goal of bariatric surgery has become the amelioration and treatment of T2DM.

Obesity, Insulin Resistance and Type 2 Diabetes Mellitus

In 1992, Pories drew attention to the dramatic improvement in T2DM following gastric bypass for morbid obesity.[3] This observation has been confirmed by many others.[1,2,4,5] Vertical banded gastroplasty (VBG) and laparoscopic adjustable gastric banding (LAGB) are restrictive operations that limit

nutrient and caloric intake. Roux-en-Y gastric bypass (RYGBP) and biliopancreatic diversion (BPD) combine both restrictive and malabsorptive components in one operation. Some groups argue that combined restrictive/bypass procedures, such as RYGBP and BPD, are superior to restrictive procedures alone, such as VBG and LAGB, in the control and prevention of diabetes in the obese, and in degree and persistence of weight loss.[1,6,7] Similarly, some authors suggest that BPD is superior to RYGBP in terms of weight loss and percentage of patients in whom T2DM improves.[1,6,8] Unfortunately, few studies directly compare outcomes in comparable groups of patients. Consequently, the mechanism or mechanisms that contribute to clinical improvement of T2DM following bariatric surgery remains ill-defined.

Proposed Mechanisms for Improved Glucose Metabolism after Bariatric Surgery

Several groups have proposed mechanisms by which weight loss surgery improves glucose metabolism, insulin resistance and T2DM. Pories' group has written most extensively on this topic.[3,9-11] Pories and Albrecht[9] hypothesized in 2001 that "Type 2 diabetes mellitus is caused by overstimulation of the foregut by food in vulnerable individuals". This hypothesis suggests that diabetics suffer from excess production of incretins such as glucagon-like-peptide-1 (GLP-1), gastric inhibitory peptide (GIP) and ghrelin.[12,13] Rubino, first with Gagner's group in New York City and later with Marescaux at the IRCAD in Strasbourg, France, has also stressed the importance of changes in foregut hormones before significant weight loss occurs, in the observed improvement in glucose and insulin metabolism following weight loss surgery.[2,14,15] Extending this general hypothesis, several groups have speculated that a specific previously unidentified gut hormone is released from the foregut that causes insulin resistance and that bariatric operations inhibit the release of this putative gut hormone.[16] Speculation on the role of the foregut following bariatric surgery in clinically improving T2DM is generally supported by outcomes from short-term studies.

Numerous groups have championed an alternative mechanism for improvement in T2DM following bariatric surgery. These authors argue that weight loss is the principle mechanism leading to improvement in T2DM and glucose metabolism following bariatric surgery.[17-20] Weight loss may significantly impact glucose metabolism and insulin resistance through changes in fat mass and changes in the release of adipocytokines such as leptin, adiponectin and resistin.[21,22] Support for the role of weight loss and fat mass loss in improvement of T2DM is generally garnered from studies with long-term outcomes.

Hypothesis

In this review, we outline the information that is available to support a role for these two putative mechanisms in the change in glucose metabolism and insulin resistance following bariatric surgery. Because we have found convincing data to support both mechanisms, we have hypothesized that following weight loss surgery:

1. Short-term changes in glucose metabolism and insulin resistance are caused by caloric restriction and modulated by the entero-insular axis; and
2. Long-term improvements in glucose metabolism and insulin resistance result from decreases in fat mass and are mediated through changes in adipocytokines.

Calorie Restriction and the Entero-Insular Axis: GIP, GLP-1 and Ghrelin

Unger and Eisentraut[23] proposed a role for the GI tract in the modulation of insulin secretion in 1969. They termed this mechanism the "entero-insular axis". In 1979, Creutzfeldt[24] updated this model. and suggested that nutrient, neural and hormonal signals from the gut participated in the regulation of beta-cell function. *Incretins* formed an important part of this putative mechanism. Creutzfeldt defined incretins as *gut hormones that were released by contact of nutrients with the GI mucosa and that stimulated the release of insulin at physiologic levels*. Sirinek and colleagues[7] in 1986 suggested that the enteroinsular axis mediated changes in hyperinsulinism following gastric bypass for morbid obesity. Partriti and colleagues[4] recently reviewed changes in the entero-insular axis following bariatric surgery.

