

Weight Loss as a Cure for Type 2 Diabetes

Fact or Fantasy?

Sangeeta R Kashyap; Emily S Louis; John P Kirwan

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Abstract and Introduction

Abstract

Although individuals with obesity and Type 2 diabetes are insulin resistant, pancreatic β -cell failure is the core defect that distinguishes individuals who eventually develop diabetes. This process is known to occur well before the onset of hyperglycemia. Although clinical trial data support the effectiveness of intensive lifestyle modification in delaying the onset of diabetes in obese subjects, less is known about the effects of, and mechanisms underlying, bariatric surgery, particularly gastric bypass surgery, on diabetes. The paper under evaluation clarifies the role of both lifestyle intervention and gastric bypass surgery on pancreatic β -cell function and raises questions regarding the role of weight loss versus incretin-related mechanisms on recovery of β -cell failure.

Introduction

The current pandemic of Type 2 diabetes and obesity has created an urgent need to identify effective therapeutic interventions targeting both of these chronic debilitating conditions. Obesity and diabetes are closely interrelated (see Figure 1) in that risk factors such as physical inactivity and poor diet lead to weight gain and precipitate insulin resistance in important insulinsensitive tissues, particularly skeletal muscle, liver and adipose tissue. It is known that obese and insulin-resistant diabetic patients have a positive energy balance, high fat and high carbohydrate intake, increased abdominal adipose tissue, elevated free fatty acids, increased secretory products of adipocytes mediating inflammation, including TNF- α and IL-6, and reduced secretion of adiponectin.^[1,2] These factors have been shown to be part of the underlying mechanisms of glucose intolerance and contribute to reduced skeletal muscle glucose disposal and increased hepatic glucose output.^[1] Although insulin resistance is common in obese patients, diabetes is not always present because the pancreas augments insulin production as a means to offset the severity of impaired insulin action. The transition from a mild state of insulin resistance to Type 2 diabetes is heralded by progressive pancreatic β -cell dysfunction and eventual failure to secrete adequate amounts of insulin; all of this occurs well before the inception of diabetes. In obese individuals with a familial tendency for Type 2 diabetes, impaired insulin secretion is documented early on in the spectrum of glucose tolerance. In certain high-risk populations, up to 80% of pancreatic β -cell failure is observed to occur during the fasting state and manifests in a condition now known as impaired fasting glucose.^[1] According to DeFronzo, as fasting hyperglycemia develops, insulin secretion decreases progressively and in patients with fasting glucose levels of 180–200 mg/dl, there is an absolute deficiency of insulin.^[3] Some major nonheritable factors implicated in β -cell failure, particularly in obesity, include elevated free fatty acids and inflammatory cytokines, termed as 'lipotoxicity',^[2] and incretin deficiency and/or resistance.^[4]

