ORIGINAL ARTICLE

Metabolic Surgery Is No Longer Just Bariatric Surgery

E. Charles Moore and Walter J. Pories

Introduction

BARIATRIC SURGERY WAS APTLY NAMED in 1953, after the Greek word “βάρος” for weight, when Varco first attempted to treat severe obesity with a bypass of the small intestine. However, since then the focus in this field has expanded far beyond obesity with the recognition that bypassing parts of the gut can also control a far more dangerous set of diseases that include type 2 diabetes mellitus (T2DM) and other expressions of the metabolic syndrome.

This year's articles reflect this maturation of “bariatric” surgery to “metabolic surgery,” because of its broad impact on the chemical processes occurring within a living cell or organism necessary for the maintenance of life.

The selected publications address the following current issues:

- If metabolic surgery is the most effective treatment for T2DM, why should it be limited to patients with a body mass index (BMI) >35?
- Metabolic surgery produces remission not only of T2DM but also other manifestations of the metabolic syndrome such as hypertension and hyperlipidemia. Should it therefore also be considered as a useful therapy for these diseases?
- If the surgery is so effective, why are over 99% of eligible patients denied access?
- What is the rate of erosion of the beneficial effects of metabolic surgery, and what are the factors that affect long-term outcomes?
- The sleeve gastrectomy (SG), an operation rapidly gaining in popularity because of its less demanding technical requirements, is also effective in the control of obesity and diabetes. How does it compare to the gastric bypass operation, long the gold standard?
- The Swedish Obesity Study is the longest ongoing population study of patients who subjected to metabolic surgery. What are the latest results?

These are critical questions. T2DM is now the most expensive disease in the United States, with costs of \$245 billion in 2012 compared with \$174 billion only 5 years earlier. Not only has the cost of treatment risen, but also the prevalence

has exploded, with the prevalence of T2DM doubling in the last 10 years. Today, in the United States, one out of every four adults over 65 has diabetes. In spite of major advances in the medical therapies that include diet, exercise, insulin secretagogues, agents to increase insulin sensitivity, and newer forms of insulin, these therapies have had limited success. In spite of increased expenditures on these agents, diabetes still remains the primary cause of blindness, amputations, and renal failure leading to dialysis. T2DM is also a major cause of heart attacks and strokes. Pretty frustrating. Fortunately, surgery appears to be providing more hopeful answers.

Effects of gastric bypass surgery in patients with type 2 diabetes and only mild obesity

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Background

To determine the impact of Roux-en-Y gastric bypass (RYGB) on patients with severe ($9.7\% \pm 1.5\%$ HbA1c) and longstanding (12.5 ± 7.4 years) diabetes and low BMIs, 30–35 kg/m².

Methods

Sixty-six patients who underwent RYGB with diabetes and BMI between 30 and 35 kg/m² were followed for a median period of 5 years. Primary outcomes were safety and resolution of diabetes (HbA1c <6.5% without use of medication).

Results

Long-term remission occurred in 88% of the patients. Mean HbA1c fell from $9.7\% \pm 1.5\%$ to $5.9\% \pm 0.1\%$ ($p < 0.001$). Weight loss failed to correlate with diabetes remission, suggesting an alternative method for diabetes resolution. There was also an increase in C-peptide, suggesting increased β -cell function. There were no mortalities or major surgical morbidities in the study.

Conclusion

RYGB is a safe and effective way to induce remission of diabetes in patients with lower BMIs.

Comment

The setting of the BMI (kg/m^2) standard makes for a curious story. In the early days of bariatric surgery, in spite of increasing evidence that it was the most effective therapy for severe obesity, we were unable to convince the commercial carriers to provide coverage for these operations. Finally, in the NIH Consensus Conference of 1991 (1), we were able to reach a common standard that made it possible to allow Medicare to recommend reimbursement for bariatric surgery for patients with a BMI ≥ 40 and for those with a BMI ≥ 35 who also had significant comorbidities such as diabetes or hypertension. At the time, this was a great victory.

In the intervening two decades, it became evident that this was a pyrrhic victory. First, the BMI is not an accurate measure of adiposity. It fails to account for fitness and muscularity. For example, at East Carolina University we studied a man who was 5'8" and weighed 307 lbs. with a BMI of 46.7, certainly a candidate for bariatric surgery. The problem was that we could not catch him. He was the fastest running back on our football team. The BMI is also unigender and, accordingly, fails to account for the major differences in adiposity between men and women. It fails to account for the increased marbling of muscle in aging. Most important, however, it discriminates against Asians and African Americans who are much more likely than Caucasians to develop diabetes and hypertension at lower BMIs. Thus, an Asian woman with a BMI of 32 has the same chance of developing the comorbidities of severe obesity as her white sister with a BMI of 35. In essence, the rule denies surgery to those who need it most.