Incretin Gut Hormones

Several endocrine insulinotropic factors exist that are secreted from the GI tract in response to contact with glucose. These hormones are known as incretins. Research on incretins has focused on the peptide products of the preproglucagon gene of the L-type endocrine cells[25,26] and glucose-dependent insulinotropic polypeptide (GIP) released by the K-type endocrine cells.[27] The L-type endocrine cells are primarily found in the terminal ileum, while the K-type cells are clustered in the proximal gut. Post-translational cleavage produces bioactive peptides of various lengths from the proglucagon peptide. In the L-type endocrine cell, these include enteroglucagon, glicentin, oxyntomodulin, glucagon-like peptide 1 (GLP-1), glucagon-like peptide 2 (GLP-2) and two spacer peptides called intervening peptide 1 (IP-1) and intervening peptide 2 (IP-2). Studies in the past which measured enteroglucagon levels or activities probably reflect GLP-1 release and bioactivity. GLP-1 and GIP may control as much as two-thirds of insulin secretion.[28] This suggests that alterations in the caloric stimulation of incretins can significantly and rapidly impact glucose metabolism and serum insulin levels. An extensive literature studying the impact of calorie-restricted diets on T2DM supports this mechanism, and, as we will see, caloric restrictions imposed by bariatric operations also rapidly improve glucose metabolism and insulin resistance in obese patients.

More recent studies have focused on ghrelin. The gut hormone ghrelin is an endogenous ligand of the growth hormone (GH) receptor (GHR).[29] Ghrelin stimulates the secretion of GH *in vivo*.[30-33] It is a peptide hormone that is produced by the stomach and duodenum that causes overeating and obesity in rodents.[34] Ghrelin levels increase before meals and are thought to be involved in meal initiation and rapidly decline postprandially.[35] Ghrelin administration leads to hyperphagia, decreased fat oxidation and increased adiposity in rodents.[31] In humans, ghrelin administration causes increased caloric intake and initiation of hunger.[36] The increase in appetite caused by this peptide is thought to be the cause of gradual weight gain that has been associated with dieting.[37] Recent investigations also indicate that ghrelin may act as an incretin and participate in the modulation of insulin secretion and insulin resistance.[12,13]

Calorie-Restricted Diets Leading to Clinical Improvement in T2DM

It has been long known that changes in diet can significantly impact glucose metabolism in a short period of time.[38] In 1985, Henry studied the impact of 40 days of a very low caloric diet on glucose metabolism in 30 obese, non-insulin dependent diabetics.[39] Average weight loss for all patients on the very low calorie diet was 4.6 ± 0.2 kg after 10 days, 7.1 ± 0.3 kg after 20 days and 10.5 ± 0.4 kg after 40 days. Fasting glucose in the very low calorie diet patients dropped from an average of 297 ± 13 mg/dl to 138 ± 9 mg/dl. Although patients lost weight steadily throughout the 40-day diet, 87% of the reduction in fasting glucose was achieved within the first 10 days. In 1993, Kelley and colleagues[40] tested the hypothesis that restricting calories had an independent role from weight loss in improving glucose metabolism. They found that a very low calorie diet substantially decreased fasting serum glucose, hepatic glucose production and insulin resistance in seven obese non-insulin dependent diabetic patients within 7 days. These rapid changes accounted for about half of the overall improvements observed in glucose metabolism following an average weight loss of 12.7 ± 2 kg. In 1998, Williams and colleagues[41] showed that brief periods of very low calorie diets improved glycemic control in T2DM patients: 54 T2DM patients who were more than 20% overweight were randomized to either a calorie-restricted diet of 1500-1800 kcal of 20 weeks or 1 or 5-day periods of very low calorie diets (VLCD) interspersed with the 1500-1800 kcal diet. All patients lost weight. Seven of 15 patients (47%) who had VLCD in the 5-day group and five of 16 patients (31%) in the 1-day group normalized their HbA1c, compared to only one patient of 15 in the standard behavior therapy group. The number of patients who normalized their HbA1c level was significantly greater (P=0.04) for the 5-day group compared to the standard behavior therapy group but did not achieve statistical significance with the 1-day group (P=0.17).

