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The Sum of Many Parts: Potential Mechanisms for Improvement in Glucose Homeostasis After Bariatric Surgery

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Abstract

Bariatric surgery has emerged as the most durably effective treatment of type 2 diabetes (DM). However, the mechanisms governing improvement in glucose homeostasis have yet to be fully elucidated. In this review we discuss the various types of surgical interventions and the multitude of factors that potentially mediate the effects on glycemia, such as altered delivery of nutrients to the distal ileum, duodenal exclusion, gut hormone changes, bile acid reabsorption, and amino acid metabolism. Accumulating evidence that some of these changes seem to be independent of weight loss questions the rationale of using body mass index as the major indication for surgery in diabetic patients. Understanding the complex mechanisms and interactions underlying improved glycemic control could lead to novel therapeutic targets and would also allow for greater individualization of therapy and optimization of surgical outcomes.

Keywords

Roux-en-Y gastric bypass; Gastric banding; Sleeve gastrectomy; Biliopancreatic diversion; Diabetes remission; GLP-1; GIP; Glucagon; PYY; Adiponectin; Bile acids; Microbiota; Amino acids; Taste receptors; Gluconeogenesis; Insulin clearance; Glucose homeostasis; Bariatric surgery

Introduction

Type 2 diabetes mellitus (DM) is a chronic and progressive disease marked by insulin resistance and eventual reduction in insulin secretion [1, 2]. Despite an overall improvement

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Compliance with Ethics Guidelines

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in diabetes care from 1999 to 2010, 47.5 % of diabetic patients still do not meet the targets for glycemic control [3, 4••].

Weight gain and obesity are clearly established causes of type 2 diabetes (DM) [5]. The rise in obesity has been associated with an increase in the prevalence of diabetes [6]. Weight loss improves glycemic control in obese patients with DM, but conventional medical management often fails to achieve sustained weight loss in severely obese patients [5]. Bariatric surgery has emerged as one of the most effective methods of achieving sustained weight loss and inducing long-term improvement in DM and its comorbidities [7, 8••, 9••, 10, 11]. Multiple studies have demonstrated the greater efficacy of bariatric surgery compared with medical therapy in achieving the treatment goals recommended by the American Diabetes Association (ADA) [8••, 9••, 12••, 13–15, 16••]. While bariatric surgery is currently reserved for patients with BMI higher than 40 kg/m^2 or higher than 35 kg/m^2 with significant comorbidities, the International Diabetes Federation has recently recommended consideration of bariatric surgery for patients with a BMI of 30–35 kg/m^2 when traditional medical management is unable to achieve adequate diabetic control [17••]. This review will discuss the impact of bariatric surgery on DM and potential mechanisms for improved glycemic control.

Effect of Bariatric Surgery on Glycemic Control

Rapid improvement in DM following bariatric surgery has been described anecdotally as early as the 1970s [18]. In 1995, Pories et al reported the long-term efficacy of bariatric surgery in achieving diabetes “remission” in 608 morbidly obese patients who underwent gastric bypass, with a 96.3 % follow-up rate over 14 years [19]. A later meta-analysis reported that DM was completely resolved in 76.8% of patients, however, a more recent analysis of randomized controlled trials indicates that figures may be lower [7, 20].

Dixon et al published the first randomized trial to compare the effect on DM of surgical vs medical weight loss interventions. Sixty patients with BMI >30 kg/m^2 but <40 kg/m^2 with recently diagnosed DM(less than 2 years) were randomized to laparoscopic adjustable gastric banding (LAGB) vs medical intervention. Of the 92 % patients who completed the 2 year follow-up, 22/29 (75.8 %) in the surgical group vs 4/26 (15%) in the conventional group achieved diabetes remission, as defined by fasting glucose <126 mg/dL and hemoglobin A1c (HbA1c) ≤6.2 % after discontinuation of medications. Remission was associated with amount of weight loss and lower baseline HbA1c levels [15].

More recently, several groups have published randomized controlled trials comparing bariatric surgery to medical management of DM. In a prospective randomized trial, Mingrone et al compared Roux-en-Y gastric bypass (RYGB) and biliopancreatic diversion (BPD) to medical therapy in obese patients (BMI≥35 kg/m^2) with DM. At 2 years, achievement of fasting glucose <100 mg/dL and HbA1c <6.5 % after stopping medications, did not occur in any medically treated patients, but occurred in 75 % of the RYGB and 95 % of the BPD patients. There was no association of diabetes remission with age, BMI, sex, or duration of DM [8••]. Schauer et al randomized 150 patients with DM to either medical treatment per ADA guidelines alone or medical treatment plus RYGB or sleeve gastrectomy.

One year later, only 12% of the medically treated patients vs 42 % RYGB and 37 % sleeve gastrectomy patients achieved diabetes remission with HbA1c <6 % as defined by the study [9••]. The Diabetes Surgery Study, a prospective, multi-center, and multinational trial randomized 120 obese patients (BMI 30–39.9 kg/m^2) with mean HbA1c of 9.6% to intensive lifestyle modification or to a combination of RYGB with intensive lifestyle modification. At 1 year, weight loss was 7.9 % of initial body weight and HbA1c was 7.8 % in the medical arm; in the surgery arm, weight loss and HbA1c were 26.1% and 6.3%, respectively. In regression analyses, improved glycemia was mostly driven by the degree of weight loss.

The variability in remission rate among earlier studies and these more recent studies likely reflect differences in study design and surgical as well as lifestyle interventions, baseline characteristics of patients, duration of follow-up, and the criteria used to define remission [21••, 22]. When the ADA definition of remission (fasting glucose <100 mg/dL and HbA1c <6 % of at least 1 year's duration in the absence of active pharmacologic therapy) [21••] was retrospectively applied to data collected prospectively in 3 bariatric centers, the total rate of complete remission was 34.4 % for all bariatric surgery, which included RYGB, sleeve gastrectomy, and gastric banding; for RYGB, the remission rate by ADA criteria was 40.6 % [21••, 22]. Preoperative BMI did not correlate with diabetic control postoperatively. Although numbers are relatively low, it appears that outcome is similar in individuals with BMI <35 kg/m^2. The efficacy of bariatric surgery in achieving "remission" is further complicated by the difficulty of defining "remission" in diabetes, as hyperglycemia exists on a continuum. Also implicit within the definition of remission is the possibility of recurrence, and the period of time afterwhich remission may be considered effectively a cure has been arbitrarily chosen [21••]. A proposed model (DiaRem) for the prediction of diabetes remission gave greatest weight to preoperative use of insulin and has not been validated prospectively [23].