Others have previously shown that even a limited bypass, that is, the duodenojejunal bypass, will produce full remission of T2DM even in lean individuals. Ramos *et al.* of Brazil (2) reported small groups with dramatic restoration of normal Hb1Ac and fasting glucose levels.

This article by Cohen *et al.*, also from Brazil, provides scientific basis with a long enough follow-up period to eliminate the unfortunate BMI $\geq 35/40$ standard. We hope this will convince Medicare and the private carriers to eliminate this unfair and dangerous standard.

Roux-en-Y gastric bypass vs intensive medical management for the control of type 2 diabetes, hypertension, and hyperlipidemia

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Background

There is a significant lack of randomized clinical trials directly comparing intensive medical management to gastric bypass surgery (RYGB).

Methods

In an unblinded randomized trial that took place at four teaching hospitals that directly compared 120 participants ($n = 60$ intensive medical therapy and $n = 60$ RYGB surgery), the primary end points were to reduce HbA1c $< 7.0\%$, low-density lipoprotein cholesterol levels $< 100 \text{ mg}/\text{dL}$, and systolic blood pressure $< 130 \text{ mmHg}$.

Results

After 12-month follow-up, 49% of the gastric bypass patients and 19% of the medically treated group achieved the set endpoints. The bypass group required three fewer medications but had more serious adverse events and more nutritional deficiency than the medical group.

Conclusion

Adding RYGB to lifestyle modification is associated with a greater chance of reducing surrogate end points for cardiovascular disease (HbA1c%, low-density lipoprotein cholesterol levels, and systolic blood pressure [SBP] levels).

Comment

The Look AHEAD trial advocating intensive medical management and lifestyle modifications in obese type 2 diabetics showed early promise. Participants achieved significant weight loss, blood pressure reduction, glycemic control, and reduction of cardiovascular risk factors. However, in July 2013, at a median follow-up analysis of 9.6 years, this study was halted because of futility (3,4). Controlling diabetes and cardiac risk factors with intensive lifestyle modifications over the long-term was not an effective approach.

Conversely, RYGB has proven to be a useful adjunct to lifestyle modification in the reduction of cardiac risk

factors. In the *ATTD 2012 Yearbook*, we reviewed two prospective, randomized clinical trials by Schauer *et al.* (9) and Mingrone *et al.*, published in the April 2012 issue of the *New England Journal of Medicine*, which documented the marked superiority of surgery over intensive medical management of T2DM. This article adds more evidence that the traditional approaches to the treatment of T2DM need reexamination.

In this study, 49% of the surgery group achieved the established diabetic and cardiovascular management goals compared with only 19% of the medical management group. These results show promise and a useful alternative to intensive medical management. The short duration of follow-up of only 12 months raises concern, but these benefits match or exceed the composite goals of the Look AHEAD trial at the same period. Detractors state that the problem is not the dramatic resolution of T2DM associated with RYGB but the paucity of long-term follow-up, but long-term studies by our group and that of Sjostrom have already proven this complaint baseless with long-term remissions, although there is some erosion of the full "cure" rate over the years.

It is frustrating that, in spite of the mounting evidence, less than 1% of those who could benefit from metabolic surgery have access to this therapy. Obesity and T2DM are two of society's most economically devastating diseases (5). According to the Centers for Disease Control, the prevalence of T2DM has doubled (yes, doubled) in the last decade. The war against both is valiantly being waged by family practitioners, endocrinologists, internists, obstetricians, and even pediatricians, but without access to the most effective therapies. Recent estimates show that close to 32% of American adults meet the criteria for obesity and 13% of all adults have diabetes (6). Deaths related to diabetes are projected to double between 2005 and 2030 (7). These statistics make it imperative that the physicians dealing with the twin epidemics have a full armament of treatments. Despite 20 years of data showing 70–80% remission rates for patients who undergo RYGB and SG, less than 1% of patients with BMI >40 kg/m² have undergone weight loss procedures (8). Physician perception of bariatric surgery, referral patterns, and disparity among third-party payers for reimbursement seem to be leading to this underutilization of surgery for treatment. The real issue is informing prospective patients about their options to treat, providing access to meaningful care, and overcoming barriers to that care.

Physicians attitudes about referring their type 2 diabetes patients for bariatric surgery

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Surg Obes Relat Dis 2012; 8: 381–86

Background

Evidence is mounting about the benefits of bariatric surgery, but little is known about physicians' attitudes toward referring patients of surgery.

Methods

Physicians who were likely to treat T2DM were surveyed about their perceptions and the efficacy of bariatric surgery.

Results

Respondents had an overall positive view of bariatric surgery as a treatment for obesity and T2DM, but only 20.85% would refer their patients with BMI 30–34.9 kg/m² and T2DM to a randomized research trial.

