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Mechanisms of improved glucose handling after metabolic surgery: The Big Six

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Abstract

For some time, it has been clear that elevated glucose is detrimental to the organism. A plethora of medicines have been introduced to reduce the fasting and postprandial glucose levels (including insulin, GLP-1 agonists, and SGLT2 inhibitors, among others). While these medications are useful to reduce tissue exposure to glucose, no single compound and no combination have been able to totally normalize the blood sugar. Thus, it was astonishing when it was reported that surgery of the gastrointestinal tract could not only reduce obesity but also normalize the blood sugar. These discoveries have transformed diabetes research. What is it about bariatric surgery that causes the remarkable amelioration of glucose homeostasis dysregulation? The answer to this million dollar question is a billion dollar answer. However, a new perspective could shed some light and help provide a clear path for investigation. Instead of asking what does bariatric surgery do to change the pathophysiology, we can be asking what pathophysiology and risk factors confer a greater success with remission and improved disease state following surgery. Work from our lab and others can help to offer a physiological basis for what mechanisms may be put into play when the anatomy is altered during surgery. Here, we do not offer an explanation of the mechanism of action of bariatric surgery, but rather provide a background on the regulation of blood glucose and how it is altered during both the diseased state and, as available, the remission state.

Introduction

It has been known for some time that bariatric, or weight-loss, surgery procedures which alter the path of foodstuffs in the gastrointestinal tract often induce type 2 diabetes (T2D) remission. The amelioration of diabetes is remarkable, considering that a plethora of medicines used to treat diabetes are not able to normalize glycemia alone or in combination. Of course part of the mechanism is the extensive weight loss which bariatric surgery causes. However, it appears clear that weight loss alone does not normalize glycemia¹, although some observers do believe it is weight loss alone which is responsible². Assuming that there is a hyperglycemia-ameliorating effect, it is of interest to examine what possible mechanisms might be responsible. In order to develop reasonable hypotheses, here we re-examine the mechanisms involved in regulation of glucose homeostasis to possibly hone in on targets which must be considered when examining the positive effects of bariatric

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surgery. In this article, we will review the overall holistic processes which are relevant to blood sugar regulation to identify those which must be examined in looking at the putative mechanism. In particular, we focus not only on the most considered mechanisms (changes in insulin sensitivity and secretion) but less appreciated mechanisms (regulation of liver glucose output and uptake, glucose effectiveness and insulin clearance).

1. Islet Function

Over the past few decades, an appreciation of the role of islet function in the etiology of T2D has gained favor. Patients with normoglycemia experience a pronounced first- and second-phase insulin response to a meal or other oral challenge. However, progression to diabetes leads to a decrease in the first-phase insulin response followed by a decrease in the second-phase response³. After biliopancreatic diversion (BPD), diabetic patients had a significant overall decrease in insulin area under the curve (AUC) while regaining a first-phase response one month post-surgery during an intravenous glucose tolerance test (IVGTT)⁴. These patients maintained a second-phase insulin response both before and after BPD. In a more experimental approach, simulating the first-phase insulin response in diabetic patients using exogenous insulin delivered to the liver improved postprandial glucose homeostasis with effects that last four hours post-infusion⁵.

Patients with longer duration diabetes show impairments in second-phase insulin response as well as in the first-phase. Duration of disease is tied strongly to decreases in both phases as well as to the improvements seen following bariatric surgery⁶. In patients who underwent Roux-en-y gastric bypass (RYGB) or sleeve gastrectomy (SG), those with shorter disease duration (less than 5 years) showed significant improvements in first-phase insulin response, and second-phase insulin response 24 months post-surgery compared to patients with those with longer disease duration (greater than or equal to 10 years) during a mixed meal tolerance test (MMTT)⁷.

Taken together, these data suggest that bariatric surgery procedures improve islet function, so long as there are islets to improve⁸. Remission of diabetes following surgery has been correlated with pre-surgery c-peptide levels⁶, suggesting that those patients who are still able to make sufficient insulin are best able to recover proper insulin secretion and function. It will be interesting to look at data from patients with type 1 diabetes (T1D) with varying degrees of beta-cell mass and function and determine the effects that bariatric surgery would have on beta-cell reserve function and time to complete beta-cell failure. It is possible that the same mechanisms that restore first-phase insulin secretion in T2D could elongate the time a patient with T1D still has functioning beta-cells and, quite possibly, improve complication outcomes due to early-stage glycemic control. This may further be used in those with pre-diabetes or who are at-risk for developing T2D.