Ash and colleagues[42] in Brisbane, Australia studied the impact of 12 weeks of isocaloric dietary intervention in 51 men with T2DM with an average BMI of 31.7 kg/m^2. Patients were placed on a calo-

rie-restricted diet of 1400-1700 kcal/day. Average weight loss at 12 weeks was 6.4 ± 4.6 kg, average decrease in body fat percent was 1.9 ± 1.5% and average decrease in HbA1c was 1.0 ± 1.4%. Significant changes in glucose metabolism become apparent as early as 4 weeks after initiation of a calorie-restricted diet. Average weight loss for 45 overweight (BMI 33.2 kg/m^2) individuals 4 weeks after starting a calorie restricted diet (average 1543 ± 18 kcal/day) was 3.6 ± 0.3 kg.[43] Fasting glucose significantly decreased an average of 6% and HbA1c significantly dropped by 3%.

Similarly, Jarvi and colleagues[44] in Lund, Sweden studied 20 patients in a randomized cross-over trial comparing two diets with different glycemic indices during two consecutive 24-day periods. Average calorie count for each diet was 1880 kcal/day and average weight loss was 1.5 ± 7.21 kg. Fasting glucose significantly dropped about 14% with both diets. Also, insulin sensitivity using the clamp technique significantly improved by 21-30%.

These studies indicate that severe restriction of calories can lead to rapid improvement in fasting glucose levels and insulin resistance in obese patients within very short periods of time. Based on studies like these, Hensrud[45] speculated that short-term glycemic control is based on both calorie restriction and weight loss. In contrast, long-term changes in glucose metabolism and T2DM are dependent primarily on weight control.

Scopinaro's group[46] in Genoa, Italy has recently examined the role of calorie restriction in improving insulin resistance in the early postoperative period following BPD. They studied 20 obese (BMI 48.4 ± 7.6 kg/m^2) non-diabetic patients undergoing BPD. Three-quarters of the patients were insulin resistant before surgery (homeostatis model assessment, HOMA IR ≥ 2.5). Average weight dropped from 136.8 ± 30.2 kg to 117.5 ± 24.6 kg by 2 months after BPD. Preoperative fasting glucose levels in these patients dropped from 87.0 ± 30.6 mg/dl to 78.6 ± 23.1 on the 5th postoperative day and 77.3 ± 10.0 mg/dl 2 months following BPD. HOMA IR dropped from 8.0 ± 8.2 preoperatively to 3.4 ± 2.6 on the 5th postoperative day and 2.1 ± 2 2 months after BPD. Scopinaro's group concluded that these rapid changes in fasting glucose and HOMA IR "could be simply accounted for by the fasting state of the immediate postoperative period". They also noted a further improvement in HOMA IR from the 5th postoperative day to 2 months after surgery. They hypothesized that "the interruption of the enteroinsular axis might play a role in the post-BPD recovery of normal metabolic conditions".

Caloric Restriction Imposed by Restrictive Operations

Several surgical groups have proposed a role of calorie restriction in the improvement of T2DM following bariatric surgery. In 1991, Deitel, Sidhu and Stone[47] observed that T2DM improved after VBG in patients before discharge from the hospital and before substantial weight loss had occurred. They postulated that this clinical improvement in T2DM correlated with the decreased caloric intake of these patients. Patients consumed an average of 575 ± 146 kcal per day at the time of discharge. In 1993, Neve and colleagues[48] reported resolution of T2DM in three patients following VBG. Like Deitel and colleagues, these authors attributed the remission of diabetes to decreased calorie intake enforced by the VBG.

Caloric Restriction after Combined Restrictive and Bypass Operations

Several groups have posited that improvement in T2DM following RYGBP and BPD is due to caloric restrictions imposed by these bariatric operations. Smith, Edwards and Goodman[49] observed that 25 of 46 insulin-dependent diabetics no longer required insulin after RYGBP while another 9 patients required smaller insulin doses. These authors speculated that improvement in glucose metabolism following RYGBP resulted from a marked reduction in caloric and carbohydrate intake. Interestingly, when a patient who was intra-operatively noted to be unamenable to RYGBP received the same postoperative diet regimen, his glucose tolerance and plasma insulin levels increased for the several weeks that he was able to maintain the diet.[11] This putative mechanism suggests that limited caloric intake leads to diminished stimulation of insulin secretion because of decreased release of incretins. This proposed

mechanism for changes in glucose metabolism following bariatric surgery has been rarely studied.

