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Ockham's razor and the metabolic syndrome

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Abstract

The broad effects of bariatric/metabolic surgery on virtually every tissue and organ system remain unexplained. Weight loss, although a major factor, does not fully account for the rapid, full, and durable remission of type 2 diabetes, return of islet function, reduction of the prevalence of cancers, increase in gray matter of the brain, and decrease in all-cause mortality. This review supports the thesis that the metabolic syndrome is not a group of separate diseases but rather multiple expressions of a shared defect in the utilization of carbohydrates and lipids. That error is probably caused by a dysmetabolic signal from the foregut, stimulated by food, that limits entry of 2-carbon fragments into the tricarboxylic acid cycle, the accumulation of lactate and, in turn, increases in glucose and insulin. Surgery limits that signal by reducing contact between food and foregut mucosa. Speciation of that signal(s) may offer a new pathway for drug development.

Keywords

Metabolic; Type 2 diabetes; Gastric bypass; Gastric sleeve; Metabolic syndrome; Bariatric surgery; Lactate

It makes no sense. How could two modest yet sharply different operations on the foregut (Fig. 1A) produce full and durable remission of our most costly diseases, including type 2 diabetes (T2D), severe obesity, and non-alcoholic steatotic hepatitis (NASH); improve cognition and mental health; and even produce a decrease in the prevalence of cancer and all-cause mortality? Further, the mechanisms for these dramatic results remain obscure, with some crediting alterations in gut signaling while others maintain that these changes are not due to the surgery and are only the result of weight loss.

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The purpose of this review is to consider these claims, evaluate these data, and apply these clues to the understanding of T2D and the other expressions of the metabolic syndrome.

What is the evidence?

The evidence is strong. Multiple clinical trials reflect the efficacy of surgery. Metabolic surgery, previously known as bariatric surgery, is the most effective treatment for severe obesity. In the Longitudinal Assessment of Bariatric Surgery (LABS) trial involving 1,738 patients with severe obesity who underwent the Roux-en-Y gastric bypass (RYGB), a mean loss of 28.4% of original weight was maintained for 7 years [1]. None regained their original weight (Fig. 1B).

The operations also offer the most effective treatment for T2D. We were startled, in 1982, when glucose values returned to normal within a week after the RYGB, an observation confirmed in our LABS series [2]. Among the 488 subjects with T2D, the rates of full remission at 1, 3, 5, and 7 years were 71.2%, 69.4%, 64.6% and 60.2%, respectively. In a comparison of intensive medical therapy versus the RYGB by Schauer et al. [3], the requirement for antidiabetic medications fell to zero in the surgical group while the level of medications remained the same in the medical cohort (Fig. 1C).

Metabolic surgery has also been shown to improve cardiac function and decrease cardiac adverse events. Aminian et al. [4], in a comparison of 287,438 adult patients with T2D versus 2,287 patients who underwent metabolic surgery, found a significantly lower risk of myocardial infarction, ischemic stroke, and mortality in the operated group. Kindel and Strande [5], in their systematic review, concluded that surgery “significantly improves cardiac geometry, function, and symptoms related to obesity cardiomyopathy. for end-stage heart failure patients, bariatric surgery has been successfully used for weight loss as a bridge to cardiac transplantation.”

Metabolic surgery can also reduce the thickness of atherosclerotic plaques. Marchesi et al. [6] reported significant reduction in carotid intima-media thickness in 22 patients at 3 levels—bulb, common, and internal carotid—with a 1-, 3-, 6-, and 12-month follow-up.

NASH, the most common cause of cirrhosis, is also improved. Lee et al. [7], based on a systematic review and meta-analysis of 32 cohort studies, found that metabolic surgery resulted in a biopsy-confirmed resolution of NASH in 66% of patients, inflammation in 50%, ballooning degeneration in 76%, and fibrosis in 40%.

The efficacy of metabolic surgery in the treatment of polycystic ovary syndrome (PCOS) led the European Society for Endocrinology [8] to recommend that surgery be included as a treatment for PCOS. In their systematic review of 13 studies involving 2,130 patients, the preoperative incidence of PCOS of 45.6% decreased to 6.8% after 12 months. Infertility decreased from 18.2% to 4.3%.

