Can Roux-en-Y gastric bypass provide a lifelong solution for diabetes mellitus?

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Background: The surgical treatment of diabetes had witnessed progressive development and success since the first case of pancreatic transplantation. Although this was a great step, wide clinical application was limited by several factors. Bariatric surgery such as gastric bypass is emerging as a promising option in obese patients with type 2 diabetes. The aim of this article is to explore the current application of gastric bypass in patients with type 2 diabetes and the theoretical bases of gastric bypass as a treatment option for type 1 diabetes.

Methods: We performed a MEDLINE search for articles published from August 1955 to December 2008 using the words "surgical treatment of diabetes," "etiology of diabetes" and "gastric bypass."

Results: We identified 3215 studies and selected 72 relevant papers for review. Surgical treatment of diabetes is evolving from complex pancreatic and islets transplantation surgery for type 1 diabetes with critical postoperative outcome and follow-up to a metabolic surgery, including gastric bypass. Gastric bypass (no immune suppression or graft rejection) has proven to be highly effective treatment for obese patients and nonobese animals with type 2 diabetes. There are certain shared criteria between types 1 and 2 diabetes, making a selected spectrum of the disease a potential target for metabolic surgery to improve or cure diabetes.

Conclusion: Roux-en-Y gastric bypass is a promising option for lifelong treatment of type 2 diabetes. It has the potential to improve or cure a selected spectrum of type 1 diabetes when performed early in the disease. Further animal model studies or randomized controlled trials are needed to support our conclusion.

Contexte : Le traitement chirurgical du diabète a évolué et s'est amélioré progressivement depuis la première transplantation du pancréas. Même si ce fut un grand pas en avant, plusieurs facteurs ont limité l'application clinique généralisée des interventions. La chirurgie bariatrique telle que le pontage gastrique devient une option prometteuse chez les patients obèses atteints de diabète de type 2. Cet article vise à analyser l'application courante du pontage gastrique chez les patients atteints de diabète de type 2 et les bases théoriques du pontage gastrique comme traitement possible du diabète de type 1.

Méthodes : Nous avons cherché dans MEDLINE des articles publiés entre août 1955 et décembre 2008 où l'on a utilisé les expressions « surgical treatment of diabetes », « etiology of diabetes » et « gastric bypass ».

Résultats : Nous avons repéré 3215 études et choisi 72 communications pertinentes à étudier. Le traitement chirurgical du diabète évolue de la chirurgie complexe de transplantation du pancréas et d'îlots dans les cas de diabète de type 1, interventions qui produisent des résultats et un suivi postopératoires critiques, jusqu'à la chirurgie métabolique, y compris le pontage gastrique. Le pontage gastrique (qui n'entraîne pas de suppression immunitaire ou de rejet du greffon) s'est révélé très efficace chez les patients obèses et des animaux non obèses atteints de diabète de type 2. Il existe certains critères communs entre le diabète des types 1 et 2, ce qui fait d'un éventail choisi de la maladie une cible possible de l'intervention chirurgicale métabolique afin d'atténuer ou de guérir le diabète.

Conclusion : Le pontage gastrique Roux-en-Y se révèle prometteur pour le traitement permanent du diabète de type 2. Il pourrait améliorer ou guérir un éventail choisi de cas de diabète de type 1 si on l'utilise au début de l'évolution de la maladie. D'autres études sur des animaux ou d'autres essais contrôlés randomisés s'imposent pour appuyer notre conclusion.

Diabetes mellitus is the most common endocrine disorder, currently affecting more than 170 million people worldwide and prospectively more than 365 million people in the year 2030.[1] Surgical treatment of diabetes in the form of pancreatic transplantation has emerged as the single most effective means of achieving normal glucose homeostasis in this patient population.[2] Since the first successful pancreas transplantation performed in 1966, there has been considerable progress in the field,[3] the most notable being combined pancreas–kidney transplantation, which was first reported in 1967.[4]

The shortage of organs available for transplantation, rejection and adverse effects associated with immune suppression have been shown to limit wide clinical application of transplantation to treat patients with diabetes. Thus, patients with type 1 diabetes have no choice but to continue insulin therapy. Although the recent advances in pancreatic islets transplantation and the success of the Edmonton group (a small series of 7 patients) are encouraging for diabetic patients, the complexity of the technique and the problems associated with transplantation could limit its clinical benefit.[5,6] Similarly, type 2 diabetes has been successfully controlled with gastric bypass surgery in morbidly obese patients; this is considered to be the breakthrough surgical treatment for type 2 diabetes.