Recently, Rubino and colleagues[50] studied changes in serum glucose and insulin 3 weeks following laparosocpic RYGBP. This study examined changes in glucose and insulin levels in 10 patients following laparoscopic RYGBP: six of these patients had T2DM treated with oral hypoglycemic agents. Preoperative BMI averaged 46.2 kg/m^2 (range 40 to 53 kg/m^2) and dropped to 43.2 kg/m^2 (difference not significant) 3 weeks following surgery. Both serum glucose and serum insulin levels significantly dropped by 3 weeks after RYGBP before significant weight loss had occurred. None of the T2DM patients required medical therapy following surgery. This group argues that the observed improvement in T2DM following RYGBP and BPD stems from alterations in circulating levels of gut hormones due to the bypass of portions of the foregut.[2] They argue that this is a unique effect of RYGBP and BPD.

Supporters of this mechanism argue against weight loss as the etiologic mechanism. The argument against weight loss as a cause for resolution of T2DM includes the observation that most patients with non-insulin dependent diabetes are obese or were when their insulin resistance began.[6] Furthermore, patients with insulinomas become insulin resistant whether they are obese or not.[6] The benefits of gastric restriction include an immediate limitation of caloric intake; unfortunately in gastroplasties this limitation may be temporary and may even increase with time.[8] In patients who do undergo gastroplasties without bypass, the resolution of T2DM is not as sustained, highlighting the importance of studies with adequate long-term follow-up. [2,3,5,6,11,51]

The bypass of the foregut as a cause for resolution of T2DM is supported by the observation that the correction in glucose metabolism occurs within days of surgery, that oral glucose boluses increase insulin levels higher than the same intravenous dose, and that the correction of T2DM is sustained even after some patients become obese again. Proponents of the missing peptide theory offer as their most compelling evidence for weight loss *not* to be the reason for resolution of T2DM the observation that patients who have exclusion of their foregut with a RYGBP have a more pronounced reduction in their glucose intolerance and hyperinsulinemia than patients who have a gastric restrictive operation alone, specifically VBG.[2,52]

Strong support for the missing foregut peptide hypothesis was recently published by Rubino and Marescaux[15] at the IRCAD-EITS in France. Gastrojejunal bypass with preservation of gastric volume was performed in Goto-Kakizaki rats. These non-obese rats spontaneously develop T2DM. A control group underwent sham operations. Both groups received similar postoperative diets that were restricted to one-third of the calories consumed by healthy ad-libitum fed rats. Daily average food intake and weight gain was similar for both groups of rats. One week following surgery, oral glucose tolerance worsened in the sham operation rats while the gastric bypass rats demonstrated a 40% reduction in the area under the glucose tolerance curve. Fasting serum glucose dropped from 159 ± 47 mg/dL preoperatively to 96.3 ± 10.1 mg/dL 3 weeks following surgery. Preoperative and postoperative glucose levels remained unchanged in the sham operation rats. In a second set of experiments, gastrojejunal bypass was compared to controls and rats treated with the insulin-sensitizing drug rosiglitazone. Gastric bypass achieved significantly lower fasting glucose levels (86.4 ± 26.3 mg/dL) than rosiglitazone treated rats (119 ± 7.9 mg/dL). The authors concluded that the resolution of T2DM in these rats was independent of obesity-related mechanisms because the rats were not obese. In addition, they suggested that the improvement in glucose metabolism was unrelated to weight loss because these rats gained weight. The authors state that "Our study pinpoints the exclusion of duodenum-jejunum as the factor responsible for control of diabetes". This conclusion, however, ignores the improvement in clinical diabetes and insulin resistance observed after gastric restrictive operations such as LAGB.[53,54]