Metabolic surgery is also associated with a decrease in the prevalence of cancer. Adams et al. [9] compared the cancer incidence and mortality data from the Utah Cancer Registry for 6,596 Utah applicants for driver’s licenses who had undergone RYGB and a group of 9,442

persons with severe obesity who had not over 24 years, with a mean of 12.5 years. Total cancer incidence and cancer mortality were significantly lower in the surgical group.

Most remarkable are the anatomic effects on brain structure, as reflected by neuroimaging. A review by Nota et al. [10] noted that the improvement of cognition following metabolic surgery is associated with a recovery from preoperative brain abnormalities, with greater white and gray matter integrity and functional brain changes. Prehn et al. [11] and Bohon and Geliebter [12] also found the improvement of cognitive function following surgery was associated with larger gray matter volumes in frontotemporal brain areas, accompanied by smaller volume in the ventral striatum. Similarly, Hankir et al. [13] found a reduction in hypothalamic inflammation. Handley et al. [14] after a systematic review of 414 publications concluded that “significant and rapid weight loss resulting from bariatric surgery is associated with prompt and sustained improvements in cognitive function including memory, executive function, and cognitive control.”

Early studies also indicate that bariatric surgery affects existing end-organ damage (e.g., diabetic microvascular complications such as nephropathy [15], neuropathy [16], and retinopathy [17]) and improves islet cell function [18].

Finally, surgery is associated with reductions in all-cause, cardiovascular, and cancer-related mortality. As early as 1997, a difference in mortality between the surgical and comparison group, 9% vs. 29%, was reported [19]. That observation has been confirmed in Canada [20], Norway [21], and Sweden [22]. In a study comparing 2,500 surgical patients versus a 7,462 person cohort in the Veterans Administration [23], Adams et al. [24] in an extensive review, concluded that “bariatric surgical patients have: 1) significantly reduced long-term all-cause mortality when compared to severely obese non-bariatric surgical control groups; 2) but still a greater mortality when compared to the general population; 3) reduced cardiovascular-, stroke-, and cancer-caused mortality when compared to severely obese non-operated controls; in spite of 4) increased risk for externally caused death such as suicide.”

Fig. 1D. summarizes the effects of metabolic surgery on cancer, infections, and musculoskeletal, endocrine, and cardiovascular disease. Surgery has also been reported to improve quality of life, especially in those with high psychosocial burdens [25,26].

Ockham’s Razor

So how do we make sense of these observations? In dealing with complex issues, history can be helpful. In the Middle Ages, William of Ockham, an English Franciscan friar and a notable philosopher and theologian (c. 1287–1347), similarly confronted with confusing information, proposed that “simpler solutions are more likely to be correct than complex ones.” That “law of parsimony” is now known as Ockham’s razor. Let’s review the clues.

Surgery, as noted, leads to rapid remission of T2D and the other co-morbidities of the metabolic syndrome, with a reduction in all-cause mortality. Reversal of diabetes after RYGB occurs very quickly before there is appreciable loss in adiposity [27]· Diabetes

remission is durable after RYGB and extends to periods when weight has stabilized and caloric intake equals caloric expenditure [27].

Decreasing contact between food and the foregut, whether by surgical means, intestinal liners [28], ablation of duodenal mucosa [29], or diet [30] reverses the syndrome. In surgery, the extent of diabetes remission depends on the amount of foregut excluded. Weight loss and diabetes resolution were greatest for patients undergoing biliopancreatic diversion/duodenal switch, followed by gastric bypass, and least for banding procedures [31]. In 1998, our research group proposed that diabetes is a “disease of the foregut.” In response to foregut contact with nutrients, individuals with the disease produce a factor (signal) that causes diabetes [32]. When nutrients are withheld (via fasting or very low caloric intake) or when the foregut is bypassed (RYGB), the signal is not generated, with remission of diabetes. The most convincing evidence for an intestinal signal is the recent report by Constantin et al. [33], who found that

> compared to 1.1B4 cells incubated with baseline sera (control), cells exposed to sera from LSG-treated participants exhibited (i) increased viability and proliferation ($p < 0.05$); (ii) diminished levels of reactive oxygen species (ROS) and p53 ($p < 0.05$); (iii) enhanced protein expression of autophagy-related (Sirtuin 1) SRT1 and p62/SQSTM1 ($p < 0.05$); (iv) significantly decreased transcript levels of ER stress markers (p, 0.05); and (v) augmented insulin expression ($p < 0.05$). Conversely, the 6-month conventional therapy appeared not to impact on circulating redox status.