As reduced first-phase insulin secretion is the first step on the path to diabetes, it also appears to be the first to recover⁹. It is reasonable that the changes in gut hormones [namely the incretins: glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP)] following bariatric surgery¹⁰ facilitate the restoration of the first-phase of insulin secretion. This improvement in initial insulin signaling and secretion would improve postprandial

glucose and decrease the need for second-phase hyperinsulinemic compensation, ultimately leading to normoinsulinemia and improved glucose homeostasis, as seen following bariatric surgery. The insulinotropic effects of GLP-1 (and the more controversial, GIP) in its increased state following surgery may compensate for the decrease in glucose transporter, type 2 (GLUT-2) expression that is seen in animal models of T2D¹¹ and that may play a causal role¹² in disease etiology. Yet, the incretins cannot tell the entire story. They are not the only effectors of beta-cell function and increase to various magnitudes following RYGB versus laparoscopic adjustable gastric banding (LAGB) despite similar improvements in beta-cell function¹³.

2. Insulin Sensitivity (Resistance)

As the hallmark of T2D, insulin resistance is frequently studied in the context of bariatric surgery^{14,15} with over 1200 hits in PubMed alone (possibly due to the ease of measurement in comparison to beta-cell function). But what can insulin resistance tell us about the effects of bariatric surgery and about remission of the disease? Placed on a moderate fat diet, similar to that eaten in the Western world, dogs first become insulin resistant a few weeks before the beta-cells compensate with an increase in first-phase insulin secretion¹⁶. Following RYGB, improvements can be seen first in hepatic insulin sensitivity after the first week followed by peripheral insulin sensitivity by the third month post-surgery¹⁷ with decreases in intestinal insulin resistance also seen by six months post-surgery¹⁸. Improvements in insulin secretion also occurred by the three-month time point in this study, with improvements seen at the one-month time point in other studies⁴.

It is interesting to note that the improvements in metabolic functions occur in the same order as detriment occurs during disease progression, just as in restoration of the two phases of insulin secretion improve in the same order as detriment occurs (see above). This suggests that the detriments that lead to disease through decreased insulin sensitivity and inadequate insulin secretion are not permanent and may be reversible⁸. If such functions can be recovered their improvement can drastically improve glucose homeostasis and lead to disease remission.

Hepatic insulin sensitivity is improved first, although this improvement may not be related to bariatric surgery *per se*. Following modest weight loss, diabetic patients first demonstrate an improvement in hepatic insulin sensitivity and return to normal function before peripheral insulin sensitivity is restored¹⁹. The change in the liver is considered secondary to improvements in liver fat deposition following weight loss. However, early one week post-surgery changes in the liver sensitivity are more likely due to changes in liver signaling. This also suggests a role for portal signaling, an interesting area for future research. The independence of improvements in insulin sensitivity between tissues (hepatic vs. peripheral) is important in highlighting newer data. Traditionally thought to be associated with insulin resistance, increases in visceral adiposity are not necessarily associated with increases in insulin resistance²⁰ or outcomes following bariatric surgery²¹ and there are conflicting reports in regards to correlations between visceral fat content and improvements in glucose homeostasis following surgery^{22,23}. This further supports the idea that signaling in the liver

(including pathways involved in insulin sensitivity) is an important player in diabetes remission.

3. Disposition Index

Beta cell function is correctly expressed in terms of islet-cell response, normalized to insulin sensitivity. Insulin sensitivity is reduced by many factors -- diet, pregnancy, puberty, polycystic ovary syndrome (PCOS) for example -- is normally associated with a responsive increase in insulin release (Figure 2). We expressed this relationship as the Disposition Index (DI), which quantifies the degree of increase in insulin associated with a given insulin resistance²⁵. This index models the hyperbolic relationship between these two factors and has stood the test of time. Previous work showed the importance of this compensation, which can be expressed as the DI. A longitudinal study following Pima Indians showed that those who went on to develop T2D showed that reduction in DI was a strong predictor of later disease development²⁶. The DI also appears to be a strong predictor of outcome in patients with T2D undergoing RYGB. Those with a lower DI at baseline were much less likely to experience diabetes remission at 4 months (0% vs. 57% of patients) and at 18 months (38% vs. 71% of patients) post-surgery²⁷ (Table 1). During a five-year follow-up study looking at insulin resistance and atherosclerosis, patients with lower modeled assessment of insulin response to glucose (AIR_g), DI, and insulin sensitivity were more likely to develop diabetes by the end of the five years. Of those with impaired glucose tolerance at baseline, over 30% of them had a T2D diagnosis by the end of the study²⁸.