Weight Loss Improves T2DM, Glucose Metabolism and Insulin Resistance

T2DM is characterized by abnormalities in glucose metabolism, fat metabolism and pancreatic beta-cell dysfunction. The prevalence of T2DM throughout the world is closely linked to obesity.[55,56] This relationship has led to the hypothesis that the adipose

tissue acts as an endocrine organ in the regulation of glucose metabolism and beta-cell function. Insulin resistance is a characteristic of T2DM and may play an important role in its pathogenesis.[57] Insulin resistance correlates with varying degrees of obesity.[58] Modest amounts of weight loss, even as low as 10 kg or 10% of total body weight, significantly decrease insulin resistance and improve T2DM.[59,60] Indeed, several lines of investigation support a causal relationship:

A. *WEIGHT GAIN*: Studies examining the association of weight gain and the onset of insulin resistance and clinical T2DM first drew attention to the etiologic role of obesity in abnormalities of glucose metabolism.
B. *WEIGHT LOSS BY DIETING*: Many studies have documented the benefit of weight loss through calorie-restricted diets or lifestyle modification programs on insulin resistance and T2DM.
C. *WEIGHT LOSS BY BARIATRIC SURGERY*: The impact of weight loss on insulin resistance and T2DM has been demonstrated following all types of bariatric surgery for morbid obesity.

A. Obesity, Insulin Resistance and T2DM

The relationship between obesity and insulin resistance is well-documented around the world. A variety of populations have been studied in North America. Kim, Abasi and Reaven[61] at Stanford University studied the relationship between obesity and various surrogate estimates of insulin resistance in 485 healthy volunteers. They divided individuals into three groups: normal weight BMI <25.0 kg/m^2 (n=208); overweight BMI 25.0-29.9 kg/m^2 (n=168); and obese BMI >30.0 kg/m^2 (n=109). All measures of insulin resistance significantly varied with BMI. The weakest correlation was found in the normal weight individuals and the greatest correlation in the obese group. Campbell and Carlson in Nashville[62] found a significant inverse relationship between insulin sensitivity of hepatic and peripheral tissues and BMI in patients with T2DM. Bermudez and Tucker[63] examined the relationship between weight, BMI and T2DM among 596 elderly Hispanics of Caribbean origin and 239 non-Hispanic whites, using the isoglycemic hyperinsulinemic clamp technique. The age range was 60 to 92 years. There was a significant linear relationship between BMI and insulin resistance.[64] There was a significant relationship between increasing weight and increasing BMI for both groups, although the risk was greater for non-Hispanic whites than for the Hispanics.

European studies support a relationship between BMI and risk of T2DM and insulin resistance. Dotevall and colleagues[65] documented the increased risk of T2DM with increasing BMI in Swedish women. They followed 1,351 Swedish women without prior T2DM for 20 years. The hazard risk of developing T2DM with a BMI of 24-27 kg/m^2 was 3.2 and with a BMI of >27 kg/m^2 was 8.3. Duman and colleagues[58] found increased rates of insulin secretion and increased insulin resistance in obese Turkish patients compared to normal weight patients in response to an oral glucose tolerance test. Wiegand and colleagues[56] demonstrated impaired glucose tolerance and increased insulin resistance among 37 of 102 obese Caucasian children in Germany. In the Czech Republic, Sindelka and colleagues[64] studied insulin resistance in 42 T2DM patients and 41 non-diabetic patients. All 83 patients had a range of BMI from 21.1 to 64.5 kg/m^2. Insulin resistance was studied using the isoglycemic hyperinsulinemic clamp technique. Of all the parameters examined, increasing BMI best correlated with increasing insulin resistance.

Pacific rim and Asian subcontinent studies also support this relationship.[66] Taniguchi and colleagues[67] studied insulin resistance (HOMA-IR) in 111 T2DM Japanese patients. Patients with increased insulin resistance (HOMA IR >2.5) had a significantly higher BMI than the insulin sensitive patients: 26.6 ± 0.8 kg/m^2 versus 21.7 ± 0.4 kg/m^2. In Korea, the most important predictor of insulin resistance, even in non-obese patients, was BMI. Chang and colleagues[68] studied 267 Korean T2DM patients with a BMI <25 kg/m^2. Linear regression found a significant correlation between BMI and HOMA (P=0.0001). Logistic regression analysis indicated that "BMI is the most important determinant of insulin resistance" in this group of non-obese type 2 diabetic Korean patients. Ramachandran and colleagues[69] compared the risk of non-insulin dependent diabetes in Asian Indians, Mexican Americans and Whites. In all three groups, age and BMI were significant predictors for the risk of non-insulin dependent diabetes. These studies indicate that obesity significantly impacts T2DM and insulin

resistance across a wide range of ethnic groups.