Glucose and insulin, fasting as well as responses to a meal, are normalized after metabolic surgery. The prevailing etiology of diabetes is as follows: 1) Insulin resistance is the underlying cause and first manifestation of the disease; 2) insulin secretion increases to overcome resistance; and 3) hyperglycemia is a result of lower insulin secretion in response to glucose because of beta cell failure. This etiology is clearly demonstrated by the oral glucose tolerance curves of patients as they become obese and then develop diabetes (Fig. 2). Based on this etiology, our original hypothesis for the remission of diabetes was that insulin sensitivity would increase or insulin secretion would increase after metabolic surgery. This was not what we observed. Fasting glucose and insulin concentrations were normalized as early as 1 week after surgery, but insulin resistance remained up to 3 months after surgery (Fig. 3A). The response of glucose to a meal was normalized (Fig. 3B) after surgery, suggesting normal peripheral glucose disposal, but peak insulin concentration was not increased after surgery (Fig. 3C). This normalization occurred in spite of continued insulin resistance (Fig. 3A).

Could lactate be the answer? Lactate levels, widely used in the assessment of the acutely ill, may be the critical clue to the puzzle of the metabolic syndrome. In a systematic review of the care of acutely ill patients, Vincent et al. [34] documented that a decrease in lactate levels was consistently associated with lower mortality rates in all subgroups. Lazzeri et al. [35] reported that higher admission lactate levels in acute cardiac patients predict high mortality levels and that higher lactate clearance is associated with better outcome. In chronic disease, lactate levels have not found wide application even though there are a number of publications indicating direct relationships between fasting blood lactate and

components of the metabolic syndrome [36–39]. In 1993, Chen et al. noted that plasma lactate concentrations are elevated in obesity and yet higher in T2D [40].

Individuals with severe obesity, with and without T2D, have elevated plasma lactate concentrations that return to levels similar to those in lean individuals after surgery [41]. Fig. 4A shows the correlation between fasting glucose and lactate from diabetic subjects before surgery, 1 week after surgery, and 3 months after surgery [42]. The remarkable correlation between glucose and lactate raises the question as to which is the chicken and which is the egg. Lactate is a major substrate for gluconeogenesis in the liver. If lactate were elevated because of depressed gluconeogenesis, one would predict that glucose production would be reduced, which is not the case. If glucose were elevated because of increased gluconeogenesis, the substrate and lactate would be reduced. This then suggests that elevated lactate may be driving glucose production. Chondronikola et al. [43] demonstrated that the rate of endogenous glucose production in patients with obesity was correlated with fasting plasma lactate, consistent with this hypothesis.

If lactate is driving gluconeogenesis to cause hyperglycemia, the question arises as to the source of the lactate. Our studies of muscle substrate oxidation using whole body studies, as well as experiments with human muscle fiber strips and human muscle homogenates, are summarized in Fig. 4B [44]. Complete oxidation of fatty acids (CO_2 production) and the complete oxidation of glucose are approximately 40% lower in obese muscle than in lean controls. Depressed oxidation of substrates was compensated by an increase in lactate production, indicating a “mitochondrial dysfunction” with production of ATP shifted toward more glycolysis and accumulation of lactate. These findings are in accord with numerous references to the altered mitochondria structure and function in muscle of diabetic patients [45].

If mitochondrial substrate oxidation is impaired, there would, of necessity, be a compensatory increase in glycolysis to lactate; this would be reflected in elevated plasma lactate. Lactate was measured during an intravenous glucose tolerance test in non-diabetic individuals with obesity 1 week before RYGB surgery and again 1 week post surgery (Fig. 4C). Lactate began to rise with the administration of glucose, and the rate of rise was increased after insulin, suggesting uptake of glucose into muscle and incomplete oxidation. A week after surgery, fasting lactate was reduced and there was only a minimal increase with the administration of glucose and insulin, suggesting complete oxidation of glucose. Since insulin sensitivity was not changed a week after surgery, the amount of glucose taken up was the same before and after surgery [46]. Lower lactate suggests that muscle mitochondrial substrate oxidation was enhanced after gastric bypass surgery.