Conclusion

The sample of physicians in this survey had a favorable response to bariatric surgery for the treatment of obesity and T2DM. Despite this, there is a relative reluctance to refer patients with lower BMI (30–34.5 kg/m²) and T2DM for bariatric procedures. This represents a large barrier to studying the effects of bariatric surgery on patients with lower BMIs and T2DM.

Comment

A central theme in the United States is access to affordable healthcare. Obesity and T2DM produce a major and growing burden of expense. So far, the medical therapies including diets, exercise, drugs, behavioral modification, nationwide publicity campaigns, and the traditional diabetes drugs have shown marginal effectiveness. Accordingly, the increasing documentation that metabolic surgery produces full, durable, and safe remissions of severe obesity, diabetes, and other expressions of metabolic syndrome should be welcome news and rapid adoption. Studies have shown that up to 80% of patients with T2DM who have undergone RYGB experience complete remission of the disease (9). In contrast, intense lifestyle modification and pharmacotherapy have not shown the same impressive results as surgery.

Even so, a minority of the patients who could benefit from surgery are actually instructed about the operative alternatives and/or referred to a surgeon. Although most physicians have a positive outlook about bariatric surgery, they still are often not comfortable with referring patients for surgery.

Sarwer *et al.* address this reluctance in this cited publication. Their results are interesting, challenging, and in accord with the experience of most metabolic surgeons. Even though physicians have a favorable view of the operations and, in fact, are generally well informed about the indications, results, and risk/benefits, most are reluctant to recommend the surgery to their patients. In addition, not studied in this article, many surgeons, including us, frequently encounter resistance by the patients who are far more afraid of the reality of pending surgery than the concerns about late-term effects of the disease. This reluctance is reflected in the plateauing of metabolic surgery at about 200,000 per year.

Perhaps, with time, this challenge will be resolved as the public recognizes the physical, medical, and emotional burdens of severe obesity and the tragic consequences of diabetes. A solution cannot come soon enough.

Improvement of type 2 diabetes mellitus (T2DM) after bariatric surgery—who fails in the early postoperative course?

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Background

Identification of factors preoperatively for responders and nonresponders to bariatric surgery in regard to T2DM.

Methods

Eighty-two of 235 patients with T2DM who underwent bariatric surgery were studied. Univariate and multivariate analyses were used to identify the predictors for metabolic response to bariatric surgery.

Results

Diabetes did not improve in 17 of 82 patients. There was no correlation between excess weight loss and response. Univariate analysis showed that duration of diabetes, higher preoperative HbA1c levels, and preoperative use of multiple medications were significant in predicting nonresponse after surgery. Multivariate analysis revealed that age, preoperative dose of insulin, and preoperative oral antidiabetics showed positive correlation to nonresponse. RYGB showed the lowest failure rate.

Conclusion

The ability to predict responders from nonresponders for the treatment of T2DM before surgery is imperative to selecting patients that would derive the most benefit from an invasive procedure.

Comment

When, in 1980, we first noted that gastric bypass produced full remission of T2DM within a few days after surgery, we followed this observation with the study of 837 patients for a mean of 16 years with a follow-up of 95% (10). In that study we documented that full remission was only seen in 83%, an observation that has been corroborated in several later series with some variation but always revealing that some patients responded better than others.

Understanding the preoperative risk factors that precede these failures will help physicians stratify these patients into the best possible treatment regimens. It will also avoid subjecting patients to invasive procedures that will not derive benefit. This is especially important as we turn to using surgery as a treatment for T2DM in patients with lower BMIs (30–35 kg/m²). Multiple studies suggest that the length of time a person has T2DM is a predictor of failure. Hall *et al.* (11) showed that a preoperative history greater than 10 years was a predictor of remission failure. In this study, preoperative HbA1c were also higher (8.3±1.2% vs. 7.8±1.7%) in the nonresponder group than in the responder group. These two factors suggest that the earlier we can intervene in the disease process, the better the outcome. To date, no conclusions have been drawn on what type of surgery has the best remission rates. In the future, developing consensus criteria for responders and nonresponders is critical in driving research forward. The ability to predict gastric bypass results will make it a viable treatment in the fight against not only obesity but also T2DM.

This article by Jurowich *et al.* provides an update on the search for explanations for the variable responses. Their findings match those of others interested in this question, that is, that patients with advanced T2DM, of longer duration, with higher HbA1c levels and who were being treated with a greater number of medications were less likely to achieve full remission. Others have observed that there are also racial differences, with African Americans not responding as well as Caucasians. Age has also been implicated by some, with older patients having a lower response rate.