The durability of the surgical effect on glycemic control is less clear due to lack of long-term studies, and in particular with newer procedures such as sleeve gastrectomy. The Swedish Obese Subjects (SOS) survey was the first long-term, prospective, nonrandomized controlled trial to compare bariatric surgery vs conventional medical treatment on diabetes. After 2 years of follow-up, 72 % of the patients with diabetes at baseline were in remission (defined by cessation of diabetes medications or fasting plasma glucose <126 mg/dL) after gastric banding, vertical banded gastroplasty, or RYGB; however, 50 % of the diabetic patients in remission at 2 years had relapsed after 10 years [11, 16••]. Similarly, other groups have found recurrence rates ranging from 19 % to 35.1 % in bariatric surgery patients who had initially achieved remission, defined variably as HbA1c <6 % and fasting plasma glucose ≤100 mg/dL or ≤124 mg/dL with cessation of medications, after follow-up ranging from 3 to 9 years [24–26]. The risk of diabetes recurrence appeared to be inversely correlated with long term excess weight loss (EWL) and directly correlated to duration of diabetes and severity of diabetes preoperatively [24–26].

Proposed Mechanisms for Improvement in Diabetes

Weight loss through bariatric surgery improves DM more effectively than conventional medical therapy, but the mechanisms by which this improvement occurs have yet to be fully elucidated. The changes in glucose homeostasis are likely the result of both weight loss dependent and weight loss independent mechanisms, and the following mechanisms are not necessarily mutually exclusive of one another.

Caloric Restriction

It is well known that significant caloric restriction improves glucose tolerance in diabetic patients [27]. Bariatric surgery has been associated with profound improvements in fasting glucose concentration and insulin action, which often occur early in the postoperative course, before significant weight loss has even occurred [28–30]. Caloric restriction, which occurs immediately after all surgical interventions, likely plays an important role in the favorable metabolic changes observed after bariatric surgery. For example, obese diabetic patients who underwent either RYGB or a 500 kcal/day diet lost an equivalent amount of weight over approximately 3 weeks and exhibited similar improvements in insulin sensitivity, acute insulin secretion, and beta cell function when assessed by an intravenous glucose challenge [31•].

Incretin Secretion and Response

Changes in the secretion pattern of gut-derived hormones from enteroendocrine cells in response to altered nutrient transit have emerged as important potential mechanisms for improvement in DM.

Due to impaired insulin secretion in DM, the incretin effect, which is the greater insulin response after oral glucose compared with an equivalent dose of intravenous glucose, is diminished [32]. Glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP-1) are the 2 incretins responsible for one-half to two-thirds of postprandial insulin secretion. GLP-1 is secreted mostly from ileal L cells while GIP is secreted from duodenal K cells. Both are rapidly inactivated by the enzyme dipeptidyl peptidase IV (DPP-IV). GLP-1 analogues and DPP-IV inhibitors are currently used as antidiabetic agents, stressing the importance of GLP-1 in glucose homeostasis [33, 34].

Multiple studies have shown that postprandial secretion of GLP-1 is substantially and durably increased after RYGB, but not after LAGB or diet-induced weight loss [35–40]. The increase in GLP-1 occurs early following RYGB, before significant weight loss has occurred [38, 39]. Moreover, the postprandial increase in GLP-1 is clearly related to the alteration in gastrointestinal anatomy following RYGB, as illustrated in 2 case reports examining the effect of peroral feeding vs gastroduodenal feeding in RYGB patients with gastric tubes inserted into the bypassed gastric remnant [41, 42]. When RYGB patients were fed via the gastric bypass pathway, exaggerated postprandial GLP-1 and insulin responses were noted. However, when patients were fed through the gastric tube via the gastroduodenal pathway, GLP-1 and insulin secretion were similar to the pattern seen preoperatively. These cases demonstrate that more rapid delivery of nutrients to the distal small intestine is a key factor

in the postoperative changes in GLP-1 and insulin secretion. Greater improvements in postprandial GLP-1 secretion and the incretin effect after bypass surgery, independent of weight loss, were also demonstrated in a study of obese diabetic women studied 1 month after being randomized to gastric bypass surgery or diet-induced equivalent weight loss [35].

Early recovery of beta cell function has been associated with exaggerated postprandial secretion ofGLP-1 after RYGB but causality has not been definitively established. Jorgensen et al expanded upon the earlier study by Salehi et al [43] to illustrate the insulinotropic role of GLP-1 in diabetic patients after RYGB. By pharmacologically blocking the GLP-1 receptor (GLP-1R) during a liquid meal tolerance test after surgery using exendin (9–39), they were able to show that improvement in beta cell glucose sensitivity, glucagon suppression, and insulin secretion were all decreased [44••]. However, Jimenez et al found only minimal decrease in glucose tolerance following blockade ofGLP-1 action [45]. GLP-1 and the incretin effect, while important to improved beta cell function, are likely not the only factors altered by bariatric surgery.

Reported postprandial changes in GIP following bariatric surgery have been inconsistent. In theory, exclusion of the duodenum, where most GIP-producing K cells reside, would lead to decrease in GIP secretion after RYGB. Instead, some studies have found an increase in GIP while others have noted lack of change or a decline [35, 37, 46, 47]. It is possible that the inconsistencies in postprandial GIP levels postoperatively are due to variability in surgical technique, particularly differences in the length of Roux anastomoses, composition of test meal stimulus, and the timing of blood sample collections that may overlook early postprandial secretion.

Glucagon and Glucagon-Like Peptide 2

An increase in meal-stimulated glucagon in the early postprandial period after RYGB has been noted in several studies and argues against GLP-1 mediated suppression of glucagon as a mechanism for improved glucose homeostasis after bariatric surgery [35, 46, 48]. However, fasting glucagon appears to decrease by 1 year after RYGB and may potentially explain some of the long-term benefits of RYGB on glucose metabolism [48].

Glucagon-like peptide 2 (GLP-2) is a member of the enteroglucagon family derived from the preproglucagon gene, which also encodes glicentin, glucagon, oxyntomodulin, and GLP-1. GLP-2 regulates gastric motility, gastric acid secretion, intestinal hexose transport, glucagon secretion, and increases absorptive area and barrier function of the gut epithelium via stimulation of crypt cell proliferation and inhibition of apoptosis in the enterocyte and crypt compartments [49–51]. In both murine and human patients, le Roux et al found that GLP-2 levels rose substantially after RYGB, peaked at 6–12 months and correlated with the period of maximal weight loss, before returning to baseline levels. Following RYGB in rats, increased GLP-2 levels were associated with increased crypt cell proliferation as early as 23 days postoperatively [52]. These accommodations in gut anatomy likely account for how well RYGB is tolerated and the relatively minimal degree of macronutrient malabsorption, but the precise role, if any, that GLP-2 may play in the improvement of glucose homeostasis following RYGB remains to be seen.