In normal physiology, we usually think about muscle lactate production in relation to intense physical exercise. During a sprint, mitochondrial substrate oxidation is not capable of providing enough ATP, and glycolysis to lactate is increased to maintain energy production at a level to continue exercise. Lactate from muscle goes to the liver, where glucose is produced, and returned to the muscle in a process called the Cori cycle. The same process occurs in the metabolic syndrome, except the muscle is producing lactate in the resting state. Mitochondrial oxidation of substrates is reduced to apoint where ATP production is below

that needed to maintain muscle function and a compensatory increase in glycolysis to lactate is required. Lactate produced by muscle causes increased plasma lactate concentration, and this drives liver gluconeogenesis by mass action. We have termed this phenomenon the “vicious Cori cycle” because it occurs during the entire day, rather than just during exercise, as in the original Cori cycle [41]. This is a dangerous metabolic condition because the liver is challenged with an elevated level of substrate and reducing equivalents, which can lead not only to the production of glucose, but also fatty acids, cholesterol, and low density lipoprotein. These synthetic processes are further driven by insulin; thus, hyperinsulinemia compounds symptoms of the metabolic syndrome. As the impairment in mitochondrial substrate oxidation progresses, lactate concentration increases to the point where endogenous glucose production generates hyperglycemia and diabetes.

Hypothesis

In applying Ockham’s razor, we believe that the simplest explanation for the remission of diabetes after metabolic surgery is the following: In vulnerable individuals, a signal(s) from the foregut, stimulated by contact with food, impairs mitochondrial oxidation of substrates, forcing a greater reliance on glycolytic flux to lactate to maintain energy production. Our data suggest that this may be the case in muscle, but it could also be the situation in other tissues and might explain the pancreatic beta cell impairment that causes fasting hyperinsulinemia and reduced insulin secretion in response to glucose. Further, by a mechanism related to the foregut, RYGB surgery reduces the intestinal signal that impairs mitochondrial substrate oxidation, allowing lactate, glucose, and possibly insulin concentrations to return to normal. This hypothesis is illustrated in Fig. 5.

Although we find this a reasonable hypothesis, there are other thoughtful investigators, such as Yoshino et al. [47], who do not agree that intestinal physiology and signaling have any role and conclude, based on their studies, that “the metabolic benefits of gastric bariatric surgery and diet were similar and were apparently related to weight loss itself with no evident clinically important effects independent of weight loss.” There are several clinical observations that counter that view: 1) Glucose and insulin levels normalize within a week after the surgery before there is any significant loss of weight; 2) insulin resistance does not return to normal levels for over 3 months in spite of the resolution of the diabetes, 3) T2D usually does not return when patients regain some weight; 4) 10% of patients who develop T2D are lean; and 5) only one third of those with severe obesity develop T2D. The most convincing evidence, however, of the role of intestinal signaling is the study by Constantin et al. [33] in which serum from bariatric patients produced the metabolic changes of T2D in human islet cultures before surgery but not after the procedures.

Even so, how can we explain the variations in the presentation of this metabolic defect? After all, only one third of those with severe obesity present with T2D, and 10% of patients with T2D are lean. We believe these variations are a reflection of the hosts’ responses, similar to other diseases due to a single cause. COVID-19 is a good example, with its outcomes that vary from no symptoms in one individual to a mortal destruction of lungs, heart, brain, and kidneys in another.

Further, how can we explain how 3 very different approaches (i.e., the gastric bypass, gastric sleeve, and intestinal liner) can have similar effects that only differ in degree? All 3 interventions could include a group of enteroendocrine cells, which respond to food, centered in the fundus of the stomach that diminish in concentration further down the duodenum and upper jejunum. The RYGB bypasses this area, the gastric sleeve removes the largest concentration, and the liner, least effective, reduces distal contact.

The next step in research is to identify the signal and seek approaches either to disable the source or develop a medication to nullify the signal. Ghrelin, as noted by Gu et al. [48], fits many of these characteristics with sharp decreases following the gastric sleeve, but it is difficult to fit that with their findings that it increases after RYGB, underscoring the complexities of this challenge.

