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Gastrointestinal

Use of Gastric Bypass Surgery for the Treatment of Type 2 Diabetes Mellitus

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Abstract:
Over the past decade, the incidence of type 2 diabetes mellitus (T2DM) has increased significantly. Evidence has shown that a clear association exists between obesity and diabetes development. This association has inspired researchers to explore bariatric surgery as an option for diabetes management and possible disease reversal. Improvement of T2DM using Roux-En-Y gastric bypass (RYGB) is thought to result from a combination of weight loss, decreased caloric intake, hormonal changes and rearrangement of the gastrointestinal anatomy. Positive outcomes resulting from the procedure include decreased mortality rates, normalization of HbA1c levels, decreased dependence on diabetic medications, and increased insulin sensitivity. Gastric bypass, specifically RYGB, appears to be a promising treatment for T2DM. Due to possible complications and limited research in some populations, treatment should be restricted to patients with a BMI > 35 with concurrent diabetes. Patients with diabetes who qualify should be counseled on the potential benefits of gastric bypass as a viable option for diabetes management.

Introduction:

The incidence of type 2 diabetes mellitus (T2DM) is rapidly increasing worldwide and is stated to be the sixth leading cause of death in the U.S.[1] More than 24 million Americans have been diagnosed with diabetes, and approximately 800,000 new cases arise each year.[2] Between 1995 and 2025, prevalence is expected to increase from 130 million to roughly 300 million.[3] Although causation cannot be linked to one specific source, rising diabetes rates are undeniably associated with the obesity epidemic. In Western countries, 15-30 percent of the adult population is obese (BMI > 30). Studies have observed that insulin resistance and diabetes often follow a large increase in body weight. One such study, the Nurses' Health Study, found that both men and women who gain 11-19.9 kg after the age of 18 have 5.5 times the risk of developing T2DM.[3] Furthermore, other analyses have linked centrally patterned fat distribution with an increased diabetic risk. Therefore, the development of diabetes depends not only on lifestyle choices, but also on genetic components.

Patients with T2DM account for approximately 90 percent of all diabetics.[4] One characteristic commonly seen in T2DM is insulin resistance. Endogenously, insulin acts to dispose of glucose within the skeletal muscle as well as to suppress hepatic glucose production. A patient is considered to have insulin resistance when these endogenous effects of insulin are decreased. The early stages of T2DM are often marked by hyperinsulinemia accompanied by accelerated endogenous glucose production. Hepatic insulin resistance is considered the major contributor to hyperglycemia in these patients. Cytokines, hormones and non-esterified fatty acids (NEFA) all moderate insulin action and arise in the adipocytes. A rise in triglyceride stores increases adipocyte size and alters the ability of insulin to suppress lipolysis. This leads to high circulating levels of NEFA and glycerol, which cause insulin resistance in the liver and skeletal muscle. Ectopic fat storage (fat storage in non-adipose cells) also may intensify insulin resistance. The American Association of Clinical Endocrinologists suggests T2DM diagnosis be based on the presence of one of three factors:[5] Symptoms of diabetes, such as polyuria, polydipsia and unexplained weight loss, and the causal plasma glucose concentrations > 200 mg/dL, fasting glucose concentration > 126 mg/dL, or a two-hour post-challenge glucose concentration ≥ 200 mg/dL during a 75 g oral glucose tolerance test.

The 2010 American Diabetes Association (ADA) Standards of Care Guidelines recommend that a physician-coordinated team, including the pharmacist, oversee the management of diabetes and provide the patient with proper medical nutrition therapy and diabetes self-management education.[6] For glucose management, the ADA recommends self-monitoring of blood glucose (if on insulin), testing HbA1c two to four times yearly dependent on patient's blood glucose control, and initiating metformin therapy and lifestyle changes at the time of diagnosis with medicinal therapy augmentation as needed. Furthermore, diabetes leads to accelerated development of micro and macrovascular disorders. Cardiovascular disease is the leading cause of morbidity and mortality among diabetic patients. The guidelines therefore indicate that blood pressure control, lipid management and aspirin therapy as needed, in addition to proper screening and treatment for coronary heart disease, nephropathy, retinopathy and neuropathy, are important components of care. Finally, for the first time, the ADA has included bariatric surgery as a treatment option for those patients with a BMI > 35 and concurrent T2DM in their 2010 guidelines.