Changes in Appetitive Hormones

GLP-1 and Peptide YY (PYY) are anorexigenic and are implicated in the decreased hunger and increased satiety that often follows RYGB [53]. Consistent with this notion is the demonstration that GLP-1R agonism enhances weight loss achieved by adjustable gastric banding (AGB) in obese rats [54]. Like GLP-1, PYY is released from intestinal L cells in response to a meal and has anorectic properties, delaying gastric emptying, slowing intestinal transit time, and increasing satiety. PYY levels are dramatically elevated following nutrient ingestion after RYGB but not after LAGB [36, 40, 55, 56]. The marked postprandial elevations in GLP-1 and PYY after bariatric surgery suggest that gut hormone mediated changes in appetite, in addition to improved insulin sensitivity and secretion, may facilitate decreased food consumption and thereby contribute to the attainment and maintenance of improved glycemic control.

Compromised secretion of ghrelin, an orexigenic peptide produced in the fund us and body of the stomach, has also emerged as a potential mechanism for both decreased hunger and improvement in glycemia after RYGB and sleeve gastrectomy [57–59]. Various studies have reported decreases in fasting and postprandial ghrelin levels after RYGB, while others have noted no change or even increases in ghrelin [46, 55, 60–63]. These seemingly discrepant results may be due in part to the postoperative interval, amount of weight loss, the time-points evaluated (single fasting vs meal-associated), and the use of assays measuring “active” octanoylated iso form vs total ghrelin.

Changes in the Direction and Rate of Nutrient Flow

A proposed mechanism for the improvement in DM following bariatric surgery is that early and rapid delivery of unabsorbed nutrients to the distal small intestine activates the “ileal brake” that potentiates the secretion of GLP-1 and PYY (the “hindgut hypothesis”). Consistent with this hypothesis is the observation that procedures with the most consistent improvement in DM shorten the route of nutrient flow from the stomach to intestine, and/or increase the rate of transport of ingested nutrients [14, 58, 64–66].

Further evidence for the role of the distal ileum in improving glucose tolerance is derived from rodent models of ileal interposition (IT), a surgical procedure whereby a segment of ileum is inserted into the proximal small intestine so that there is no gastric restriction or duodenal bypass. IT in different diabetic rodent models results in elevated levels of GLP-1 and PYY and improvements in insulin sensitivity, glucose tolerance, and beta-cell function [67–70]. Inhibition of GLP-1R with exendin (9–39) reversed the improvement in oral glucose tolerance after IT, lending further support to the hypothesis that early and increased activation of GLP-1R leads to subsequent improvement in glucose metabolism [71]. In humans, IT associated with sleeve gastrectomy has shown some promise for the treatment of T2DM in patients with BMI of 21– 34 kg/m^2 [72, 73••].

Exclusion of nutrients from the proximal small intestine (the “foregut hypothesis”) has also been proposed to restore euglycemia. In animal studies of both non obese and diet induced obese diabetic rats, duodenal-jejunal bypass (DJB) without gastric restriction led to improvement in hyperglycemia independent of food intake and weight reduction [74–76].

Intestinal glucoregulatory hormones and vagal innervation may also contribute to alleviation of hyperglycemia in the DJB model [76]. DJB in humans had only a moderate effect on glucose homeostasis in patients with DM resulting in a change in mean HbA1c from 9.3 % at baseline to a nadir of 6.5% at 3 months followed by a progressive increase to 7.7% at 12 months postsurgery [77••]. It is unclear if the improvements observed were due to altering the intestinal site of delivery of ingested nutrients and/or moderate weight loss.

Novel, less invasive endoscopic therapies are also being explored for the treatment of DM. By using a rat model of the endoluminal sleeve (ELS) to mimic 2 components of RYGB, bypass of the proximal intestine and early exposure of the jejunum to partially digested nutrients, Aguirre et al demonstrated that despite less weight loss than similar rats that had undergone RYGB, rats with the ELS attained comparable improvement in glucose homeostasis [78]. In humans, reductions in HbA1c have been demonstrated after implantation of various types of endoluminal duodenal-jejunal bypass sleeves [79, 80••]. Further investigations into the safety, efficacy, and long-term outcomes of the ELS are ongoing.

“Hindgut” and “foregut” hypotheses have both been proposed as mechanisms that alter glucose homeostasis [64, 81]. Current evidence suggests that multiple factors are at play that are not mutually exclusive, and may in fact act in concert, to achieve the striking improvements observed using different devices and surgical approaches.

Other Mechanisms for Improvement in Diabetes

Adipose Tissue and Adipokines

Weight loss following RYGB consists of a significant reduction in whole body fat including 50 %–60 % reduction in visceral adipose tissue [82]. Adiponectin, a 244 amino acid protein secreted from white adipose tissue, is inversely proportional to body fat mass, BMI, waist-to-hip ratio, serum insulin, and glucose levels; low levels are closely correlated with insulin resistance and suspected to play a role in DM pathogenesis [83]. Most studies have shown an increase in adiponectin after RYGB, which correlates with the improvement in insulin resistance following surgery [60, 63]. Changes in body composition, inflammation, and adipokines contribute to improvement but most are likely not unique to surgery-induced, as opposed to diet-induced, weight loss.

Bile Acids and FGF 19

Increased bile acid reabsorption has also been proposed as a potential mechanism for improved insulin sensitivity after RYGB [84]. Based on rodent studies suggesting that bile acids increase energy expenditure through activation of G-protein coupled receptor TGR5 and thereby type 2 thyroid hormone deiodinase, Patti et al performed a cross-sectional analysis of fasting serum bile acid composition and various metabolic variables in a group of nondiabetic post-RYGB, matched obese, and overweight patients. Total serum bile acid concentrations were 2-fold higher in post-RYGB patients and were inversely correlated with 2-hour postprandial glucose levels as well as fasting triglycerides, and positively correlated with adiponectin and peak postprandial GLP-1 [84]. The altered enterohepatic recycling of bile acids and consequently elevated serum bile acid levels induced by IT in rats may also

contribute to improved glucose homeostasis [85••, 86]. Bile acids also act on the farnesoid X receptor stimulating secretion of fibroblast growth factor (FGF)19 secretion with subsequent inhibition of hepatic gluconeogenesis. In prospective human and animal studies, Pournaras et al concluded that RYGB but not LAGB leads to more rapid delivery of bile acids to the terminal ileum, which in turn causes an increase in total bile acid concentrations, plasma GLP-1, PYY and FGF19 [87]. Other studies in humans have also shown increases in plasma bile acids and FGF19 after RYGB [88–90].