The relationship between BMI and insulin resistance becomes unreliable when study groups of patients are limited to only morbidly obese patients. In some studies of preoperative bariatric patients, insulin resistance linearly correlates with BMI but in others it does not. Scopinaro's group in Genoa,[46] for example, found that HOMA IR significantly correlated (P=0.027) with preoperative BMI in patients undergoing BPD. In contrast, Stubbs and Wickremesekera[70] in New Zealand found no significant correlation between preoperative BMI and insulin resistance in 80 patients who underwent RYGBP for morbid obesity. These findings, coupled with the results listed above, suggest that the relationship between BMI and insulin resistance might exhibit the classical shape of a dose-response curve. The linear relationship may be stronger in the physiological range of BMI between 20 and 40 kg/m^2 while this physiologic response may deteriorate in the pathologic range of morbid obesity (BMI > 40 kg/m^2).

B. Weight Loss and Increased Insulin Sensitivity

Weight loss by any modality leads to improved glucose metabolism and decreased insulin resistance.[71] *The Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults: The Evidence Report* published by the National Institute of Health in 1998 summarized the available information that weight loss improved glucose tolerance and decreased serum glucose.[72] Nine randomized trials studied lifestyle therapy, weight loss and changes in glucose and insulin levels. Forty-nine randomized trials assessed the effect of weight loss on fasting glucose and insulin levels. Eight additional randomized trials examined the impact of pharmacotherapy on weight loss and resulting changes in blood glucose. The recommendation of the NIH report based on this evidence was: "Weight loss is recommended to lower elevated blood glucose levels in overweight and obese persons with type 2 diabetes".

Ongoing research has continued to link weight loss with improvement in T2DM, serum glucose and serum insulin levels. Monzillo and colleagues[73] at the Joslin Diabetes Center of Harvard Medical School studied changes in insulin resistance in 24 insulin resistant obese patients after a 6-month program consisting of a calorie-restricted diet and light exercise. On average, participants lost 6.9 ± 0.1 kg and their BMI dropped from 36.7 ± 0.9 to 34 ± 1.05 kg/m^2. Insulin sensitivity significantly increased from 1.8 ± 0.3 10^{-4} min^{-1} (mU/mL)$^{-1}$ to 2.9 ± 0.4. Harder and colleagues[74] in Denmark placed 11 obese T2DM patients on a calorie-restricted diet for 8 weeks. The average age of patients was 62 ± 5.7 years. Average weight loss was 10.9 kg or about 11% of initial body weight. HbA1c percent dropped from an average of 7.0 ± 0.1% to 6.1 ± 0.1%, and serum insulin levels dropped from 176.1 ± 43.0 pmol/l to 85.5 ± 19.2 pmol/l. Unfortunately, weight loss from lifestyle modifications including diet, exercise and behavioral modification are generally short-lived. As a result, the net improvement in glucose metabolism and insulin resistance generally rescinds within 1 year of the weight loss.[45] Ash and colleagues[42] in Australia examined the long-term impact of weight loss on glycemic control. A calorie-restricted diet of 1400 to 1700 kcal per day achieved an average of 6.4 ± 4.6 kg weight loss in 12 weeks among 51 men with an average age of 54 years and BMI of 31.7 kg/m^2. Percent body fat dropped by 1.9 ± 1.5% and HbA1c by 1.0 ± 1.4%. When patients were assessed 18 months later, net weight loss had dropped to 1.8 kg and fat percent loss to 0.1%. HbA1c levels had increased from pre-weight loss levels of 7.9 ± 2.0% to 8.3 ± 2.3%. Thus, patients regained the lost body fat and glycemic control worsened 18 months after weight loss from a calorie-restricted diet.