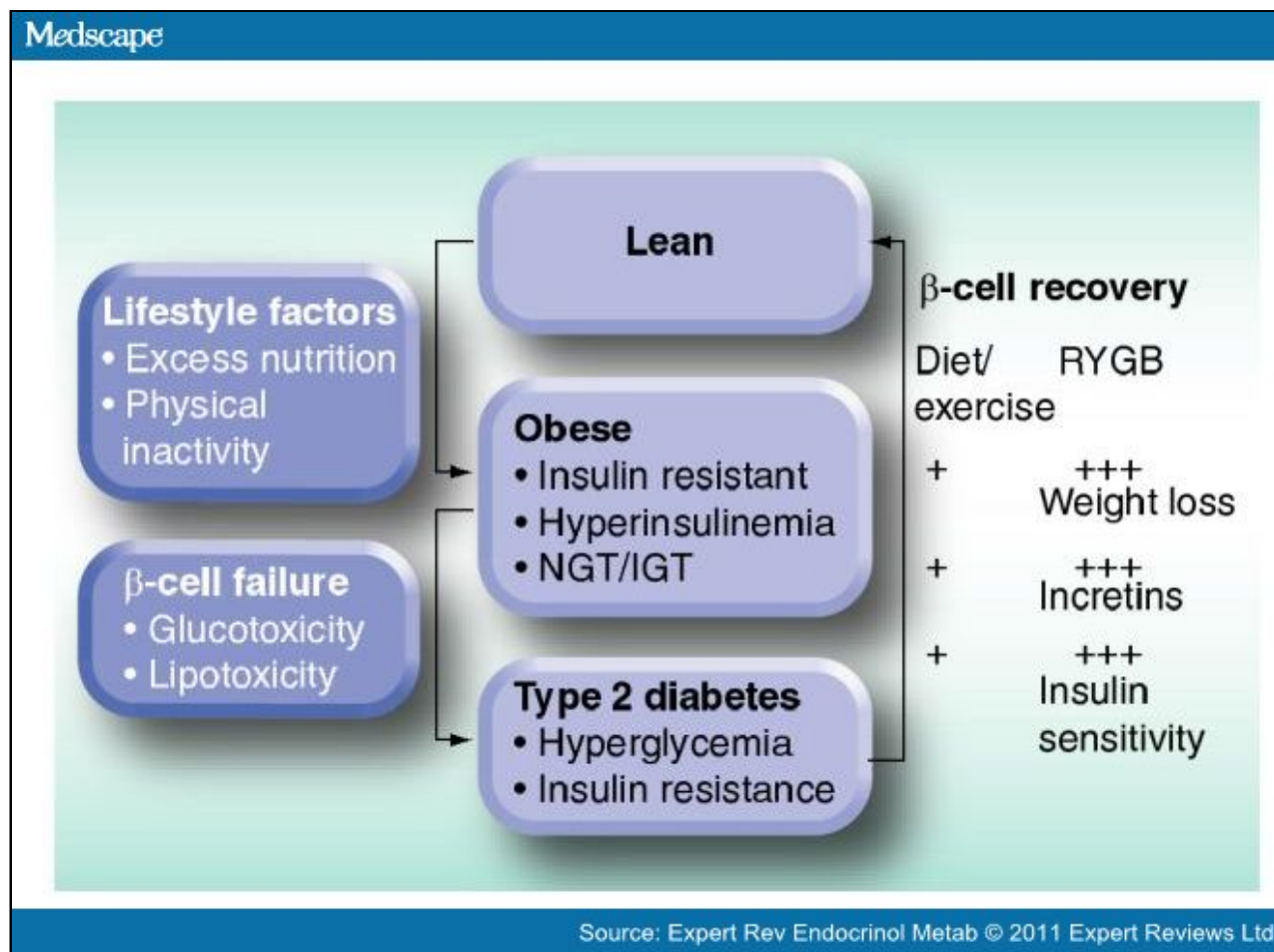


Figure 1. Pathophysiology of Type 2 diabetes in the setting of obesity. Chronic caloric surplus and physical inactivity lead to obesity and insulin resistance. β -cell failure is required in this setting to drive the transition from obesity/insulin resistance to Type 2 diabetes. Both Roux-en-Y gastric bypass surgery and diet/exercise contribute to β -cell recovery through weight loss, restoration of incretin function and improvement of insulin sensitivity. Evidently, the magnitude of these effects (represented by the '+' symbol) is far greater following bariatric surgery than diet/exercise interventions.

IGT: Impaired glucose tolerance; NGT: Normal glucose tolerance; RYGB: Roux-en-Y gastric bypass.