Bariatric surgery

Due to the evident association between obesity and diabetes, many researchers are exploring the option of bariatric surgery for diabetes management and possibly disease reversal. Currently, four types of gastric bypass are generally performed. The adjustable gastric band (AGB) is a band that can be placed around the top of the stomach to form a small pouch.[7] Band size is controlled by modifying the amount of saline solution in the band in order to increase or decrease the size of the band's circular balloon, thereby altering stomach outlet size. In Roux-en-Y gastric bypass (RYGB), digestive tract size is reduced through bypassing most of the stomach, duodenum and upper intestine. This not only limits food intake to that which can fit in a small pouch, but also decreases gastrointestinal absorption. Biliopancreatic diversion with a duodenal switch (BPD-DS) consists of a reduction in stomach size to reduce food intake, a redirection of food away from the small intestine to drastically decrease absorption, and a redirection of bile and digestive juices to impair digestion. Typically, BPD-DS results in the most weight loss but also has the highest risk of long-term complications because of the malabsorption that results. Lastly, vertical sleeve gastrectomy (VSG), one of the three components of BPD-DS, drastically reduces stomach size as mentioned previously. This size reduction also may decrease the amount of ghrelin produced, reducing hunger to a greater extent than the lap band operation and aiding in patient success.

How it works

Since the 1980s, research has been conducted to assess the efficacy of using gastric bypass surgery for the treatment of T2DM, and, as previously stated, the ADA has recently included gastric bypass as a therapeutic option for T2DM within their guidelines.[2,6] Scientists hypothesized that the excessive amount of weight loss resulting from the surgery may diminish the symptoms of T2DM. It has been verified that surgery is the most effective way to produce sustained and substantial weight loss in patients.[8] The weight reduction strategies that have been used include gastric restriction via the reduction of stomach volume and intestinal malabsorption due to the shortening of the small intestine and decreasing the surface area available for nutrient absorption.[9]

One of the main surgeries currently being investigated that has shown the most promising results is RYGB. During this surgery, the stomach is divided into two sections, where a small stomach pouch (15-30 ml in volume) is formed in the upper part of the stomach by using surgical staples or a gastric band.[2] This small pouch is directly connected to the middle portion of the jejunum, thus bypassing the lower part of the stomach, the duodenum and part of the jejunum. Gastric juices, bile and pancreatic enzymes continue to flow from the lower part of the stomach and duodenum through the small intestines and meet the other channel at a Y-shaped junction.

Improvement of T2DM using RYGB is thought to be a result of a combination of weight loss, decreased caloric intake, hormonal changes and rearrangement of gastrointestinal anatomy.[2] The amount of overall weight loss does not prove to be the primary mechanism of treatment for diabetes because the resolution of diabetes occurs within days after surgery, prior to the majority of the weight loss. Complete eradication of the disease, however, is seen more frequently in those patients who lose more weight. It has been observed that the decreased caloric intake resulting from RYGB may help with short-term glycemic control, but overall resolution of T2DM cannot be accounted for due to decrease in caloric intake. Hormonal changes are thought to be one of the main reasons for this possible success in T2DM. RYGB has shown to result in increased levels of GLP, Peptide YY (PYY), adiponectin and decreased levels of GIP, acylation-stimulating protein (ASP), leptin, and ghrelin. These hormones have a major impact on the function of the GI tract and, when altered due to RYGB, may lead to many of the positive effects of the surgery (table 1).

Benefits

Diabetes often is a life-altering and life-defining disease that many individuals have difficulty managing. Gastric bypass surgery can be very beneficial for some patients that have had difficulty in achieving adequate diabetes control. Positive outcomes resulting from the surgery include decreased mortality rates, normalization of HbA1c levels, decreased dependence on diabetic medications, and increased insulin sensitivity. A study including 608 morbidly obese patients that were followed for 14 years post-gastric bypass operation reported an average excess weight loss of 49 percent.[9] Of the 608 patients, 330 had either diabetes (n=165) or impaired glucose tolerance (n=165) at baseline. At the end of the study, 82 percent of those with T2DM had normal HbA1c levels. Another study including 232 morbidly obese patients, all with T2DM, was conducted to assess long-term mortality rates. It was found that the mortality rate of the control group was significantly higher ($P<0.0003$) than the surgical group. The number of cardiovascular deaths was the major variant between the two groups. By decreasing mortality rates and HbA1c levels, a diabetic patient may have a prolonged and better quality of life.