Microbiota

Data from mouse studies and recent small studies in humans have provided evidence that gut microbiota may play an important role in energy storage and possibly the development of obesity and associated complications. It remains unclear whether changes in the gut microbiome are a consequence or cause of obesity in humans. Bariatric surgery, in particular, induces environmental, systemic, and anatomic changes that may all impact the composition of gut microbiota. Initial studies have suggested a shift in bacterial flora after surgery toward profiles more similar to that of lean patients [91–94]. Gastrointestinal reconfiguration may play a key role in the changes in microbiota, as changes in the microbial ecology were most notable distal to the site of surgical manipulation in rat models. Moreover, transfer of gut microbiota from RYGB treated mice to non-operated, aseptic mice was sufficient to cause decreased weight and adiposity, possibly due to altered microbial synthesis of short-chain fatty acids [94]. Whether these changes in microbiota or those involving other digestive processes such as the thermic effect of feeding contribute to improved glucose homeostasis remains to be elucidated.

Genetics

Various studies have begun to examine the potential of obesity associated single nucleotide polymorphisms (SNPs) to predict weight loss outcomes following bariatric surgery. Higher pre and postoperative BMI following RYGB has been associated with an increased number of obesity SNPs or homozygous SNP genotypes [95]. The SOS group looked at 11 obesity candidate genes and found that the *FTO* SNP rs16945088 was associated with maximal weight loss [95, 96].

The melanocortin system is an integral component in the regulation of energy homeostasis. Loss of a single functional copy of the melanocrtin-4 receptor (*MC4R*) gene is the most common mutation associated with obesity in humans. Mirshahi et al found that carriers of the *MC4R* I251L allele were more likely to lose weight during dietary and surgical interventions and had less insulin resistance [97]. A later study provided further confirmation of the crucial role *MC4R* signaling plays in the weight loss effects of RYGB: while mice heterozygous for *MC4R* remained fully responsive to RYGB, *MC4R* null mice lost substantially less weight after surgery. By sequencing the *MC4R* gene in 972 patients undergoing RYGB, Hatoumet al also showed that a single normal copy of the *MC4R* gene was sufficient to conserve the weight loss effects of RYGB. However, given the few number of diabetics in the study, it is not clear if *MC4R* mutations have a clinically significant effect on glycemic outcome [98].

Genetic polymorphisms in the gene encoding transcription factor 7-like 2 (*TCF7L2*) are associated with an increased risk of developing DM. Inheritance of 2 specific *TCF7L2* variants, rs1225372 and rs7903146, has been associated with relatively reduced insulin secretion and an increased probability of progression from impaired glucose tolerance to DM, but no impairment of insulin sensitivity [99]. The insulinotropic effect of exogenous GLP-1 in carriers of these variants has been reported as impaired in some but not all studies, so it is unclear if carriers would reap equivalent benefits from bariatric surgeries that enhance GLP-1 secretion [100–102].

More recently, fetal and adult ablation of the transcription factor *Foxo1* in mouse enteroendocrine progenitors have given rise to the development of gut cells with the ability to produce biologically active insulin in a glucose-responsive manner. Unlike embryonic stem cell-derived insulin producing cells, the gut-derived insulin producing cells demonstrated a singular plasticity and ability to regenerate and produce insulin [103]. It is feasible that bariatric surgery, through changing hormonal and nutrient cues, may somehow influence insulin secretion from the gut through *Foxo1* mediated alterations in Notch and Wnt signaling pathways, both of which have been shown to regulate gut and pancreatic cell differentiation.

Taste Receptors of the Gut

G-protein coupled taste receptors detect gut luminal contents and transmit signals that regulate nutrient transporter expression and nutrient uptake, as well as the release of gut hormones and neurotransmitters involved in the regulation of energy and glucose homeostasis. Sweet taste receptors, TAS1R2, have been shown to be dysregulated in DM and may potentially increase the risk of postprandial hyperglycemia by increasing glucose absorption via Na^+/glucose co-transporter SGLT1 during hyperglycemia. Rapid delivery of undigested nutrients to the lower small intestine after RYGB may also affect the regulation of taste receptors or glucose transporters on L cells, leading to increased PYY and GLP-1 secretion. In rodent models, it has been demonstrated that DJB leads to decreased TAS1R2 and TAS1R3 expression in the alimentary limb and decreased SGLT1-mediated glucose transport. Given the decreased preference for sweet and fatty foods demonstrated by many patients after RYGB, it has been postulated that increased intensity of sweet perception following surgery leads to changes in gut hormones and ultimately alterations in the reward circuitry and energy homeostasis [104].

Insulin Clearance

The rapid decrease in fasting glucose and fasting insulin after RYGB suggests that early improvement in hepatic glucose production and hepatic insulin sensitivity may account for this change. Bojsen-Moller et al prospectively studied 32 diabetic and 32 normoglycemic patients recruited for RYGB and found that fasting hepatic insulin clearance increased after 1 week and further at 3 months for both groups, regardless of diabetic status [105]. Postprandial insulin clearance increased only in the DM patients, in whom the increase was noted as early as 1 week following surgery and maintained at 3 months and 1 year. Based on this study and others that have noted the rapid improvement in fasting glucose and fasting insulin before significant weight has even occurred, it is quite plausible that nonenteral

factors, such as increased hepatic insulin sensitivity and insulin clearance, may be responsible for some of the early improvement in response to energy restriction [106]. Early postoperative increases in plasma free fatty acids are then followed by increased suppression that likely contributes to improved peripheral insulin sensitivity later on as demonstrated during clamp studies in diabetic patients 1 year after RYGB [107].

Intestinal Gluconeogenesis

In mice, enterogastric anastomosis (EGA, analogous to RYGB in humans) but not gastric banding increased gastrointestinal gluconeogenesis. Following EGA, researchers noted decreased food intake in the mice and direct secretion of enteral glucose into the portal vein, suppressing endogenous hepatic glucose production. They illustrated the importance of hepato-portal glucose sensing in mediating appetite by performing EGA in a GLUT-2 knockout mouse and confirming that without the specific glucose sensor, there was no inhibition of food intake in the mice even after EGA. The authors linked increased intestinal gluconeogenesis to improved hepatic insulin sensitivity with subsequent suppression of hepatic gluconeogenesis and improved glucose tolerance overall, asserting that this occurred independently of GLP-1 and is only partially explained by weight loss [108].

Amino Acids

Dietary macronutrients function as signaling molecules to affect feeding behavior, fuel efficiency, enteric hormones, insulin release and insulin sensitivity [109–111]. Obesity and DM are known to alter circulating concentrations of many metabolites [111, 112]. Metabolite profiling in diabetic patients has shown that weight loss after RYGB but not equivalent diet-induced weight loss is associated with a decrease in fasting plasma concentrations of branched chain amino acids and their C3 and C5 acylcarnitine metabolites and correlated negatively with insulin sensitivity [113]. Similar changes were also noted after AGB or RYGB in a nondiabetic group after equivalent weight loss [114••]. It is, therefore, unclear whether the changes in amino acid metabolism, and possibly transport, are unique to RYGB or are causal to the improvements in insulin action. The use of metabolomics will undoubtedly further this area of study [115].

