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Clues from Bariatric Surgery: Reversing Insulin Resistance to Heal the Heart

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Abstract

Obesity is a state of metabolic dysregulation of the whole organism and a major contributing factor to the epidemic of insulin resistant diabetes. The non-pharmacological treatment of obesity with bariatric surgery results in a dramatic and almost instantaneous reversal of insulin resistance. The present review collectively addresses the evidence for this phenomenon in the literature and discusses potential metabolic and neurohumoral mechanisms. We propose that nutrient restriction lowers the cell's defense mechanisms for nutrient overload in insulin responsive organs.

Keywords

Insulin Resistance; Diabetes; Obesity; Bariatric Surgery; Gastric Bypass; Lipotoxicity

Introduction

Obesity is a state of metabolic dysregulation of the whole organism and a major contributing factor to the epidemic of diabetes [1]. Among Americans age 20 and older, approximately 150 million are overweight or obese accounting for nearly half of the population [2]. Although the American Diabetes Association (ADA) and World Health Organization (WHO) differ in their definition and diagnostic criteria of “prediabetes” or “impaired glucose regulation” [3], they are in full agreement with regards to the devastating impact obesity and diabetes has and will continue to have on healthcare.

Dr. Walter Pories began performing gastric bypass surgery in the 1980s. He quickly realized that when he operated on obese patients with diabetes the patients no longer required insulin[4]. Furthermore, this early change in glucose metabolism seemed to occur even prior to substantial weight loss. When it was first proposed, the notion that diabetes can be cured with gastric bypass seemed rather outlandish. Fifteen years passed by since the first gastric bypass procedure before Dr. Pories published his data showing that among his 146 person diabetic cohort, 121 (83%) had become diabetes-free post-operatively[5].

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Disclosure

No potential conflicts of interest relevant to this article were reported.

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This surgical success raises questions about the mechanisms underlying the reversal of insulin resistance after weight loss surgery. The molecular mechanisms underlying insulin resistance and the metabolic syndrome are extremely complex, especially with respect to the cardiovascular system [6–8]. The effects of bariatric surgery on insulin resistance and other metabolic markers of obesity have provided us with a gateway into this remarkable area of research.

Consequences of Insulin Resistance

Insulin resistance is defined as the diminished ability of muscle and other insulin-responsive tissue to transport glucose from the bloodstream into the cell [9]. In reality, however, insulin resistance is a metabolic disorder of extraordinary complexity that is not yet completely understood. Insulin resistance due to nutrient excess is a well-known phenomenon [10]. For example, insulin resistance and altered free fatty acid (FFA) metabolism are intrinsically related [11]. Elevated levels of plasma free fatty acids and increased hepatic lipogenesis are typically observed in the insulin resistant state [12] [13]. Furthermore, several studies have shown a strong relationship between insulin resistance and increased intramyocellular triglyceride content through muscle biopsy and nuclear magnetic resonance imaging [14, 15]. This concept is exceedingly important with regards to lipotoxicity, which will be discussed later.

It has been known since the 1960s that fatty acids compete with glucose for substrate oxidation; this intracellular war was conventionally thought to involve elevated citrate levels and the accumulation of glucose-6-phosphate and inhibition of hexokinase II activity [11]. The fatty acid inhibition of glycolysis ultimately results in increased intracellular glucose concentrations and decreased glucose uptake [11]. This conventional hypothesis has been challenged as of recent, and it is now thought that the accumulation of fatty acid metabolites may directly interfere with downstream insulin receptor signaling, reducing glucose transport activity via the GLUT-4 receptor [16].

The most important effect of insulin resistance is the disparity in the increased supply of energy providing substrates and their reduced oxidation. In essence, excess fuel supply and decreased oxidation are key features of insulin resistance with profound consequences on cellular metabolism. It has been proposed that the imbalance in partitioning between the adipocyte to the muscle and liver that is most responsible for impaired glucose metabolism and insulin resistance. The consequences of obesity and insulin resistance include high glucose and free fatty acid levels, elevated insulin and leptin concentrations and low adiponectin levels; other metabolic markers include high C-reactive protein (CRP) and tumor necrosis factor (TNF) alpha levels [17].

It took quite some time before experts reached a consensus on the diagnostic criteria of the metabolic syndrome [18] and a brief discussion on the metabolic syndrome is needed in the context of obesity and insulin resistance. The hinge point in its definition is central obesity manifested by enlarged waist circumference; other parameters include elevated triglyceride levels, fasting elevated blood glucose levels and blood pressure levels in addition to a low HDL cholesterol. The utility of the metabolic syndrome as a predictor of cardiovascular disease (CVD) and diabetes is not shared by all. In 2004, the ADA submitted a report suggesting that ‘providers should avoid labeling patients with the term metabolic syndrome’ arguing that ‘adults with any major CVD risk factor should be evaluated for the presence of other CVD risk factors’, and ‘that all CVD risk factors should be individually and aggressively treated’ [19]. At the same time criteria for the metabolic syndrome exist in the metabolically obese, normal weight individual [20].