Conclusion

The salutary outcomes of bariatric surgery compel a re-evaluation of our concepts about T2D and its comorbidities. The metabolic syndrome is not a group of separate diseases, but rather, multiple expressions of a shared defect in the utilization of carbohydrates and lipids [49–51]. That error is probably caused by a dysmetabolic signal from the foregut, stimulated by food, that limits entry of 2-carbon fragments into the tricarboxylic acid cycle, the accumulation of lactate, and, in turn, increases in glucose and insulin. Speciation of that signal(s) may offer a new pathway for drug development. These changes have been attributed by some solely to weight loss but are far more complex, as indicated by their occurrence before there is any significant change in adiposity.

These observations also indicate that the use of insulin or drugs that increase insulin secretion and/or sensitivity needs careful review. If the “vicious Cori cycle” is the underlying mechanism causing diabetes, treating downstream insulin resistance and insulin secretion only hides the symptom (i.e., hyperglycemia). It would be rather like treating whooping cough with cough syrup; the cough is better, but the disease is unchecked.

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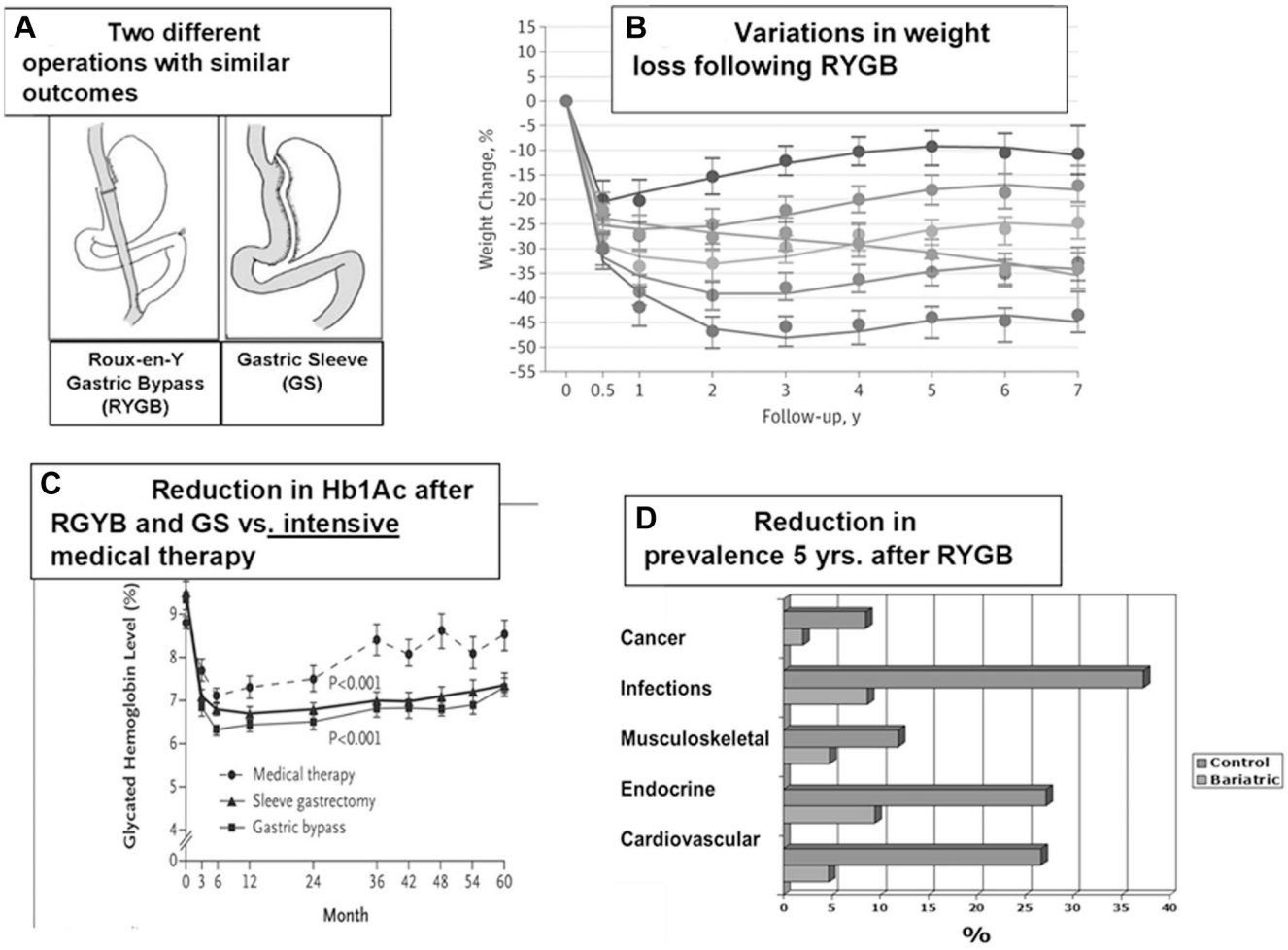

Fig. 1.