Once diagnosed with diabetes, it is rare that there will be a day that a patient will go without taking a pill again. Gastric bypass has shown to minimize the number of medications needed for a diabetic patient, which will help with patient compliance issues and allow for simpler medication therapy.[2] In general, RYGB shows a reduction in the dependence on diabetic medication of 80-98 percent of patients for up to 14 years of follow-up. Surgery is more effective than medicinal treatment alone for improving diabetes for long-term effects. A study comparing 154 morbidly obese type 2 diabetics that had gastric bypass surgery to 78 control patients showed that 87 percent of the control group required medication intervention after nine years of follow-up. After 6.2 years of follow-up, medication intervention required for the surgery group fell from 31 percent to 9 percent. Another study, which included 378 type 2 diabetic patients that underwent weight reduction surgery, 72 of which were medicated, showed that there was a significant reduction in blood sugar level from 9.1 mmol/L (preoperative) to 6.6 mmol/L (postoperative) with a $P=0.005$.[8] Of the 72 patients who were medicated, 36 patients had stopped all medication for diabetes, and none had an increase in dose post-operation. There was a 75 percent reduction in patients that

Table 1: Effect of RYGB on Gastrointestinal Tract (GIT) Hormones[2]

Hormone	Increase/Decrease in Hormone following RYGB	Endogenous Effect
GLP-1	Increase	Acts to suppress glucagon, reduce glucose production by the liver, increase insulin production, slow gastric emptying, and enhance satiety
GIP	Decrease	Stimulates insulin release and synthesis
ASP	Decrease	Increased glucose uptake and fatty acid esterification
Ghrelin	Decrease	Appetite-stimulating hormone
PYY	Increase	Decreases food intake by inhibiting gut motility
Adiponectin	Increase	Stimulates glucose utilization and fatty acid oxidation in skeletal muscle
Incretin	Decrease	Secreted after meals to enhance insulin secretion

required insulin after the operation. Sixty-nine percent of all patients that underwent RYGB surgery as the weight reduction surgery were off all medications post-operation (P<0.0001). There was no significant relationship between the amount of weight loss and change in diabetic status. While a complete reversal of diabetes may be life-changing for an individual, a reduction in diabetes medication use in those who do not achieve complete reversal also can be very beneficial. Currently available studies have generally shown a decreased need for medications following gastric bypass surgery for the diabetic patient. More studies need to be performed to further confirm and more accurately assess the benefits and mechanisms surrounding this matter.

One of the most challenging issues for diabetic patients is glucose control. It is a constant struggle for doctors and pharmacists to counsel patients on ways to minimize fluctuations in glucose levels. Gastric bypass may be a beneficial option for patients who struggle to maintain normal glucose levels. After gastric bypass surgery, a normalization of glucose metabolism is often seen within weeks of surgery.[2] Long-term effects are better seen within two to five years post-operation. In a trial investigating 4,047 subjects treated for obesity, 72 percent of the patients surgically treated recovered from T2DM within two years of surgery, compared to only 21 percent of the control group.

Gastric bypass has shown its best effects in its long-term treatment of T2DM. A resolution rate of diabetes is between 83-85 percent in the long term for gastric bypass surgery.[8] RYGB is more effective for the treatment of T2DM in patients with a milder form and a shorter duration of the disease.[2] Patients who do not experience significant improvement from the surgery tend to be older. Unlike insulin sensitivity, B cell function improvement is more closely related to duration of diabetes rather than weight loss.[9] While gastric bypass surgery has proven to show many benefits for the treatment of T2DM, these benefits should be weighed against the risks of surgery before using this method in any patient. Also, the characteristics of the patient must be considered in determining if qualifications for this surgery are met, including obesity and BMI criteria.

Risks

Along with any surgery comes risk of treatment, possible complications and death, in addition to potential hardships from expenses and medical bills. Figures show that there is less than 1 percent risk of mortality for patients undergoing RYGB, and a risk of complications range from less than 10 to 20 percent.[8] Medical bills for RYGB, including hospital stays, anesthesia, lab costs and surgeon fees, costs approximately $26,000 without health insurance.[10] Insurance coverage varies from plan to plan, but bariatric surgery is frequently not covered in full, if at all.