Conclusions

The mechanisms by which bariatric surgeries cause improvement in DM are multifactorial and dependent upon both weight loss associated and weight loss independent factors. Expedited delivery of nutrients to the distal gut, as well as duodenal exclusion and hormonal changes, likely contribute to the improvement in glucose homeostasis. Given the profound metabolic effects of bariatric surgery and the known long-term benefits of glycemic control, it may be worthwhile to reconsider the applicability of “remission” in defining successful treatment of diabetes, and to advocate for improved glycemic control and decreased use of medications as better parameters of treatment efficacy. Evidence indicating that some of the positive outcomes are at least partially independent of weight loss renders use of BMI as a major criteria for surgery in diabetics somewhat arbitrary. Improved understanding of the complex mechanisms and interactions involved in glucose homeostasis after bariatric

surgery could identify potential therapeutic targets including less invasive techniques, optimize surgical outcomes, and also encourage greater individualization of therapy.

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References

Papers of particular interest, published recently, have been highlighted as:

• Of importance

•• Of major importance

1. Vella A, Camilleri M, Rizza RA. The gastrointestinal tract and glucose tolerance. Curr Opin Clin Nutr Metab Care. 2004; 7:479–484. [PubMed: 15192453]
2. DeFronzo RA. Pathogenesis of type 2 (non-insulin dependent) diabetes mellitus: a balanced overview. Diabetologia. 1992; 35:389–397. [PubMed: 1516769]
3. Ali MK, Bullard KM, Gregg EW. Achievement of goals in U.S. Diabetes Care, 1999–2010. N Engl J Med. 2013; 369:287–288. [PubMed: 23863067]
4. Stark Casagrande S, et al. The prevalence of meeting A1C, blood pressure, and LDL goals among people with diabetes, 1988–2010. Diabetes Care. 2013; 36:2271–2279. [PubMed: 23418368] The authors assess the improvements in achievement of ADA goals for diabetic care.
5. Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults—The Evidence Report. National Institutes of Health. Obes Res. 1998; 6(Suppl 2):51S–209S. [PubMed: 9813653]
6. Gregg EW, et al. The relative contributions of different levels of overweight and obesity to the increased prevalence of diabetes in the United States: 1976–2004. Prev Med. 2007; 45:348–352. [PubMed: 17889292]
7. Buchwald H, et al. Bariatric surgery: a systematic review and meta-analysis. JAMA. 2004; 292:1724–1737. [PubMed: 15479938]
8. Mingrone G, et al. Bariatric surgery vs conventional medical therapy for type 2 diabetes. N Engl J Med. 2012; 366:1577–1585. [PubMed: 22449317] A randomized control trial of RYGB or BPD vs medical management of diabetes.
9. Schauer PR, et al. Bariatric surgery vs intensive medical therapy in obese patients with diabetes. N Engl J Med. 2012; 366:1567–1576. [PubMed: 22449319] A randomized control trial of RYGB or sleeve gastrectomy vs medical management of diabetes.
10. Sjostrom L. Bariatric surgery and reduction in morbidity and mortality: experiences from the SOS study. Int J Obes. 2008; 32(Suppl 7):S93–S97.
11. Sjostrom L, et al. Lifestyle, diabetes, and cardiovascular risk factors 10 years after bariatric surgery. N Engl J Med. 2004; 351:2683–2693. [PubMed: 15616203]
12. Ikramuddin S, et al. Roux-en-Y gastric bypass vs intensive medical management for the control of type 2 diabetes, hypertension, and hyperlipidemia: the Diabetes Surgery Study randomized clinical trial. JAMA. 2013; 309:2240–2249. [PubMed: 23736733] A randomized control trial of RYGB vs intensive lifestyle modification.
13. Leslie DB, et al. Efficacy of the Roux-en-Y gastric bypass compared with medically managed controls in meeting the American Diabetes Association composite endpoint goals for management of type 2 diabetes mellitus. Obes Surg. 2012; 22:367–374. [PubMed: 21918925]
14. Buchwald H, et al. Weight and type 2 diabetes after bariatric surgery: systematic review and meta-analysis. Am J Med. 2009; 122:248–256. e5. [PubMed: 19272486]

15. Dixon JB, et al. Adjustable gastric banding and conventional therapy for type 2 diabetes: a randomized controlled trial. JAMA. 2008; 299:316–323. [PubMed: 18212316]
16. Sjostrom L. Review of the key results from the Swedish Obese Subjects (SOS) trial—a prospective controlled intervention study of bariatric surgery. J Intern Med. 2013; 273:219–234. [PubMed: 23163728] Long-term prospective controlled intervention study of bariatric surgery vs medical management.
17. Dixon JB, et al. Bariatric surgery: an IDF statement for obese Type-2 diabetes. Diabet Med. 2011; 28:628–642. [PubMed: 21480973] IDF statement regarding consideration of bariatric surgery for treatment of DM in patients with BMI <35 kg/m^2.
18. Ahmad U, et al. Remissions of diabetes mellitus after weight reduction by jejunoileal bypass. Diabetes Care. 1978; 1:158–165. [PubMed: 729440]
19. Pories WJ, et al. Who would have thought it? An operation proves to be the most effective therapy for adult-onset diabetes mellitus. Ann Surg. 1995; 222:339–350. *discussion 350–2*. [PubMed: 7677463]
20. Guo X, et al. The effects of bariatric procedures vs medical therapy for obese patients with type 2 diabetes: meta-analysis of randomized controlled trials. Biomed Res Int. 2013; 2013:410609. [PubMed: 23971035]
21. Buse JB, et al. How do we define cure of diabetes? Diabetes Care. 2009; 32:2133–2135. [PubMed: 19875608] Definition of diabetes remission.
22. Pournaras DJ, et al. Effect of the definition of type II diabetes remission in the evaluation of bariatric surgery for metabolic disorders. Br J Surg. 2012; 99:100–103. [PubMed: 22021090]
23. Still CWG, Benotti P, Petrick AT, Gabrielsen J, Strodel WE, Ibele A, et al. Preoperative prediction of type 2 diabetes remission after Roux-en-Y gastric bypass surgery: a retrospective cohort study. The Lancet Diabetes and Endocrinology. 2014 Jan.2:38–45. [PubMed: 24579062]
24. Breather SA, et al. Can diabetes be surgically cured? Long-term metabolic effects of bariatric surgery in obese patients with type 2 diabetes mellitus. Ann Surg. 2013; 258:628–636. *discussion 636–7*. [PubMed: 24018646]
25. DiGiorgi M, et al. Re-emergence of diabetes after gastric bypass in patients with midto long-term follow-up. Surg Obes Relat Dis. 2010; 6:249–253. [PubMed: 20510288]
26. Arterburn DE, et al. A multisite study of long-term remission and relapse of type 2 diabetes mellitus following gastric bypass. Obes Surg. 2013; 23:93–102. [PubMed: 23161525]
27. Kelley DE, et al. Relative effects of calorie restriction and weight loss in noninsulin-dependent diabetes mellitus. J Clin Endocrinol Metab. 1993; 77:1287–1293. [PubMed: 8077323]
28. Wickremesekera K, et al. Loss of insulin resistance after Roux-en-Y-gastric bypass surgery: a time course study. Obes Surg. 2005; 15:474–481. [PubMed: 15946424]
29. Schauer PR, et al. Effect of laparoscopic Roux-en Y gastric bypass on type 2 diabetes mellitus. Ann Surg. 2003; 238:467–484. *discussion 84–5*. [PubMed: 14530719]
30. Isbell JM, et al. The importance of caloric restriction in the early improvements in insulin sensitivity after Roux-en-Y gastric bypass surgery. Diabetes Care. 2010; 33:1438–1442. [PubMed: 20368410]
31. Jackness C, et al. Very low-calorie diet mimics the early beneficial effect of Roux-en-Y gastric bypass on insulin sensitivity and beta-cell Function in type 2 diabetic patients. Diabetes. 2013; 62:3027–332. [PubMed: 23610060] Role of caloric restriction in acute improvement in beta cell function and insulin sensitivity.
32. Nauck M, et al. Reduced incretin effect in type 2 (non-insulin-dependent) diabetes. Diabetologia. 1986; 29:46–52. [PubMed: 3514343]
33. Drucker DJ, Nauck MA. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. Lancet. 2006; 368:1696–1705. [PubMed: 17098089]
34. Eckerle Mize DL, Salehi M. The place of GLP-1-based therapy in diabetes management: differences between DPP-4 inhibitors and GLP-1 receptor agonists. Curr Diabetes Rep. 2013; 13:307–318.