The reluctance to accept the metabolic syndrome as an exact science is somewhat understandable. For example, not all obese individuals are insulin resistant, but there is a strong correlation between obesity and insulin resistance. In a study of nearly 5000 participants, the National Health and Nutrition Examination Surveys (NHANES), [21] categorized their patient population into weight groups based on body mass index (BMI). Utilizing the diagnostic criteria of the metabolic syndrome, homeostasis model assessment (HOMA) of insulin resistance, and CRP measurements, 32% of obese subjects were found to be “metabolically healthy” and 24% of normal-weight individuals were metabolically abnormal. What do we make of “metabolically healthy” obese individuals who do not exhibit features of the metabolic syndrome apart from a rotund waistline? The answer still is not clear.

Metabolic Changes with Bariatric Surgery

The metabolic changes that accompany bariatric surgery, such reversal of insulin resistance, occur even before substantial weight loss has occurred [22] [23] [24, 25]. This unexpected discovery was somewhat counter-intuitive, but it is well established fact. It is not the actual weight loss that is most responsible for the improvement in one’s metabolic profile following bariatric surgery. In this context the alteration in enteric hormones and their “crosstalk” with the brain has become an area of interest. The type of surgical intervention also plays a role in predicting reversal of metabolic derangements [25, 26]. A long-term study has recently shown that bariatric surgery is probably more efficient than standard care in the prevention of type 2 diabetes in obese individuals [27]

Although all forms of successful bariatric surgery show improvement in comorbidities, malabsorptive procedures, such as Roux-en-Y gastric bypass (RYGB), have shown a more dramatic amelioration of diabetes in comparison with more restrictive procedures (*i.e.* gastric banding)[28]. This complements one of our previous studies which showed that, compared with patients undergoing RYGB, weight loss and normalization of metabolic parameters were less pronounced after 2 years in patients undergoing gastric banding[26].

Our earlier studies also show a dramatic reversal of derangements in muscle metabolism [24]. Prospective enrollment included 43 patients who underwent extensive metabolic and cardiovascular profiling as well as skeletal muscle biopsies performed at time of surgery, 3 and 9 months post operatively. Table 1 shows a reduction in fasting glucose and insulin levels as well as improvements in insulin sensitivity and leptin levels 3 months post operatively. Between 3 and 9 months post-operatively, we also observed a considerable decreases in plasma FFA, triglyceride and leptin concentrations. It is important that improvements in glucose metabolism and insulin resistance were a relatively early perceived phenomenon.

It is well established that non-adipose tissue like heart and skeletal muscle will store extra FFAs as intra-myocellular triglycerides [29], which can fairly easily be assessed histologically with oil-red-O stain. Figure 1 shows oil-red-O stains of skeletal muscle biopsy samples at time of surgery, 3 and 9 months post operatively[24]. We demonstrated a striking reduction in staining at nine months; the decrease in staining between three and nine months correlated significantly with a decrease in weight and fat mass. Furthermore, there was also an association between staining intensity and plasma FFA levels. The decrease in intra-myocellular triglycerides is likely a result of decreased FFA supply, increased rates of triglyceride hydrolysis, and increased rates of FFA oxidation. Such a phenomenon is likely a stepwise, complex process with the aim of reversing the effects of lipotoxicity.

Obesity is also considered a chronic state of inflammation, and the anti-inflammatory changes observed with weight loss play a large contribution to improvement in overall

health [30]. Adiponectin is an anti-inflammatory adipokine secreted from adipose tissue that has gained much attention with respect to those that have lost a lot of weight. Through alterations in glucose and fatty acid metabolism, lower levels of this polypeptide hormone are considered an independent risk factor for development of the metabolic syndrome [31], while higher concentrations are linked to lower risk of developing type 2 diabetes [32]. Adiponectin levels rise following weight loss, and studies have shown that these changes are predictive of improvement in insulin resistance [33]. Following RYGB, several studies have noted inverse relationships between circulating adiponectin and insulin, independent of BMI [34, 35].

Several humoral factors precipitously decline in the wake of gastric bypass surgery. There are a number of speculations on this phenomenon. In part, there is less absorption of food. Furthermore, there is more production of glucagon-like peptide-1 (GLP-1), and delayed gastric emptying [36]. The incretin GLP-1 is a gut peptide hormone secreted by intestinal L cells which mediates the enteroinsular axis. GLP-1 is secreted in response to intestinal nutrients and is inhibited by dipeptidyl peptidase IV (DPP-IV) [37]. Another important feature of this incretin is a decrease in gastric emptying, delaying digestion and blunting postprandial glycemia [38]. Other enteric hormones that affect insulin sensitivity altered by bariatric surgery include gastric inhibitory polypeptide (GIP), ghrelin and peptide YY (PYY).