Several classes of antidiabetic agents, including insulin and insulin analogs (e.g., glucagon-like peptide-1 [GLP-1] receptor agonists such as exenatide) are currently in use either as monotherapies or in combination to improve glycemic control in patients with diabetes.[7] However, failure of these medications to address all the pathophysiological defects of diabetes has been frequently reported during the course of the disease.

Friedman and colleagues[8] reported in 1955 the first evidence that gastric surgery (subtotal gastrectomy) improved the conditions of diabetic patients. This finding received little attention until almost 30 years later. One study published in 1982 suggested that massive weight loss in patients after gastric bypass was accompanied by an improvement in insulin receptor number, basal hyperinsulinemia and glucose tolerance.[9] In 1984, Hughes and colleagues[10] concluded after studying 6 morbidly obese patients that gastric bypass improved glycemic control. Furthermore, a report published in 1992 suggested that type 2 diabetes could be controlled in severely obese patients by gastric bypass.[11] Many subsequent gastric bypass studies suggested high glucose controlling success rates ranging from 76.5% to 97.0%.[12] Although randomized controlled trials are needed to verify the effectiveness of surgery on nonobese patients with diabetes, gastric bypass surgery has the potential to change the current concepts of the pathophysiology of type 2 diabetes and, possibly, the management of this disease.[13] However, as there is very little evidence to support the effectiveness of gastric bypass surgery to treat nonobese patients with type 2 diabetes, further studies are needed.

Based on the prevalence of diabetes and the fact that surgery could be a promising treatment option, we sought to explore the theoretical and clinical applicability of gastric bypass surgery in glycemic control for diabetic patients.

Methods

Literature search and study selection

We performed a MEDLINE database search for relevant articles published from August 1955 to December 2008 for our review. We used the following keywords: "surgical treatment of diabetes," "etiology of diabetes" and "gastric bypass." We chose to review studies published after 1955 to highlight the development of surgical treatment of diabetes.

We selected original studies that reported outcomes of gastric bypass and extracted information on the surgical treatment and etiology of diabetes from relevant articles. We excluded studies that focused on other bariatric procedures such as biliopancreatic diversion, gastric banding, sleeve gastrectomy and gastroplasty as well as studies that focused on other aspects of bariatric surgery and metabolic syndrome.

Results

Our search yielded 3215 studies, and we selected 72 relevant papers for review. Surgical treatment of diabetes is evolving from complex transplantation surgery with critical postoperative outcome and follow-up to a gastric bypass.

Gastric bypass surgery is reported to be an effective treatment for obese patients and nonobese animals with type 2 diabetes. Certain substances, including incretins, are secreted from the digestive tract and contribute to glycemic control following bariatric surgery, especially gastric bypass and biliopancreatic diversion. The degree of severity of type 1 diabetes is different from patient to patient depending mainly on the extent of β-cell damage, and patients' insulin requirements vary. Types 1 and 2 diabetes represent a spectrum of a single disease sharing common etiological, metabolic and pathophysiological criteria that can be potentially influenced by gastric bypass.