35. Laferrere B, et al. Effect of weight loss by gastric bypass surgery vs hypocaloric diet on glucose and incretin levels in patients with type 2 diabetes. J Clin Endocrinol Metab. 2008; 93:2479–2485. [PubMed: 18430778]
36. Korner J, et al. Prospective study of gut hormone and metabolic changes after adjustable gastric banding and Roux-en-Y gastric bypass. Int J Obes. 2009; 33:786–795.
37. Korner J, et al. Exaggerated glucagon-like peptide-1 and blunted glucose-dependent insulinotropic peptide secretion are associated with Roux-en-Y gastric bypass but not adjustable gastric banding. Surg Obes Relat Dis. 2007; 3:597–601. [PubMed: 17936091]
38. Pournaras DJ, et al. Remission of type 2 diabetes after gastric bypass and banding: mechanisms and 2 year outcomes. Ann Surg. 2010; 252:966–971. [PubMed: 21107106]
39. Laferrère B, et al. Incretin levels and effect are markedly enhanced 1 month after Roux-en-Y gastric bypass surgery in obese patients with type 2 diabetes. Diabetes Care. 2007; 30:1709–1716. [PubMed: 17416796]
40. le Roux CW, et al. Gut hormone profiles following bariatric surgery favor an anorectic state, facilitateweight loss, and improve metabolic parameters. Ann Surg. 2006; 243:108–114. [PubMed: 16371744]
41. McLaughlin T, et al. Reversible hyperinsulinemic hypoglycemia after gastric bypass: a consequence of altered nutrient delivery. J Clin Endocrinol Metab. 2010; 95:1851–1855. [PubMed: 20133462]
42. Dirksen C, et al. Postprandial diabetic glucose tolerance is normalized by gastric bypass feeding as opposed to gastric feeding and is associated with exaggerated GLP-1 secretion: a case report. Diabetes Care. 2010; 33:375–377. [PubMed: 19918005]
43. Salehi M, Prigeon RL, D'Alessio DA. Gastric bypass surgery enhances glucagon-like peptide 1-stimulated postprandial insulin secretion in humans. Diabetes. 2011; 60:2308–2314. [PubMed: 21868791]
44. Jorgensen NB, et al. Exaggerated glucagon-like peptide 1 response is important for improved beta-cell function and glucose tolerance after Roux-en-Y gastric bypass in patients with type 2 diabetes. Diabetes. 2013; 62:3044–3052. [PubMed: 23649520] Association between exaggerated GLP-1 response and improved beta cell function and glucose tolerance.
45. Jimenez A, et al. GLP-1 action and glucose tolerance in subjects with remission of type 2 diabetes after gastric bypass surgery. Diabetes Care. 2013; 36:2062–2069. [PubMed: 23359363]
46. Falken Y, et al. Changes in glucose homeostasis after Roux-en-Y gastric bypass surgery for obesity at day 3, 2 months, and 1 year after surgery: role of gut peptides. J Clin Endocrinol Metab. 2011; 96:2227–2235. [PubMed: 21543426]
47. Rubino F, et al. The early effect of the Roux-en-Y gastric bypass on hormones involved in body weight regulation and glucose metabolism. Ann Surg. 2004; 240:236–242. [PubMed: 15273546]
48. Jorgensen NB, et al. Acute and long-term effects of Roux-en-Y gastric bypass on glucose metabolism in subjects with Type 2 diabetes and normal glucose tolerance. Am J Physiol Endocrinol Metab. 2012; 303:E122–E131. [PubMed: 22535748]
49. Drucker DJ. Glucagon-like peptide 2. J Clin Endocrinol Metab. 2001; 86:1759–1764. [PubMed: 11297614]
50. Meier JJ, et al. Glucagon-like peptide 2 stimulates glucagon secretion, enhances lipid absorption, and inhibits gastric acid secretion in humans. Gastroenterology. 2006; 130:44–54. [PubMed: 16401467]
51. Nagell CF, et al. Glucagon-like peptide-2 inhibits antral emptying in man, but is not as potent as glucagon-like peptide-1. Scand J Gastroenterol. 2004; 39:353–358. [PubMed: 15125467]
52. le Roux CW, et al. Gut hypertrophy after gastric bypass is associated with increased glucagon-like peptide 2 and intestinal crypt cell proliferation. Ann Surg. 2010; 252:50–56. [PubMed: 20562614]
53. Drucker DJ. The role of gut hormones in glucose homeostasis. J Clin Invest. 2007; 117:24–32. [PubMed: 17200703]
54. Habegger KM, et al. GLP-1R agonism enhances adjustable gastric banding in diet-induced obese rats. Diabetes. 2013; 62:3261–3267. [PubMed: 23775764]