Following food consumption, GLP-1 and GIP account for up to 60% of insulin release from the beta cell. GLP-1 increases following RYGB, but changes little with restrictive surgery [39]. Furthermore, when comparing diabetic patients who underwent gastric bypass with patients who had equivalent weight loss through diet and exercise alone, incretin levels significantly increased one month post-operatively while there was no change in the diet and exercise control group [40].

Two major hypotheses, both of them not necessarily mutually exclusive, have been proposed to explain the occurrence of enhanced glucose metabolism and improvement in diabetes following gastric bypass surgery. Cummings, et al. [41] describes the “hindgut hypothesis” in which the accelerated delivery of foodstuff to the distal intestine following bariatric surgery is responsible for increased secretion in GLP-1 and other anorexigenic gut hormones. Supporting evidence for this hypothesis exists through studies in which rodents underwent intestinal rearrangement by anastomosis of the ileum or hindgut to the proximal intestine while leaving the stomach intact. Transit time, as well as secretion of GLP-1 and PYY was substantially increased. Rubino, et al. [42] provides us with an alternative explanation, the “foregut exclusion hypothesis.” The authors propose that the bypass of food and nutrients from the upper intestine may prevent some unidentified ‘putative signal’ from exerting its effect on insulin resistance. The putative signal appears to be anti-incretin in nature. Studies supporting this hypothesis arise in rodents who underwent either duodenojejunal bypass (DJB) or gastrojejunostomy [43]. In both scenarios, the same amount of intestine is bypassed; however, DJB preserves nutrient transit through the proximal intestine. When glucose tolerance was calculated, rodents who underwent DJB had less insulin resistance in comparison to the gastrojejunostomy group that showed no improvement. Furthermore, this phenomenon was also appreciated in translational research as overweight diabetic patients underwent a DJB-like procedure [44]. Stomach volume remained intact and weight loss was not observed, but study subjects demonstrated significant improvement glucose intolerance and resolution of diabetes mellitus. Another, more straight-forward explanation would be the normalization of substrate levels in the blood. This hypothesis can be tested with pharmacological agents that lower blood glucose levels by excreting glucose through the kidney. For example, the drug phlorizin, a competitive inhibitor of SGLT1 and SGLT2, reduces renal glucose transport, lowers blood

glucose levels, and, as a consequence of lower blood glucose levels, reverses insulin resistance in muscle [45]. However, the precise mechanism by which bariatric surgery promotes rapid improvements in systemic metabolism and long term weight loss remains incompletely understood[46].

Healing the Heart with Bariatric Surgery

Cardiac mass is increased in obese individuals. The heart has the highest rate of energy turnover per unit of tissue in the body. The high rate of myocardial oxygen consumption merits consideration with regards to fatty acid and glucose metabolism, both of which interact [11]. Alterations in hemodynamic load ultimately result in structural and functional changes in the heart, but these changes are accompanied by metabolic modifications as well, including insulin resistance and lipid overload. The question arises: Why would a failing heart become insulin resistant? We propose that the failing, lipid rich heart exhibits less insulin sensitivity to protect itself from substrate overload of oxidizable fuel [47]. An enhancement in substrate uptake would only contribute to lipotoxicity and continue to overwhelm an exhausted organ.

Following bariatric surgery, Gaborit, et al.[48] describe a decrease in systemic insulin resistance and improvement in diastolic dysfunction, suggesting that the beneficial changes appreciated in the heart may be related to a decrease in the size of the epicardial fat pad. We have made similar observations [49–51] and propose that the improvement in diastolic dysfunction following weight loss surgery is an indirect result of resolving lipotoxicity and, thus, less insulin resistance. The concentric left ventricular hypertrophy in obesity is reversible as shown in a recent observational study reporting that sustained 10-year weight loss results in lower left ventricular size, wall thickness and mass [52].

The lipotoxic effects on the heart include impaired intracellular calcium cycling and, consequently, impaired cross bridge cycling. We observed a significant relationship between FFAs and diastolic dysfunction in our study subjects[49]. Furthermore, our studies demonstrated a remarkable decline in FFA levels in conjunction with improved cardiac function[50]. Not only does cardiac function tend to improve post-operatively, left ventricular mass also decreases as well. Hallmarks of obesity such as BMI tend to plateau following surgical intervention, but left ventricular mass continued to decline in a linear fashion over a two-year period[51]. As long-term weight loss data become available [53], it would be of interest to know at which time point the two curves converge. The Australian laparoscopy adjustable gastric banding (LAGB) study demonstrated a durable weight loss over 15 years [53]. Whether the beneficial effects on cardiac hypertrophy are sustained over the same period remains to be seen.