Clinical outcomes of metabolic surgery. (A) Configuration of the Roux-en-Y gastric bypass (RYGB) and gastric sleeve surgeries. (B) Weight loss of patients who had RYGB surgery [1]. (C) Remission of diabetes after RYGB surgery [3]. (D) Effects of metabolic surgery on diseases [20].

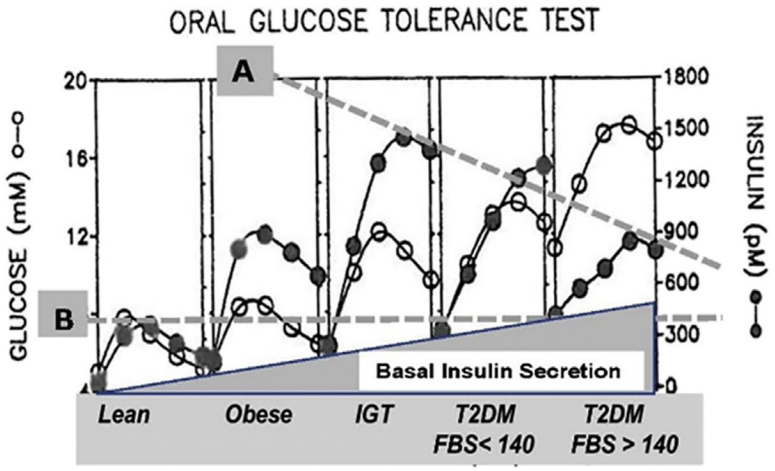

Fig. 2.

Plasma glucose and insulin during oral glucose tolerance tests [27]. Fasting blood insulin levels increase with progression of type 2 diabetes (T2D), but maximum secretion of insulin falls with advancement of the disease in response to a meal (A). However, even in advanced T2D, the response is almost double that of a normal individual (B). The most striking effect, however, of the progression of the disease is the continued increase in fasting basal insulin secretion, a finding that indicates that in advanced T2D, even when these individuals are sleeping and fasting, they secrete insulin at levels that exceed the normal response after meals.