Why is the DI a good predictor of diabetes remission after bariatric surgery? In fact, DI is a stronger predictor of diabetes risk compared to commonly used risk assessment tools including HOMA-%B (a modeled assessment of beta-cell function), HOMA-%S (a modeled assessment of insulin sensitivity), insulin sensitivity, or AIR_g (a measure of beta-cell function and of first-phase insulin secretion)²⁹. DI is not a measure of a single aspect of glucose control but rather an assessment of how well the body can maintain proper glucose control when some part of the machinery is operating sub-optimally. With that in mind, using DI as a predictor of patients likely to receive the most benefit from bariatric surgery falls in line with predictions made above; namely, those patients with the largest reserve of beta-cell function will have a higher DI and, therefore, more likely to experience remission.

If patients with less severe disease respond best to bariatric surgery, what can be done for patients with more severe disease or longer disease duration? Targeting therapy to the proper population of patients to gain the most benefit is ideal. This is the case especially due to the more risky and expensive therapy discussed here, compared to oral medications. However, this highlights the importance of improving existing therapies and increasing research efforts to bring more severe cases to a disease state that can benefit from our best and most effective therapies.

4. Insulin Clearance (Degradation)

Most of the degradation of secreted insulin is by the liver. Insulin released from the pancreatic islets enter the portal vein and then the liver directly; in normal, insulin resistant

individuals half or more of the secreted molecules are degraded by the liver before entering the hepatic veins and hence the systemic circulation³⁰ (Figure 3).

“There's always the hyena of morality at the garden gate, and the real wolf at the end of the street (D.H.Lawrence).”

For many years it was not understood why evolution had chosen such a large fraction of secreted hormone to be at risk for degradation by the liver. In studies performed in our laboratory, we demonstrated that insulin clearance is not constant, but in fact is changed by metabolic conditions. Inducing insulin resistance by fat feeding in the canine model can reduce insulin clearance up to 50%³¹ (Figure 4). Increases in insulin resistance and insulin secretion are both independently associated with a decrease in insulin clearance³², highlighting the importance of this third aspect of glucose homeostasis and emphasizing the importance of the DI to incorporate insulin sensitivity and beta-cell function. Reduction in insulin clearance by the liver occurs around the same as the increased secretion of insulin by the pancreas during disease progression¹⁶. In one study, where hepatic insulin sensitivity did not improve in women two weeks post- RYGB surgery, insulin clearance, on the other hand, did improve³³. Interestingly, in a population of non-diabetic Mexican Americans (an ethnic group three times more likely to develop T2D) clearance was significantly lower than in the matched non-diabetic white population³⁴.

What can insulin clearance tell us about diabetes remission and bariatric surgery? As a compensatory mechanism, decreasing insulin clearance helps to relieve the stress placed on beta-cells and to help preserve their function. It also allows an increased amount of insulin into circulation to alleviate the stress of insulin resistance and ensure that an appropriate amount of insulin can access peripheral tissues. This evidence would suggest that insulin clearance may be the catch-all that maintains proper glucose homeostasis. However, evidence showing that insulin clearance improves before insulin sensitivity changes following RYGB would indicate a more central and causal role. These improvements would also suggest changes in signaling in the liver.

Postprandial hypoglycemia is a serious complication following bariatric surgery. In a study of 65 patients who experienced postprandial hypoglycemia following RYGB, they also experienced inappropriate insulin secretion and decreased insulin clearance during a MMTT³⁵. This is another example of insulin clearance functioning independently of beta-cell function and shows that insulin clearance is regulated under different mechanisms. In an animal study of high-fat feeding, key regulators in the insulin clearance pathway are altered³⁶. Taken together, this further suggests an important, perhaps, causal role for insulin clearance in diabetes progression as well as in remission. Improvements in liver signaling that include insulin sensitivity as well as insulin clearance are key to the improvements in disease state following bariatric surgery.

5. Glucose Effectiveness

Glucose effectiveness was defined by our laboratory as the “ability of glucose to normalize itself independent of dynamic changes in plasma insulin³⁷.” Glucose effectiveness is a

measure of how well glucose delivered from a meal is able to stop endogenous glucose production and to get into cells independently of insulin action. We showed that even if insulin response is blocked, glucose will renormalize itself, albeit at a slower rate than in the face of a dynamic insulin response³⁸. While the rate of disappearance of glucose is an independent measure, it is important to note that a decrease in second-phase insulin response (as mentioned above) suggests a decrease in beta-cell function as well as in the rate of disappearance of glucose³⁹. Improvements in the rate of disappearance of glucose are seen after RYGB in glucose tolerant⁴⁰ as well as in T2D patients^{17,41}.