Complications of these operations include bleeding, infection and blood clots that can move to the heart or lungs.[7] Later problems, such as malnutrition, strictures and hernias, also may occur. Studies suggest that up to 10 percent of patients receiving bariatric surgery may experience inadequate weight loss or may regain much of the weight that is initially lost. Experts recommend that these procedures be performed only on adolescents that are extremely obese (typically with BMI greater than 40), have reached their adult height (usually 13 or older for girls and 15 or older for boys), and have serious weight-related health problems, such as T2DM, sleep apnea, heart disease, or significant functional or psychosocial impairment. Surgery should only be considered after candidates have attempted weight reduction for at least six months and have failed.

Following RYGB, the risk of developing vitamin and mineral deficiency is significantly increased. RYGB can lead to decreased levels of vitamin B12, folate, iron and calcium either through malabsorption or insufficient intake.[11] Supplementation of these specific vitamins is vital following RYGB surgery.

Cost Analysis

As previously mentioned, comprehensive medical costs for RYGB without insurance are an estimated $26,000.[10] Insurance coverage varies, and, if coverage is provided, it normally does not cover the entire cost of surgery. Comparatively, a 2010 study employed a Cost of Diabetes Model to estimate the U.S. economic burden related to diabetes.[12] The study analyzed information from peer-reviewed literature, government statistics and national survey, and medical claim databases. The average annual cost per patient standardized to 2007 dollar amounts was $2,864 for undiagnosed diabetes and $9,677 for diagnosed T2DM. As a reference, the median age of diagnoses for T2DM was 57 with annual costs increasing with age. Depending on quality of insurance coverage, length of life, age of diagnosis and success of surgery in treatment of symptoms, gastric bypass offers potentially great long-term cost savings, although the actual magnitude of these savings is still to be determined. More cost-effectiveness studies need to be completed to fully and more adequately compare the costs of bariatric surgery as treatment for T2DM versus the current standard of care.

Effect on Drug Absorption

Data examining the effect of bariatric surgery on drug absorption is lacking. A recent review of the literature suggests that, although there is little known, the effect of bariatric surgery on drug absorption appears to be drug-specific.[13] In some cases, substantial reductions in drug absorption may occur, which may be temporally associated with the need for dosage adjustment. Overall, evidence for decreased drug absorption was found in 15 of 22 studies involving jejunoileal bypass, one of three studies of gastric bypass/gastroplasty, and none in the one study examining biliopancreatic diversion. Specifically, multiple reports described decreased absorption for anti-rejection drugs (cyclosporine and tacrolimus), thyroxine, phenytoin and rifampin. Single instances of diminished absorption of ethosuximide, amoxicillin, macrodantin, tacrolimus, sulfisoxazole and hydrochlorothiazide were reported. Conflicting evidence was present for ethambutol, digoxin and oral contraceptives. Further study is needed to assess the degree of malabsorption specific to each medication and whether there are major differences among procedure types that exist.[13]

Conclusion

Gastric bypass, specifically RYGB, appears to be a promising treatment for T2DM. RYGB not only slows progression of the disease, but also offers potential disease resolution. The average long-term diabetes resolution rate for those who undergo surgery is an impressive 83-85 percent, which considerably improves quality and duration of life, achieved through a significant reduction in diabetes-associated complications. Also, it is suspected that a cost savings will be incurred through medication reduction or cessation. Although RYGB has shown great success, studies have revealed better outcomes in younger individuals newer to diagnosis with a

milder form of the disease. RYGB as a treatment for T2DM should be restricted to patients with a BMI > 35 with concurrent diabetes, due to potential complications of surgery and limited research support beyond use in other populations. Patients should be able and willing to exhibit high levels of compliance to current medication therapy, as physician visits and daily vitamin supplementation will be required following surgery. It is vital that patients comply with continual follow-up visits to promote optimal results. Much focus should be placed on these parameters when electing candidates for surgery. This strategy has grabbed the attention of many health care professionals, and with 30 years of supporting research, gastric bypass now has been included in clinical guidelines as an appropriate treatment option for some T2DM patients.

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