C. Clinical Improvement of T2DM following Weight Loss from Bariatric Operations

Surgery for obesity has been carried out since the 1950s and was originally based on the principal that partial bypass of the small intestine (JI-bypass) decreased the absorptive area of the GI tract, creating a situation similar to the short-gut syndrome.[75,76] Sanderson and colleagues[77] first reported immediate resolution of T2DM following JI-bypass in 1983; poor absorption of nutrients led to a flat glucose tolerance test. Serum glucose and insulin levels became normal once 30% weight loss was achieved. Sylvan, Sjolund and Januhger[78] documented long-term remission of T2DM following JI-bypass among a rural population in Sweden. Because of the

stable nature of this population, complete follow-up to 20 years was obtained in 87 patients. Preoperatively, these patients had an average BMI of 41.5 ± 5.8 kg/m^2. Their BMI dropped to an average of 26.7 ± 3.8 kg/m^2 at 2 years after the operation and 29 ± 3.9 kg/m^2 at 16 years. Serum glucose averaged 4.4 mmol/l and serum insulin 8.9 ± 5.4 mmol/l at their last follow-up visit. None of the patients developed T2DM following the JI-bypass.

Subsequently, gastric restrictive operations, or gastroplasties, were developed that reduced the size of the stomach, which was felt would lead to an earlier sensation of satiety. These procedures included the horizontal gastroplasty, the VBG and more recently gastric banding.[79] Surgeons began to combine elements of intestinal bypass with gastric bypass to obtain increased weight loss. These combined procedures include the BPD, the loop gastric bypass and the RYGBP.[1] T2DM improves after all of these weight loss operations.

Vertical Banded Gastroplasty

VBG and LAGB both clinically improve T2DM. The beneficial effect of VBG on T2DM was reported by two groups at the American Society for Bariatric Surgery in 1991. Deitel, Sidhu and Stone[47] detailed 2-year follow-up outcomes on 27 T2DM patients who underwent VBG. Three of the four insulin-dependent diabetics were off insulin before discharge from the hospital. At 2 years, fasting glucose was normal in all patients without medication. At the same meeting, Jensen and Mason[80] reported on improvement in T2DM following VBG. Among 787 patients treated with VBG between 1980 and 1989, 83 were afflicted with T2DM: 62% of the insulin-dependent patients no longer required medication and 79% of the patients treated with oral hypoglycemic agents were off of all medications. In 1993, Neves and colleagues[48] at Manchester Royal Infirmary reported the resolution of T2DM in three patients following VBG. Bourdages and colleagues[81] at the University of Minnesota described significant improvement in T2DM in 7 of 9 patients following VBG. VBG also resolved T2DM in 3 of 4 patients in Moscow, Russia.[82] In 1995, Letiexhe and colleagues[83] at the University of Liege, Belgium compared glucose and insulin metabolism between eight obese women before and after VBG with 8 weight-matched (weight after surgery) controls. BMI for the 8 women dropped from 37.7 ± 0.5 kg/m^2 to 23.7 ± 0.6 kg/m^2 by 14 ± 2 months after VBG. Insulin secretion, insulin clearance and insulin action on glucose metabolism returned to normal levels once weight normalization was achieved. These articles indicate that weight loss following VBG caused remission of T2DM in the majority of patients.

Laparoscopic Adjustable Gastric Banding

Dixon and O'Brien[54] in Australia reported that LAGB induced remission in the majority of T2DM patients. Pontiroli and colleagues[84] in Italy documented the changes in HbA1c and insulin resistance as measured by the HOMA IR index among 143 patients following LAGB. T2DM was present in 46 patients. Average HbA1c levels dropped from 6.3 ± 0.08 to 5.7 ± 0.06 at 1 year, 5.5 ± 0.07 at 2 years and 5.3 ± 0.11 at 3 years. The HOMA IR index of insulin resistance dropped from an initial average of 5.1 ± 0.28 to 2.5 ± 0.14 at 1 year, 2.7 ± 0.21 at 2 years and 3.1 ± at 3 years. A HOMA IR index of ≤2.5 is considered normal. These authors concluded that these metabolic effects were directly proportional to the amount of weight loss. Gazzaruso and colleagues[85] reported similar outcomes among 51 premenopausal obese women in Italy following LAGB. Average BMI of these women dropped from 43.3 ± 6.9 kg/m^2 before banding to 34.5 ± 7.4 kg/m^2 1 year following surgery. Their HOMA IR index decreased from 4.2 ± 2.0 preoperatively to 2.4 ± 1.0 at 1 year postoperatively. Hanusch-Enserer and colleagues[86] in Australia studied changes in oral glucose insulin sensitivity index in 18 patients following LAGB.[86] The BMI of these patients decreased from 45.2 ± 5.6 to 36.9 ± 4.3 kg/m^2 at 1 year after LAGB. Average fasting glucose dropped from 123.1 ± 62.5 mg/dL to 100.5 ± 27.2 mg/dL and insulin sensitivity index increased from 343.0 ± 86.4 mL/min/m^2 to 442.6 ± 94.7 mL/min/m^2 1 year after surgery. Both restrictive procedures, VBG and LAGB, decrease insulin resistance and clinically improve T2DM.