Discussion

The etiology of diabetes

Type 1 diabetes accounts for only about 5%–10% of all cases of diabetes; however, its incidence continues to increase worldwide, and it has serious short- and long-term implications.[14] Thirty years ago, a convergence of investigational observations lead to the now widely accepted notion that type 1 diabetes results from an autoimmune destruction of insulin-producing β-cells in individuals who

are genetically predisposed to the disease.[15] The rate of destruction is quite variable.[16] This destruction and yet undefined environmental factors act together to precipitate the disease.[17] The selective destruction of insulin-producing pancreatic β-cells during islet inflammation involves inflammatory cytokines and free radicals and causes a series of pathological damage with subsequent β-cell death.[18]

The direct involvement of the human leukocyte antigen class II DR-DQ genes in patients with type 1 diabetes is well established, and these genes display a complex hierarchy of risk effects at the genotype and haplotype levels.[19] Natural killer T-cells have been implicated in regulating the progression of type 1 diabetes in human patients and in an animal model.[20]

The idiopathic form of type 1 diabetes represents a permanent insulinopenia and patients are prone to ketoacidosis without evidence of autoimmunity.[21] Because of the difficulty of understanding the etiology of type 1 diabetes, a recent study indicates that it is currently misclassified and provides evidence that insulin resistance drives types 1 and 2 diabetes in the same way.[22] Whereas β-cell damage, whether it is due to autoimmunity or is idiopathic, is the principle cause of type 1 diabetes, there is similar but progressive deterioration in β-cell functions and mass in patients with type 2 diabetes. One study reported islet function to be 50% of normal at the time of diagnosis of type 2 diabetes, and a reduction in β-cell mass of about 60% was reported at necropsy.[23]

In patients with type 2 diabetes, there is a diminished and delayed insulin response to carbohydrates owing to defective incretins (substances released by the digestive tract in response to food ingestion). The mechanisms of the impaired incretin effect were found to be due to the reduced secretion of GLP-1 and a severely impaired effect of glucose-dependent insulinotropic peptide (GIP).[24] As a result, glucagon is not suppressed and may be inappropriately elevated. Hepatic glucose production is not attenuated and contributes substantially to postprandial hyperglycemia.[25]

Enlarged visceral adipocytes flood the portal circulation with free fatty acids at metabolically inappropriate times — when free fatty acids should be oxidized — thus exposing nonadipose tissues to fat excess. This leads to ectopic triglyceride accumulation in muscles, liver and pancreatic β-cells, resulting in insulin resistance and β-cell dysfunction.[26] Although the precipitating factors are different, there are certain similarities in the underlying molecular and biochemical failure between types 1 and 2 diabetes.

Shared criteria between types 1 and 2 diabetes that could be influenced by Roux-en-Y gastric bypass

Several shared criteria between types 1 and 2 diabetes could be influenced by Roux-en-Y gastric bypass (Box 1).

It has been confirmed that the defect of glucose utilization in patients with type 1 diabetes could not be reversed by acutely increasing insulin.[27] Moreover, glucose resistance, which is the ability of glucose itself to promote glucose utilization, is impaired in both type 1 and 2 diabetes.[28] A small group of patients with type 1 diabetes is characterized by a severe instability of glycemic values with frequent and unpredictable hypoglycemic and/or ketoacidosis episodes, which cannot be explained by errors of patients or diabetologists.[29] Varying degrees of insulin resistance are often observed in children and adolescents with type 1 diabetes.[30] In addition, for certain diabetic patients increasing the dose of insulin does not control blood glucose, indicating insulin resistance. These brittle diabetic cases indicate multifactorial and complex mechanisms controlling and regulating the blood glucose and not only the insulin.

In obese patients with type 2 diabetes glycemic control is achievable before weight loss, and this is related to humoral factors of forgut exclusion following the Roux-en-Y gastric bypass. Early after the procedure, factors such as greater GLP-1 and GIP release could be a potential mediator of improved insulin secretion.[31] The proven efficacy of Roux-en-Y gastric bypass in a nonobese animal model and more recently on non–morbidly obese humans with type 2 diabetes indicates the effectiveness of the procedure, regardless of body mass index.

As mentioned, types 1 and 2 diabetes are characterized by a reduction of β-cell mass. Researchers have suggested the need to measure β-cell mass and T-cell autoreactivity as an important tool for future studies. If a model is created to balance effectors of β-cell destruction against regulators (suppressors) of β-cell destruction, the balance can be tipped toward prevention or control of type 1 diabetes by removing effectors or adding regulators.[32] This is exactly what Roux-en-Y gastric bypass achieves.