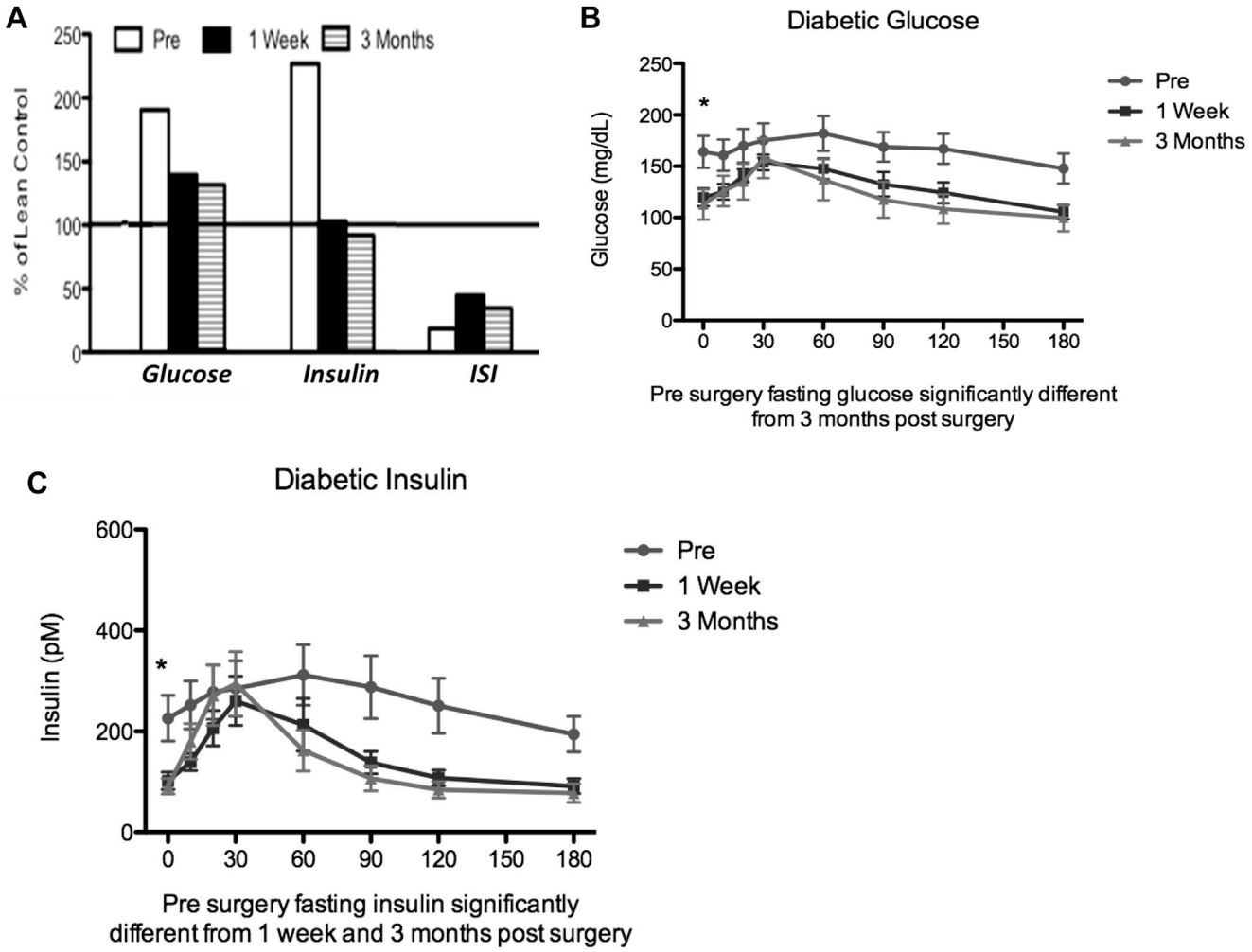

Fig. 3.

Changes in glucose, insulin, and insulin sensitivity index (ISI) after Roux-en-Y gastric bypass (RYGB). (A) Glucose, insulin, and ISI for diabetic patients before surgery (Pre) and after RYGB (1 wk and 3 mo) expressed as a percent of lean control subjects. (B) Time course for changes in glucose after a meal challenge in diabetic patients before surgery (Pre) and after RYGB (1 wk and 3 mo). Data redrawn from Reed et al. [46]. (C) Time course for changes in insulin after a meal challenge in diabetic patients before surgery (Pre) and after RYGB (1 wk and 3 mo). Data redrawn from Reed et al [46].