Gastric Bypass

Improvement in T2DM following RYGBP is well-documented. Pories[11] reported improvement in T2DM in 83% of 146 patients. Sugerman and colleagues[87] documented their results following 1,025 open RYGBPs in 2003, where 15% of patients had

been afflicted by T2DM. At 1 year, average percent excess weight loss (%EWL) was 66% and percent total weight losss was 35%. T2DM resolved in 83% of patients. DeMaria and colleagues[88] observed clinical improvement in 93% of 15 patients with T2DM following laparoscopic RYGBP. Smith, Edwards and Goodman[49] achieved long-term follow-up for 133 T2DM who had 55% EWL following RYGBP. Among the 46 insulin-dependent diabetics, only 11 continued to require insulin, and 8 of 64 patients on oral hypoglycemic agents before RYGBP continued to require medication. Overall 68% of the 133 patients required no medication for T2DM following RYGBP. Schauer and colleagues[5] achieved clinical improvement of 40 patients and remission of 137 patients out of 177 patients with T2DM. When VBG was compared to RYGBP, 76% of patients who underwent VBG had resolution of their T2DM compared to 84%.[6] These studies indicate that RYGBP reliably improves T2DM.

Biliopancreatic Diversion

Scopinaro and colleagues have extensively studied outcomes following BPD. In a study of 248 patients who had preoperative impaired glucose tolerance and 108 with diagnosed T2DM out of 1,773 patients that underwent BPD, all patients with impaired glucose tolerance or T2DM had normalization of their glucose levels postoperatively.[8] In a smaller study, Noya and colleagues[89] observed improvement in T2DM in 1 and remission in 9 of 10 patients following pylorus-preserving BPD. Castagneto and colleagues[18] compared insulin sensitivity between 14 normal weight controls (BMI 22.4 ± 0.9 kg/m^2), 7 patients who had stable weight for at least 2 years following BPD (BMI 25.6 ± 2.1 kg/m^2) and 8 obese patients (BMI 47.4 ± 2.3 kg/m^2). The response to intravenous glucose tolerance tests and oral glucose tolerance tests were similar for the normal weight and BPD patients but significantly different for the obese patients. Also, insulin sensitivity index was similar for the normal weight controls and BPD patients, while the obese patients were significantly less insulin sensitive. Together, these studies suggest that any bariatric operation that results in significant weight loss will result in clinical improvement of T2DM in the vast majority of patients.

Future Research

In this review, we propose that bariatric surgery leads to improved glucose metabolism and insulin resistance through caloric restriction in the short-term and weight loss in the long-term. This implies that all types of bariatric operations improve T2DM through these same two mechanisms. As a result, our hypothesis makes several predictions that can be easily tested in the future:

1) Early postoperative increases in insulin resistance (within 1-2 days) should be observed following both restrictive and bypass operations;
2) Short-term improvement (1-3 months following surgery) in insulin resistance following bariatric surgery should correlate with decreased caloric intake;
3) Short-term improvement (1-3 months following surgery) in insulin resistance should precede significant weight loss in both restrictive and bypass operations;
4) Improvement in insulin resistance 1-year following weight loss surgery should correlate with weight loss but not BMI; and
5) Long-term (>2 years) insulin resistance after bariatric surgery should correlate with BMI.

A final appraisal of mechanisms regulating insulin resistance following weight loss surgery will require substantial additional research in the future. For the time being, studies on bariatric surgery and changes in insulin resistance should include various types of bariatric operations.

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