Evidence suggests distinctive metabolic changes precede the development of type 1 diabetes.[33] Although the metabolic changes leading to type 1 diabetes have not been fully identified yet, the current evidence suggests they are similar to those that lead to type 2 diabetes. Further studies may demonstrate a metabolic link to the etiology of both types of diabetes.

Patients with early-onset (younger than 30 years) type 2 diabetes have more acute β-cell failure and coped less well than older diabetic patients.[34] This criteria can be seen in patients with type 1 diabetes. It is not yet known why early-onset type 1 diabetes has more acute β-cell damage; further research is needed to determine the cause.

Box 1. Shared criteria between types 1 and 2 diabetes mellitus

- Glucose use in insulin resistance
- Affects obese and nonobese patients
- β-cell mass is affected
- Distinctive metabolic changes that precede the development of diabetes
- Acute β-cell failure is a feature of type 1 and early type 2 diabetes
- Increasing evidence suggests that diabetes is a single disease

Wilkin[22] has suggested the possibility that types 1 and 2 diabetes, rather than being different, are merely poles of a single spectrum in which variation in the tempo of β-cell loss determines age at onset, and symptoms at presentation have important implications. The author presents evidence that latent autoimmune adult diabetes represents one end of a specturm that encompasses type 1 diabetes. The clinical nature and management of autoimmune diabetes raises important therapeutic questions regarding conventional therapy for hyperglycemia and therapy aiming to protect residual β-cell function.[35]

There are atypical forms of young adult–onset ketosis-prone diabetes that are initially diagnosed as type 1 diabetes. They differ from type 1 diabetes in the absence of β-cell autoimmunity, persistent β-cell function capacity, fluctuating insulin requirements and ketosis-prone episodes; they also have different clinical features than type 2 diabetes.[36] On the other hand, some patients who present with a clinical picture consistent with type 2 diabetes have autoantibodies similar to those found in type 1 diabetes, and type 2 diabetes may be diagnosed if antibody determinations are not made.[37]

A classic patient with type 2 diabetes is a patient who has hyperglycemia, β-cell reserve, insulin resistance and abnormal levels of other active substances such as incretins, peptide tyrosine tyrosine (PYY), leptin and adiponectin. Obese patients with an early diagnosis of type 1 diabetes share some of these characteristics.

Biochemical changes after Roux-en-Y gastric bypass

Multiple stimuli, including neural signals and gut hormones, in addition to glucose cause β-cells to secrete insulin. The role of gut hormones is particularly important because they may affect many aspects related to glycemic control, including glucose-dependent insulin secretion, glucagon inhibition, gastric emptying and satiety.[38]

A number of studies, including that of Goldfine and colleagues,[39] have highlighted the role of the so-called incretin hormones, GLP-1 and GIP, in β-cell function and development (Box 2). Other substances such as adiponectin are also important glycemic regulators.[40] Up to two-thirds of the insulin normally secreted in connection with meal intake is thought to be owing to the insulinotropic actions of these hormones.[41] Under physiologic circumstances, incretin-mediated stimulation of insulin secretion results from an enhancement of all dynamic aspects of β-cell function, particularly β-cell glucose sensitivity, stimulation of insulin secretion and preservation and expansion of β-cell mass.[42,43]

Glucagon-like peptide-1 and GIP potentiate glucose-induced insulin release when present at the time of nutrient stimulation. It also increased the secretory response to a subsequent stimulation by glucose and GLP-1.[44] Glucose-dependent insulinotropic peptide and GLP-1, which are both secreted from the enteroendocrine cells in the gastrointestinal tract within minutes of nutrient ingestion, share common actions on islet β-cells acting through structurally distinct yet related receptors. Incretin-receptor activation leads to glucose-dependent insulin secretion, induction of β-cell proliferation and enhanced resistance to apoptosis.[45]

The hyperinsulinism of morbid obesity and its improvement after gastric bypass may be caused by markedly elevated levels of GIP before surgery and its reduced release after bypass. Reduced release of GIP after Roux-en-Y gastric bypass may partly occur because of exclusion of ingested glucose from contact with the mucosa of the duodenum and proximal jejunum, sites with the highest concentration of GIP.[46] Interestingly, the resolution or improvement of type 2 diabetes occurs within 6 days after surgery, before any appreciable weight loss has occurred.[47] Therefore, the weight loss is not the reason why Roux-en-Y gastric bypass controls diabetes.