55. Korner J, et al. Effects of Roux-en-Y gastric bypass surgery on fasting and postprandial concentrations of plasma ghrelin, peptide YY, and insulin. J Clin Endocrinol Metab. 2005; 90:359–365. [PubMed: 15483088]
56. Morinigo R, et al. Glucagon-like peptide-1, peptide YY, hunger, and satiety after gastric bypass surgery in morbidly obese subjects. J Clin Endocrinol Metab. 2006; 91:1735–1740. [PubMed: 16478824]
57. Cummings DE, et al. Plasma ghrelin levels after diet-induced weight loss or gastric bypass surgery. N Engl J Med. 2002; 346:1623–1630. [PubMed: 12023994]
58. Peterli R, et al. Metabolic and hormonal changes after laparoscopic Roux-en-Y gastric bypass and sleeve gastrectomy: a randomized, prospective trial. Obes Surg. 2012; 22:740–748. [PubMed: 22354457]
59. Bohdjalian A, et al. Sleeve gastrectomy as sole and definitive bariatric procedure: 5-year results for weight loss and ghrelin. Obes Surg. 2010; 20:535–540. [PubMed: 20094819]
60. Harvey EJ, et al. Hormone changes affecting energy homeostasis after metabolic surgery. Mt Sinai J Med. 2010; 77:446–465. [PubMed: 20960548]
61. Peterli R, et al. Improvement in glucose metabolism after bariatric surgery: comparison of laparoscopic Roux-en-Y gastric bypass and laparoscopic sleeve gastrectomy: a prospective randomized trial. Ann Surg. 2009; 250:234–241. [PubMed: 19638921]
62. le Roux CW, et al. Gut hormones as mediators of appetite and weight loss after Roux-en-Y gastric bypass. Ann Surg. 2007; 246:780–785. [PubMed: 17968169]
63. Faraj M, et al. Plasma acylation-stimulating protein, adiponectin, leptin, and ghrelin before and after weight loss induced by gastric bypass surgery in morbidly obese subjects. J Clin Endocrinol Metab. 2003; 88:1594–1602. [PubMed: 12679444]
64. Thaler JP, Cummings DE. Minireview: hormonal and metabolic mechanisms of diabetes remission after gastrointestinal surgery. Endocrinology. 2009; 150:2518–2525. [PubMed: 19372197]
65. Romero F, et al. Comparable early changes in gastrointestinal hormones after sleeve gastrectomy and Roux-En-Y gastric bypass surgery for morbidly obese type 2 diabetic subjects. Surg Endosc. 2012; 26:2231–2239. [PubMed: 22302537]
66. Lee WJ, et al. Changes in postprandial gut hormones after metabolic surgery: a comparison of gastric bypass and sleeve gastrectomy. Surg Obes Relat Dis. 2011; 7:683–690. [PubMed: 21996600]
67. Patriti A, et al. Early improvement of glucose tolerance after ileal transposition in a non-obese type 2 diabetes rat model. Obes Surg. 2005; 15:1258–1264. [PubMed: 16259883]
68. Cummings BP, et al. Ileal interposition surgery improves glucose and lipid metabolism and delays diabetes onset in the UCD-T2DM rat. Gastroenterology. 2010; 138:2437–2446. 2446, e1. [PubMed: 20226188]
69. Strader AD, et al. Ileal interposition improves glucose tolerance in low dose streptozotocin-treated diabetic and euglycemic rats. Obes Surg. 2009; 19:96–104. [PubMed: 18989728]
70. Strader AD, et al. Weight loss through ileal transposition is accompanied by increased ileal hormone secretion and synthesis in rats. Am J Physiol Endocrinol Metab. 2005; 288:E447–E453. [PubMed: 15454396]
71. Gaitonde S, Kohli R, Seeley R. The role of the gut hormone GLP-1 in the metabolic improvements caused by ileal transposition. J Surg Res. 2012; 178:33–39. [PubMed: 22929182]
72. de Paula AL, et al. Laparoscopic sleeve gastrectomy with ileal interposition (“neuroendocrine brake”)—pilot study of a new operation. Surg Obes Relat Dis. 2006; 2:464–467. [PubMed: 16925382]
73. De Paula AL, et al. Prospective randomized controlled trial comparing 2 versions of laparoscopic ileal interposition associated with sleeve gastrectomy for patients with type 2 diabetes with BMI 21–34 kg/m(2). Surg Obes Relat Dis. 2010; 6:296–304. [PubMed: 20096647] Ileal interposition as a potential treatment for DM in humans.
74. Rubino F, Marescaux J. Effect of duodenal-jejunal exclusion in a non-obese animal model of type 2 diabetes: a new perspective for an old disease. Ann Surg. 2004; 239:1–11. [PubMed: 14685093]

75. Rubino F, et al. The mechanism of diabetes control after gastrointestinal bypass surgery reveals a role of the proximal small intestine in the pathophysiology of type 2 diabetes. Ann Surg. 2006; 244:741–749. [PubMed: 17060767]
76. Jiao J, et al. Restoration of euglycemia after duodenal bypass surgery is reliant on central and peripheral inputs in Zucker fa/fa rats. Diabetes. 2013; 62:1074–1083. [PubMed: 23248171]
77. Klein S, et al. Moderate effect of duodenal-jejunal bypass surgery on glucose homeostasis in patients with type 2 diabetes. Obesity. 2012; 20:1266–1272. [PubMed: 22262157] Duodenal jejunal bypass and improvement in DM in humans.
78. Aguirre V, et al. An endoluminal sleeve induces substantial weight loss and normalizes glucose homeostasis in rats with diet-induced obesity. Obesity. 2008; 16:2585–2592. [PubMed: 19279655]
79. Sandler BJ, et al. Human experience with an endoluminal, endoscopic, gastrojejunal bypass sleeve. Surg Endosc. 2011; 25:3028–3033. [PubMed: 21487876]
80. Verdam FJ, et al. An update on less invasive and endoscopic techniques mimicking the effect of bariatric surgery. J Obes. 2012; 2012:597871. [PubMed: 22957215] Endoluminal sleeve as a novel surgical alternative.
81. Cummings DE, et al. Hormonal mechanisms of weight loss and diabetes resolution after bariatric surgery. Surg Obes Relat Dis. 2005; 1:358–368. [PubMed: 16925248]
82. Olbers T, et al. Body composition, dietary intake, and energy expenditure after laparoscopic Roux-en-Y gastric bypass and laparoscopic vertical banded gastroplasty: a randomized clinical trial. Ann Surg. 2006; 244:715–722. [PubMed: 17060764]
83. Weyer C, et al. Hypoadiponectinemia in obesity and type 2 diabetes: close association with insulin resistance and hyperinsulinemia. J Clin Endocrinol Metab. 2001; 86:1930–1935. [PubMed: 11344187]
84. Patti ME, et al. Serum bile acids are higher in humans with prior gastric bypass: potential contribution to improved glucose and lipid metabolism. Obesity. 2009; 17:1671–1677. [PubMed: 19360006]
85. Mencarelli A, et al. Dissociation of intestinal and hepatic activities of FXR and LXRalpha supports metabolic effects of terminal ileum interposition in rodents. Diabetes. 2013; 62:3384–3393. [PubMed: 23835330] Ileal interposition leads to increased expression of FXR and FXR regulated genes in the intestine, leading to decreased hepatic gluconeogenesis.
86. Kohli R, et al. Intestinal adaptation after ileal interposition surgery increases bile acid recycling and protects against obesity-related comorbidities. Am J Physiol Gastrointest Liver Physiol. 2010; 299:G652–G660. [PubMed: 20595624]
87. Pournaras DJ, et al. The role of bile after Roux-en-Y gastric bypass in promoting weight loss and improving glycaemic control. Endocrinology. 2012; 153:3613–3619. [PubMed: 22673227]
88. Kohli R, et al. Weight loss induced by Roux-en-Y gastric bypass but not laparoscopic adjustable gastric banding increases circulating bile acids. J Clin Endocrinol Metab. 2013; 98:E708–E712. [PubMed: 23457410]
89. Jansen PL, et al. Alterations of hormonally active fibroblast growth factors after Roux-en-Y gastric bypass surgery. Dig Dis. 2011; 29:48–51. [PubMed: 21691104]
90. Sachdev, S.; Korner, J. Effect of Roux-en-Y Gastric Bypass on Fasting and Postprandial Concentrations of Bile Acids and FGF19. Oral presentation at Obesity Society Annual Meeting; Atlanta, GA. 2013.
91. Furet JP, et al. Differential adaptation of human gut subject to bariatric surgery-induced weight loss: links with metabolic and low-grade inflammation markers. Diabetes. 2010; 59:3049–3057. [PubMed: 20876719]
92. Zhang H, et al. Human gut microbiota in obesity and after gastric bypass. Proc Natl Acad Sci U S A. 2009; 106:2365–2370. [PubMed: 19164560]
93. Aron-Wisnewsky J, Dore J, Clement K. The importance of the gut microbiota after bariatric surgery. Nat Rev Gastroenterol Hepatol. 2012; 9:590–598. [PubMed: 22926153]
94. Liou AP, et al. Conserved shifts in the gutmicrobiota due to gastric bypass reduce host weight and adiposity. Sci Transl Med. 2013; 5:178ra41.
95. Still CD, et al. High allelic burden of four obesity SNPs is associated with poorer weight loss outcomes following gastric bypass surgery. Obesity. 2011; 19:1676–1683. [PubMed: 21311511]