Decreases in glucose effectiveness occur late in disease progression⁴², suggesting a secondary role likely due to other factors or consequences of glucose dysregulation such as elevated free fatty acid levels or decreased GLP-1 in circulation. In contrast, patients who experience postprandial hypoglycemia following RYGB (as mentioned above) show an inappropriate increase in glucose effectiveness⁴³ that is likely a strong contributing factor to the hypoglycemia. Similar to insulin clearance, this inappropriate increase may be due to hepatic signaling.

6. Endogenous Glucose Production

The factors determining the fasting glucose level remain somewhat controversial. It is clear that the glucose results from a balance between glucose production and uptake: production primarily by the liver (but also the kidneys) and uptake under fasting conditions, 50% by the brain and 50% by other tissues, including muscle and heart. Clearly, glucose output by the liver is insulin-dependent, and in T2D the rate of output is high despite normal or elevated insulin levels. Patients undergoing RYGB show decreases in endogenous glucose production by about 25% following surgery⁴⁴.

Elevated fasting glucose is evidence for liver insulin resistance⁴⁵. But it is not insulin alone which determines fasting liver (and kidney) glucose output. Other factors include glucagon levels, and factors which can regulate glucose output, including free fatty acids (FFA) and glucose itself. In fact, it is often believed that insulin is the primary regulator of glucose production under fasting conditions. We have examined this concept and shown that FFA levels are equally or even more important than insulin in determining the fasting glucose⁴⁶. In fact, when insulin suppression of lipolysis is prevented, we discovered that endogenous glucose production does not decline. We posited the “single gateway hypothesis” which suggested that the primary control by insulin of liver glucose production is mediated via suppression of lipolysis at the level of adipose tissue^{47,48}. This concept, which was controversial has recently been supported by Perry and Shulman and colleagues^{49,50}.

Thus, in examining the putative effects of metabolic surgery on fasting glucose level (reflecting fasting endogenous glucose production rates) it is critical examine whether metabolic surgery itself can alter metabolism of fat in the visceral and subcutaneous compartment, and examine whether improved effect of insulin to regulate glucose output by the liver and the kidneys is reflective of a change in fat metabolism, wherein there may be an improved insulin effect to lower FFA which may then be reflected in fasting glucose

production rates. Studies related to metabolic surgery and FFA-mediated insulin action remain to be done.

Newer data has also highlighted the role of the intestines in overall glucose homeostasis. Animal work in mice has suggested that following entero-gastric anastomosis (EGA) procedures, intestinal gluconeogenesis is increased and necessary for the improvements in glucose homeostasis. Interestingly, the increased glucose secreted from the cells of the intestine is detected in the hepatic portal vein⁵¹. This further highlights the importance of hepatportal sensing in glucose regulation. Activation of these sensors by intraportal infusion of glucose improved glycemia independently of any pancreatic changes⁵². Taken together, these data suggest that by changing the amount glucose dumped into the portal vein from the intestines through increased transport or increased gluconeogenesis, we can effectively improve hepatportal signaling and, consequently, glucose homeostasis.

Conclusions

The exact mechanisms responsible for diabetes remission following bariatric surgery have eluded researchers for some time. Examining changes in glucose homeostasis leading to disease may assist in the search. The five factors of glucose homeostasis discussed here were islet function, insulin sensitivity, disposition index, insulin clearance, glucose effectiveness, and endogenous glucose production. Together, evidence from studies looking into each of these factors suggests that remission occurs when the first factors to change (such as the decrease in first-phase insulin response and hepatic insulin sensitivity) revert to a normal level and that remission is most likely to occur in patients that have less severe disease. This may be due to changes that improve signaling, especially in the liver. Research focusing on the causal roles that these changes may play in remission rather than studies of associations will be important to delve further into mechanism and hopefully elucidate a potential cure for this disease.

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Figure 1.
How can we piece together the elephant of bariatric surgery and its effects on T2D?

Figure 2.
Ethnic Differences in the Relationship Between Insulin Sensitivity and Insulin Response²⁴

Figure 3.

Why is insulin secreted into the portal vein? More than 50% of the insulin that is secreted into the portal vein is cleared by the liver and never enters the systemic circulation (adapted from Ref. 30).

Figure 4.
Reductions in insulin clearance with fat feeding (adapted from Ref. 31).

Table 1

Diabetes remission by the Disposition Index (DI) (Adapted from Ref. 27)

DI at basal	Rate of remission after surgery	
	4 months	18 months
Low	0%	38%
High	57%	71%