Certain theories have been proposed in the literature to explain why the procedure can control diabetes. Authors have concluded that bypassing the foregut and reducing food intake produce the profound long-term alterations in glucose metabolism and insulin action.[48] Wickremesekera and colleagues[49] suggested a humoral mechanism emanating from the gastrointestinal tract as an explanation. Gumbs and colleagues[50] proposed that the improvement in glucose control and insulin resistance resulted from decreased stimulation of the enteroinsular axis owing to decreased caloric intake in the short-term and decreased fat mass and the resulting changes in adipocytokinesin release in the long-term.

There is strong evidence to suggest that GLP-1 plays a key role in the resolution of type 2 diabetes after bariatric surgery, which expedites nutrient delivery to the hindgut by bypassing the duodenum and proximal small bowel. Subsequently, GLP-1 and GIP defects have a great influence on glucose homeostasis. This finding supports the

Box 2. GLP-1 and GIP are the 2 major incretin hormones involved in β-cell function and development

Glucagon-like peptide-1 (GLP-1)

- Produced by L-cells mainly located in the distal gut (ileum and colon) but secreted also from the proximal gut
- Stimulates glucose-dependent insulin release
- Suppresses hepatic glucose output by inhibiting glucagon secretion in a glucose-dependent manner
- Inhibits gastric emptying; reduces food intake and body weight
- Enhances β-cell proliferation and survival in animal models and isolated human islets

Glucose-dependent insulinotropic peptide (GIP)

- Produced by K-cells in the proximal gut
- Stimulates glucose-dependent insulin release
- Minimal effects on gastric emptying; no significant effects on satiety or body weight
- Potentially enhances β-cell proliferation and survival in islet cell lines
- Stimulates glucagon secretion

hypothesis that the incretin defect plays an important role in insulin deficiency and that administration of excess GLP-1 to patients may completely restore glucose-induced insulin secretion and the sensitivity of β-cells to glucose.[51] This incretin action results not only in the control of blood glucose following Roux-en-Y gastric bypass, but also in the normalization of liver enzymes, uric acid, lipids, blood pressure and metabolic syndrome.[12]

Evidence of efficacy of Roux-en-Y gastric bypass in glycemic control

Bariatric surgeries, including Roux-en-Y gastric bypass, are the most effective methods of curing type 2 diabetes and the other major components of the metabolic syndrome.[52] Roux-en-Y gastric bypass is frequently reported to achieve glycemic control and even cure type 2 diabetes in obese patients by reducing insulin resistance.[53–57] Case reports have also documented remission of type 2 diabetes in non–morbidly obese individuals undergoing biliopancreatic diversion (BPD) for other indications.[13] As such, a proximal intestinal bypass could be considered for the treatment of diabetes, and potentially undiscovered factors from the proximal bowel may contribute to the pathophysiology of type 2 diabetes.[58] In addition, the crucial role of the hindgut in the resolution of diabetes following Roux-en-Y gastric bypass and BPD have been confirmed in an animal model.[59]

The mechanisms underlying the dramatic effects of Roux-en-Y gastric bypass on insulin sensitivity and β-cell function are poorly understood. Major weight loss following primarily restrictive surgery does not lead to such changes, so "some specific consequence of surgery must be involved."[60] Alexandrides and colleagues[61] reported resolution of type 2 diabetes in 89% and 99% of the patients following Roux-en-Y gastric bypass and BPD, respectively; 2 years after surgery, all patients had blood glucose levels less than 6.1 mmol/L. Similar outcomes have been reported elsewhere.[62]

Pacheco and colleagues[63] concluded that gastrojejunal bypass in nonobese diabetic animals improves glycemic control with a substantial decrease in leptin levels. On the other hand, Patriti and colleagues[64] reported that ileal transposition was effective in inducing an improvement in glucose tolerance in lean diabetic rats without affecting weight and food intake. They suggested this improvement might have been caused by the terminal ileum through an insulin-independent action.