96. Sarzynski MA, et al. Associations of markers in 11 obesity candidate genes with maximal weight loss and weight regain in the SOS bariatric surgery cases. Int J Obes. 2011; 35:676–683.

97. Mirshahi UL, et al. The MC4R(I251L) allele is associated with better metabolic status and more weight loss after gastric bypass surgery. J Clin Endocrinol Metab. 2011; 96:E2088–E2096. [PubMed: 21976721]

98. Hatoum IJ, et al. Melanocortin-4 receptor signaling is required for weight loss after gastric bypass surgery. J Clin Endocrinol Metab. 2012; 97:E1023–E1031. [PubMed: 22492873]

99. Florez JC, et al. TCF7L2 polymorphisms and progression to diabetes in the Diabetes Prevention Program. N Engl J Med. 2006; 355:241–250. [PubMed: 16855264]

100. Smushkin G, et al. Diabetes-associated common genetic variation and its association with GLP-1 concentrations and response to exogenous GLP-1. Diabetes. 2012; 61:1082–1089. [PubMed: 22461567]

101. Pilgaard K, et al. The T allele of rs7903146 TCF7L2 is associated with impaired insulinotropic action of incretin hormones, reduced 24h profiles of plasma insulin and glucagon, and increased hepatic glucose production in young healthy men. Diabetologia. 2009; 52:1298–1307. [PubMed: 19288077]

102. Schafer SA, et al. Impaired glucagon-like peptide-1-induced insulin secretion in carriers of transcription factor 7-like 2 (TCF7L2) gene polymorphisms. Diabetologia. 2007; 50:2443–2450. [PubMed: 17661009]

103. Talchai C, et al. Generation of functional insulin-producing cells in the gut by Foxo1 ablation. Nat Genet. 2012; 44:406–412. S1. [PubMed: 22406641]

104. Depoortere I. Taste receptors of the gut: emerging roles in health and disease. Gut. Published Online First: 16 Oct 2013 doi: 10.1136/gutjnl-2013-305112.

105. Bojsen-Moller KN, et al. Increased hepatic insulin clearance after Roux-en-Y gastric bypass. J Clin Endocrinol Metab. 2013; 98:E1066–E1071. [PubMed: 23609835]

106. Dirksen C, et al. Mechanisms of improved glycaemic control after Roux-en-Y gastric bypass. Diabetologia. 2012; 55:1890–1901. [PubMed: 22538359]

107. Bojsen-Moller KN, et al. Early enhancements of hepatic and later of peripheral insulin sensitivity combined with increased postprandial insulin secretion contribute to improved glycemic control after Roux-en-Y gastric bypass. Diabetes. 2013 Nov. Published online before print November 15, 2013, doi: 10.2337/db13-1307.

108. Troy S, et al. Intestinal gluconeogenesis is a key factor for early metabolic changes after gastric bypass but not after gastric lapband in mice. Cell Metab. 2008; 8:201–211. [PubMed: 18762021]

109. Potier M, Darcel N, Tome D. Protein, amino acids and the control of food intake. Curr Opin Clin Nutr Metab Care. 2009; 12:54–58. [PubMed: 19057188]

110. Tremblay F, et al. Role of dietary proteins and amino acids in the pathogenesis of insulin resistance. Annu Rev Nutr. 2007; 27:293–310. [PubMed: 17666010]

111. Newgard CB, et al. A branched-chain amino acid-related metabolic signature that differentiates obese and lean humans and contributes to insulin resistance. Cell Metab. 2009; 9:311–326. [PubMed: 19356713]

112. Tome D, et al. Protein, amino acids, vagus nerve signaling, and the brain. Am J Clin Nutr. 2009; 90:838S–843S. [PubMed: 19640948]

113. Laferrere B, et al. Differential metabolic impact of gastric bypass surgery vs dietary intervention in obese diabetic subjects despite identical weight loss. Sci Transl Med. 2011; 3:80re2.

114. Magkos F, et al. Effect of Roux-en-Y gastric bypass and laparoscopic adjustable gastric banding on branched-chain amino acid metabolism. Diabetes. 2013; 62:2757–2761. [PubMed: 23610059] RYGB and LAGB affect amino acid metabolism in nondiabetic patients.

115. Mutch DM, et al. Metabolite profiling identifies candidate markers reflecting the clinical adaptations associated with Roux-en-Y gastric bypass surgery. PLoS One. 2009; 4:e7905. [PubMed: 19936240]