Modest weight loss of 5–10% bodyweight is known to improve diabetes by reducing insulin resistance in obese individuals.^[5] In clinical trials, caloric restriction, exercise and weight loss have been shown to prevent and reduce diabetes in obese individuals,^[5,6] in part by attenuating insulin resistance and subsequent hyperinsulinemia, thereby preserving β -cell function.^[7,8] It has also been shown that weight loss surgery, particularly gastric bypass surgery, has a profound effect on metabolism and can induce remission of Type 2 diabetes defined by normal glycemic control without the need for diabetic medications.^[9] The fundamental questions brought forth regarding these latter observations include: Can weight loss effectively reverse pancreatic β -cell dysfunction? If so, which specific therapeutic weight-loss modality (i.e., lifestyle, pharmacotherapy or surgery) produces the most effective and sustained reversal of pancreatic β -cell dysfunction in individuals with diabetes or a predisposition towards diabetes?

Summary of Methods & Results

Hofso *et al.* compared the effects of either lifestyle intervention or gastric bypass surgery on pancreatic β -cell function in subjects with morbid obesity (mean BMI 45.5 kg/m²) without known diabetes.^[10] At the time of baseline testing, some subjects were found to have either impaired fasting glucose, impaired glucose tolerance or diabetes. Subjects self-selected (thus not randomized) their treatment options: either Roux-en-Y gastric bypass (RYGB) surgery or lifestyle change. The lifestyle group engaged in a program of organized physical activity and psychosocial intervention, with inpatient stays totaling 7 weeks. A standard glucose tolerance test was performed before and at 1

year of follow-up. Insulin sensitivity was assessed by the homeostatic model assessment and insulin secretion was measured by the insulinogenic index and the Stumvoll first-phase index during a standard oral glucose tolerance test. β -cell function was determined from the disposition index and the proinsulin/insulin ratio. Mean weight loss following gastric bypass was 30%, while it was 9% in the lifestyle group. Glucose intolerance was resolved in all patients who underwent RYGB and in 41% of those who followed the lifestyle intervention. However, it is noteworthy that post-challenge hypoglycemia was significantly more prevalent after RYGB. Insulin sensitivity was significantly improved after both interventions, but the magnitude of improvement was greater after surgery. Overall insulin secretion was reduced after both interventions, but there was an increase in the early-phase insulin secretion after surgery. Looking at the study population as a whole, percentage weight change was correlated with the change in the disposition index. The change in the disposition index was also correlated with the change in proinsulin/insulin ratio. The authors conclude that these physiological changes may contribute to restored glycemic control following bariatric surgery, but may also in part be responsible for the higher incidence of postprandial hypoglycemia in the surgery group.

Discussion of Significance of Results

The authors are to be commended for conducting this relatively large clinical trial examining both intensive lifestyle and surgical approaches in morbidly obese subjects, since these strategies represent two important treatment modalities for weight loss and share common physiological outcomes of improved insulin sensitivity and insulin secretion. As acknowledged by the authors, the main strengths of their study include the controlled design and the intensity of the lifestyle approach. Previous studies of bariatric surgery for diabetes have been primarily observational, with a lack of appropriate control groups that encompass nonsurgical/medical weight loss. However, a major weakness when comparing two groups that are not randomized is that differences in baseline characteristics may account for different outcomes. For example, the surgical group was substantially younger and heavier than the lifestyle group. However, despite the difference in baseline characteristics, the prevalence of glucose intolerance and baseline levels of insulin sensitivity and secretion were similar between the two groups. A second weakness pertains to the failure to examine the incretin hormone hypothesis, which is considered an important mechanism underlying improvement in β -cell function, particularly after obesity surgery. Other weaknesses include the use of oral glucose tolerance test-derived indices for insulin sensitivity and β -cell function, since these have not been validated for bariatric surgery, the lack of stratification and separate analysis of normal glucose-tolerant, impaired glucose-tolerant and Type 2 diabetic patients and the inclusion of primarily Caucasian subjects. As expected, surgery resulted in a threefold greater weight loss and a 1.5-fold greater improvement in insulin sensitivity as compared with the lifestyle intervention. Other studies have observed similar improvements in insulin sensitivity, particularly in skeletal muscle, after gastric bypass surgery.^[11–13] The data reported by Hofso and colleagues is consistent with these studies and is supportive of previously published work from our group in which we examined the effects of gastric bypass and gastric restrictive surgery in patients with Type 2 diabetes.^[14] In that study, we noted a markedly greater increase in insulin sensitivity (determined during hyperglycemic clamp studies) with gastric bypass versus other gastric restrictive procedures at 1 month after surgery when both groups had lost an equivalent amount of bodyweight (~10%). Whether these effects are related to reduced intra- or extra-myocellular lipid, lipid mobilization or changes in lipid species such as ceramides, all of which have previously been linked with impaired insulin action in obesity, is currently not clear. More studies like those by Hofso are needed in order to identify the specific mechanistic defects that are being targeted by surgery and/or lifestyle-induced weight loss.