Meier and colleagues[65] suggested that hypoglycemia following Roux-en-Y gastric bypass is not due to increases in β-cell mass or formation. Rather, they suggest that postprandial hypoglycemia is related to a combination of gastric dumping and inappropriately increased insulin secretion, which can be either an acquired phenomenon or a failure to adaptively decrease insulin secretion following Roux-en-Y gastric bypass. Furthermore, it has been reported that a robust insulin secretory response causing postprandial hypoglycemia in patients who had Roux-en-Y gastric bypass surgeries and experienced neuroglycopenia; the authors suggested increased incretin levels as the cause.[39] Moreover, other authors have suggested that gastric bypass–induced weight loss may unmask an underlying β-cell defect or contribute to pathological islet hyperplasia, perhaps via GLP 1–mediated pathways.[66]

The secretion of GLP-1 influences glucose metabolism by inhibiting glucagon secretion, stimulating insulin secretion, delaying gastric emptying and stimulating glycogenogenesis.[67] It also improves insulin sensitivity and maintains β-cell mass and activity. Immunohistochemistry revealed remodeled islets strictly resembling those in euglycemic rats and signs of β-cell neogenesis starting with exocrine structures.[59] Therefore, the action of the hormonal factors associated with foregut exclusion following Roux-en-Y gastric bypass influenced the glucose-regulating mechanism in patients with type 2 diabetes, regardless of obesity. Thus, the question is whether these factors have any effect on type 1 diabetes.

Czupryniak and colleagues[68] reported 2 cases of gastric bypass on morbidly obese patients with type 1 diabetes. They noticed a 4200–7200 pmol/L reduction in insulin requirement and a 3%–4% reduction in glycated hemoglobin (HbA1c). Clinical observations of surgeons who perform a high volume of bariatric surgeries are needed to support this finding. However, based on the published literature, there is no strong evidence supporting the efficacy of gastric bypass surgery to cure or control type 1 diabetes. Similarly, there is no strong evidence to suggest that patients with type 2 diabetes who do not experience remission or improvement after gastric bypass have more difficulty achieving glycemic control or experience clinical deterioration.

Timing Roux-en-Y gastric bypass early for patients with type 1 diabetes may be more effective than timing the surgery later. This may explain why Roux-en-Y gastric bypass is less effective on the obese patients with type 1 diabetes when performed late in the course of disease. When performed early, the procedure may also decrease pancreatic β-cell damage and prevent the action of environmental and dietary precipitating factors for diabetes,[17] which play a fundamental role in the pathophysiology of type 1 diabetes. DePaula and colleagues[69] reported the efficacy of ileal transposition associated with diverted sleeve gastrectomy, a form of bypass surgery, in controlling diabetes in 95.7% of patients with body mass indexes ranging from 21 to 29 during a mean follow-up period of 21.7 months. Such evidence supports gastrointestinal bypass surgery as a potential method of controlling or curing diabetes. However, the lack of clear and strong clinical evidence supporting Roux-en-Y gastric bypass to control or cure type 2 diabetes in lean patients and type 1

diabetes in general makes the eminent application of the procedure in these patients extremely difficult. Current discussions and scientific activities to explore the underlying mechanisms of bariatric and metabolic surgery are encouraging, as they represent a shift from the traditional treatment of diabetes by increasing insulin to a hope of cure owing to Roux-en-Y gastric bypass.

CONCLUSION

The effectiveness of Roux-en-Y gastric bypass in controlling type 2 diabetes is well documented in the literature. In lean patients with type 2 diabetes and patients in the early stages of type 1 diabetes, Roux-en-Y gastric bypass has the potential to protect the β-cell mass reserve by improving HbA1c and thus glycemic control. Performing Roux-en-Y gastric bypass procedure on nonobese animals in the early stages of type 1 diabetes and randomized controlled trials are needed to confirm this finding.

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