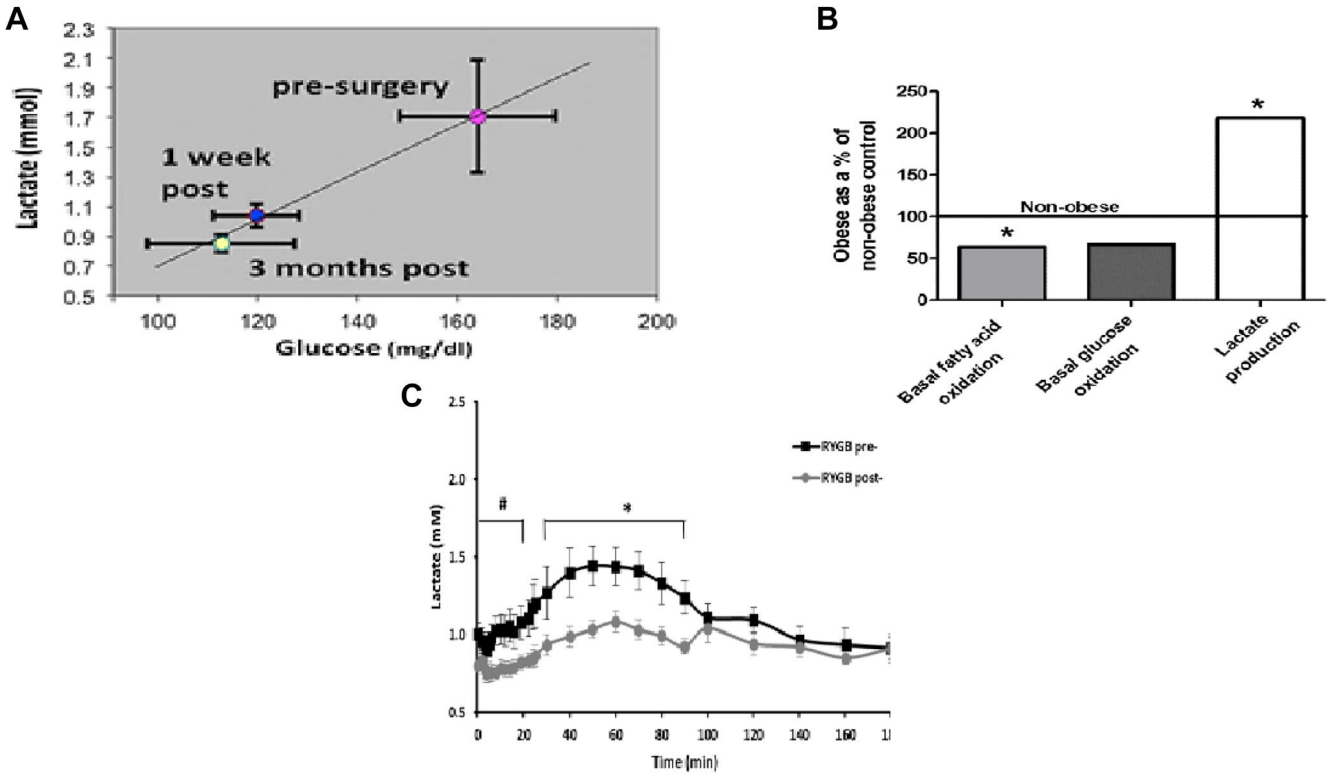

Fig. 4.

Changes in plasma lactate and muscle metabolism after Roux-en-Y gastric bypass (RYGB). (A) Relationship of lactate and glucose before surgery and 1 week and 3 months after RYGB [41]. (B) *In vitro* metabolism of glucose and fatty acids in muscle fiber strips from patients with obesity (data expressed as a percent of lean controls) [50,51]. Plasma lactate from non-diabetic individuals with obesity during an intravenous glucose tolerance test 42.

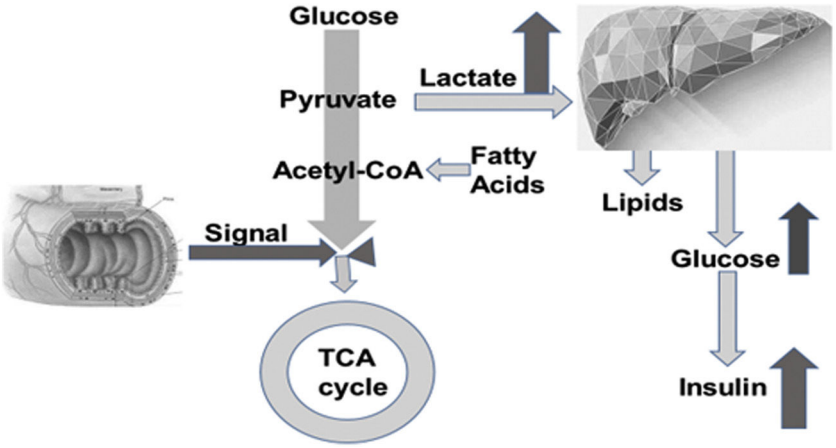

Fig. 5.

A representation of the “vicious Cori cycle” hypothesis. By this hypothesis, the metabolic syndrome is caused by a signal from the gut that is generated in response to contact with food. This gut signal impairs oxidation of glucose and fatty acids. Glycolysis to lactate is accelerated to supply energy to offset impairment of substrate oxidation. Lactate concentration in the plasma is elevated, and the liver is supplied with excess substrate and reducing equivalents throughout the day. Overproduction of glucose and lipids from lactate results in hyperinsulinemia and symptoms of the metabolic syndrome.