Expert Commentary

The twofold or greater increase in the disposition index in normal glucose-tolerant and abnormal glucose-tolerant individuals noted by Hofso *et al.* following gastric bypass surgery is of tremendous scientific interest and helps to explain the restoration of glucose homeostasis in diabetes.^[10] The timing of improved glycemic control following bariatric surgery is important. In most cases, a dramatic decrease in fasting glucose levels is seen within days to weeks following surgery, before major weight loss, but in the setting of enforced caloric restriction.^[9,15] Persistent cases of diabetes after this initial period gradually improve in parallel with weight loss.^[16] Patients who undergo malabsorptive procedures improve sooner and maintain glucose control for longer periods than do patients treated by purely restrictive procedures. However, compared with patients following a very low calorie diet who achieve

similar weight loss, patients who undergo RYGB experience increased glucose-induced secretion of insulin, c-peptide, glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) consistent with an incretin effect.^[15] When we studied glucose regulation in morbidly obese patients with Type 2 diabetes following similar amounts of weight loss related to enforced caloric restriction at 1 and 4 weeks following gastric restrictive (sleeve gastrectomy and gastric banding) versus RYGB procedures, we also noted a greater improvement in fasting and postprandial glucose levels following RYGB.^[14] We attributed this to enhanced insulin secretion and β -cell responsiveness. Importantly, we observed this effect in response to a mixed meal, but the effect was not evident during intravenous glucose administration, highlighting a potent and important incretin effect. A greater improvement in insulin sensitivity during glucose infusion was also noted acutely after RYGB but not after gastric restrictive procedures. The incretin effect is characterized by robust increases in GLP-1 and either no change or increases in GIP levels.^[14,17,18] In subjects with profound hypoglycemia and neuroglycopenia following RYGB, Goldfine *et al.* observed markedly higher postprandial insulin and GLP-1 levels as compared with those without hypoglycemia following RYGB.^[19] Collectively, these data provide insights into the metabolic effects of RYGB to increase insulin sensitivity and preserve β -cell function, and to enhance insulin secretion through an incretin-mediated mechanism. Whether these effects, particularly hypoglycemia following RYGB, are specific to increased GLP-1 or GIP levels is currently under investigation.

Modest improvements in β -cell function following lifestyle intervention as documented by Hofso *et al.*^[10] are consistent with a number of other studies,^[20–23] as well as our own.^[24–27] Exercise training has been shown to improve insulin sensitivity independent of weight loss.^[23] These effects are primarily due to improved insulin action in skeletal muscle, leading to increased glucose and lipid oxidation, as well as effects independent of insulin. Dela *et al.*^[21] and others^[20,22,23] have provided strong evidence of exercise training-induced increases in β -cell function in response to intravenous glucose in Type 2 diabetic and obese subjects. In addition, some studies have found elevated insulin responses to an oral glucose load after caloric restriction and exercise-induced weight loss and, more recently, we demonstrated a possible incretin effect related to GIP that may contribute to increased insulin secretion following a hypocaloric diet and exercise training intervention.^[27] Following a moderate-to-high-intensity 12-week aerobic exercise program, older obese normal glucose tolerant subjects demonstrated marked improvements in insulin sensitivity and a reduction in fasting and postprandial hyperinsulinemia, which was associated with a decrease in GIP secretion. By contrast, Type 2 diabetic individuals showed increases in both insulin secretion and the disposition index. These changes directly corresponded to increased GIP secretion. It is noteworthy that these subjects only had a modest weight loss of approximately 5%, similar to levels observed in the study by Hofso.