However, another point still needs to be considered. Gastric bypass surgery is not associated with a durable remission of type 2 diabetes in all severely obese patients. In a retrospective cohort study of 4434 adults with severe obesity and type 2 diabetes, more than one-third redeveloped diabetes following an initial remission within 5 years after surgery[54]. The cardiovascular consequences of this relapse are not known.

Conclusions

We have shown that multiple mechanisms contribute to the remission of diabetes and cardiac function after bariatric surgery. Furthermore, gastric bypass specifically appears to have added benefit with regards to improvements in insulin resistance. Proposed mechanisms for this phenomenon include rapid delivery of nutrients to the distal intestine enhancing incretin secretion and exclusion of the proximal intestine which may inhibit an anti-incretin signal.

Moreover, one may reasonably conclude that improvements in cardiac function following weight-loss surgery are a result of reduced lipotoxicity. By targeting the source of excess energy, we suggest that bariatric surgery improves cardiac function by limiting substrate supply to a metabolically overloaded heart. The complexity of insulin resistance and cardiac function as it relates to bariatric surgery is complex, and there is much more to be gained from this fascinating area of research. We propose that nutrient restriction lowers the cell's defense mechanisms for nutrient overload in insulin responsive tissues.

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Figure 1.

Oil-red-O stain of muscle biopsies. Samples were obtained at baseline, 3 and 9 months after surgery. The slides are representative of sections for each patient at each of the time points (baseline, 3 and 9 months). Baseline vs 3 months 4.2 AU (−2.4–10.9), $p < 0.2$. Three months vs 9 months 8.7 AU (2.4–15.1), $p < 0.009$. See text for further details. AU-Arbitrary Units. (Reprinted from: Dramatic reversal of derangements in muscle metabolism and diastolic left ventricular function after bariatric surgery. Leichman JG, Wilson EB, Scarborough T, Aguilar D, Miller CC, III, Yu S, Algahim MF, Reyes M, Moody FG, Taegtmeier H. *Am J Med* 2008;121:966–973, with permission from Elsevier.) [24••].

Table 1**Physical and Hemodynamic and Metabolic Changes after Surgery**

	Significance (p value)	Baseline to 3 Months Mean Difference* (CI 95%)	Significance (p value †)	3 Months to 9 Months Mean Difference (CI 95%)
<i>Measurements</i>				
<i>Weight Related</i>				
Weight (kg)	21.5 (18.07–25.00)	<0.0001	16.4 (12.80–20.08)	<0.0001
BMI (kg/m ²)	7.7 (6.70–8.89)	<0.0001	5.6 (4.45–6.80)	<0.0001
Waist Circ. (cm)	9.7 (–1.52–20.95)	<0.088	16 (5.6–26.3)	0.004
Fat Mass (kg)	8.3 (6.23–10.48)	<0.0001	6.1 (4.78–7.49)	<0.0001
Lean Mass (kg)	2.2 (1.35–3.07)	<0.0001	1.0 (0.71–1.48)	<0.0001
<i>Hemodynamic</i>				
<i>Measurements</i>				
SBP (mmHg)	1.3 (–6.23–8.91)	0.72	4.4 (–1.30–10.24)	0.13‡
DBP (mmHg)	3.9 (–1.11–8.95)	0.12	1.7 (–3.45–6.79)	0.51
HR (bpm)	10.0 (5.53–14.53)	<0.0001	2.4 (–3.10–7.99)	0.38
<i>Metabolic</i>				
<i>Measurements</i>				
Glucose (mg/dL)	19.1 (5.00–33.23)	0.009	2.0 (–7.21–11.21)	0.66
Insulin (μU/mL)	11.2 (5.62–16.76)	<0.0001	–0.51 (–3.20–3.09)	0.97
HOMA-S (%)	–31.2 (–46.62–15.78)	<0.0001	–45.2 (–77.65–12.71)	<0.0001
FFA (mmol/L)	–0.029 (–0.149–0.090)	0.62	0.20 (0.084–0.315)	0.001
Triglycerides (mg/dL)	43.9 (05.90–93.67)	0.082	18.7 (7.17–30.26)	0.002
Leptin (mg/mL)	27.2 (20.81–33.51)	<0.0001	7.7 (2.74–12.67)	0.003

All values are the mean differences (CI: 95%)

* Mean Difference is a decrease in the outcome value unless indicated by a negative value.

† Significance for a difference at alpha <0.05.

‡ There was a significant decrease in SBP from Baseline to 9 Months.

CI 95% - Confidence Interval for Difference; BMI – Body Mass Index; Waist Circ. – Waist Circumference; SBP – Systolic Blood Pressure; DBP – Diastolic Blood Pressure; HR – Heart Rate; FFA – Plasma Free Fatty Acids.