Alterations in dietary composition also have profound effects on β -cell function. We studied older obese prediabetic individuals participating in a moderate-to-high-intensity 12-week aerobic exercise program in combination with isocaloric diets consisting of either high- or low-glycemic index carbohydrates.^[26] Both groups lost approximately 9% bodyweight and had equal improvements in insulin sensitivity and basal insulin secretion rates (ISR), but only the low-glycemic diet group reduced glucose-stimulated ISR, which was associated with a decrease in glucose-stimulated GIP secretion. After correction for improved insulin sensitivity, oral glucose-induced ISR was not different from preintervention in the low-glycemic diet group, while it was increased in the high-glycemic diet group, indicating further β -cell dysfunction. Thus, diet alone may have profound effects on β -cell function and incretin secretion. Considering the findings of these studies, it is evident that incretin hormones play a pivotal role in lifestyle-induced changes in glucose metabolism and that these changes differ based upon where an individual is on the β -cell dysfunction spectrum. Besides the effect on insulin secretion, incretin hormones induce satiety. This may account for weight loss or maintenance of weight loss following lifestyle interventions in individuals with Type 2 diabetes and may further decrease lipotoxicity, leading to improvements in insulin sensitivity. Alternatively, in nondiabetic or prediabetic populations, lifestyle-induced reductions in incretin hormones may decrease β -cell secretion independent of weight loss.

In summary, weight loss alone improves the pathophysiology of Type 2 diabetes and may reverse it in certain clinical situations. As shown in Figure 1, exercise and gastric bypass surgery have weight-independent effects on insulin sensitivity and incretin stimulation, which collectively work to reverse β -cell dysfunction and restore normal glucose regulation.

Five-year View

Future research in this area will require randomized controlled trials examining the effects of intensive lifestyle modification versus various bariatric procedures on clinical outcomes in patients with Type 2 diabetes in the setting of morbid and modest obesity. Feasibility and pilot studies are already underway at several centers. Given the potential role of the intestine in treating Type 2 diabetes, future studies will target manipulations (surgical and/or biochemical via pharmacotherapy and lifestyle modifications) of intestinal biology to reverse pancreatic β -cell dysfunction, insulin resistance and cardiovascular risk associated with diabetes. Investigations into less invasive and safer methods for weight loss that achieve similar efficacy and durability following bariatric surgery are underway. Finally, consideration must be given to developing new drugs that mimic the effects of bariatric surgery and produce durable weight loss and remission of Type 2 diabetes.

Sidebar

Key Issues

- Obesity is an insulin-resistant state that increases the risk for Type 2 diabetes. Pancreatic β -cell failure is the core defect that leads to the manifestation of diabetes and occurs well before the onset of hyperglycemia.
- Weight loss through lifestyle modification and bariatric surgery is known to improve insulin resistance and glycemic control related to diabetes.
- Exercise training independent of weight loss improves glucose intolerance and insulin sensitivity. Weight loss achieved through caloric restriction may favorably influence incretin biology to enhance β -cell function, particularly in diabetic individuals.
- Intake of a low glycemic index diet may improve β -cell function, whereas consumption of a high glycemic diet may further exacerbate β -cell dysfunction in prediabetic individuals.
- Key features of gastric bypass surgery that lead to restoration of glycemic control in diabetes include marked weight loss, improved insulin sensitivity and incretin-related effects that enhance pancreatic β -cell function.

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Papers of special note have been highlighted as:

- of interest
- of considerable interest

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