The important implication of these results is that metabolic surgery should be considered early in the treatment of the disease before irreversible changes occur in the islets, liver, and blood vessels. In many ways, the history of bariatric surgery recapitulates the rise of cardiac surgery in which the surgery for the first few decades was limited to the cases with the highest risk. The high failure rates then, naturally, discouraged referrals. Today, the cases are referred early with clear improvements in outcomes. Similar beginnings, guided by the timeless injunction “first, do no harm” occurred also in thoracic surgery, hip replacements, and transplantation. In each of these, the value of early intervention is now clear. It's time for metabolic surgery to learn from this history.

Comparable early changes in gastrointestinal hormones after sleeve gastrectomy and Roux-en-y gastric bypass surgery for morbidly obese type 2 diabetic subjects

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Background

The mechanisms for resolution of T2DM in both RYGB and SG have not fully been elicited. This study compares the early changes in gastrointestinal hormones in patients undergoing SG and RYGB.

Methods

Twelve subjects were compared as to levels of glucose, glucagon-like peptide (GLP-1), glucose-dependent insulintropic polypeptide (GIP), and GLP-2 after a standardized mixed liquid meal before and 6 weeks after both RYGB and SG.

Results

Six weeks postoperatively, 5 of 6 patients in each group had remission of their T2DM. The indices for both the RYGB and SG had similar insulin and glucagon secretion; the GLP-1, GLP-2, and GIP response increased in both surgical groups.

Conclusion

SG and RYGB are comparable for glucose tolerance and exhibit similar changes in gastrointestinal hormones.

Comment

The gold standard in metabolic surgery for the last three decades has been the RYGB. Surprisingly, even before durable weight loss has occurred, RYGB leads to improved glucose control. The last decade has seen the emergence of a simpler operation that requires only partial resection of the stomach and no anastomosis. It also does not alter the stream of digesting food with bypasses of portions of the foregut.

The SG has now been shown to be a safe alternative to the RYGB, with comparable T2DM remission rates. These results provide a critical new clue in the mystery of how metabolic surgery leads to not only weight loss but also resolution, in only a matter of days before there is significant weight loss, that is, reduction in adiposity, of T2DM, hypertension, dyslipidemias, nonalcoholic steatohepatitis (NASH), gastrointestinal reflux diseases, polycystic ovary syndrome, and pseudotumor cerebri, among others.

These observations force us to reconsider the explanation that the "metabolic factor signals" arise in the duodenum; they question the tenets of the foregut and hindgut theories and, at the same time, stimulate new concepts about not only the effects of the surgery but also a long-needed reexamination of the pathophysiology of T2DM and the relationships of that entity to the other diseases in the metabolic syndrome.

This article by Romero *et al.* documents that both RYGB and SG are associated with similar increases of GLP-1, GIP, and GLP-2 in the early periods after surgery, although other reports dispute these findings, claiming that the RYGB produces far greater changes in GLP-1. Both surgeries led to similar paracrine profiles in this patient population. These increased incretin effects from L-cell-derived hormones with their significant insulintropic actions and glucagonostatic properties are

believed by some to lead to resolution of glucose intolerance even before significant weight loss has occurred (12). After RYGB, studies, including the SOS study, have shown a positive and durable response up to 20 years after bypass (13). We recently saw one of our patients, 32 years after her RYGB, still free of the T2DM with which she presented in 1980! Time will tell whether SG will yield similar long-term results. Obviously, this study was limited by population size but provides significant insight to the mechanism of SG.

These articles also lead us to ask whether surgical intervention can prevent T2DM. Historically, most studies look at weight loss as a primary end point in bariatric surgery. Remission rates of diabetes after surgery were often secondary. Data over the last decade have shown that gastric bypass can lead to durable remission to T2DM. Lifestyle modification and medical treatment are the current standard used to decrease the micro and macro effect of diabetes. These strategies have met with mixed results especially in obese populations (BMI ≥ 35 kg/m²) (14). Most randomized medical management studies show good results in the initial period (<3 years) with relapse within 10 years. To our knowledge, there are no studies that look at gastric surgery for the prevention of T2DM. This study takes a novel approach to answer the question: Is gastric bypass a protective strategy against the development of T2DM? As we enter an era where prophylactic mastectomy and oophorectomy are now indicated for BRCA mutations, this is not an idle question.

Bariatric surgery and prevention of type 2 diabetes in Swedish obese subjects

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N Engl J Med 2012; **367**: 695–704

Background

Studies that take into consideration behavior modifications and medical management to protect against T2DM have been met with mixed results. This study examined the effects of bariatric surgery on the prevention of T2DM.

Methods

In total, 1,658 patients were followed prospectively after one of three types of bariatric surgery (adjustable band 19%, vertical band gastroplasty 69%, or gastric bypass 12%) and

compared with obese match-controlled nonoperative patients for the rate of incidence of T2DM. The participants were followed for 15 years.

Results

During the follow-up period, T2DM developed in 392 patients in the nonsurgical group and in only 110 patients in the gastric bypass group. The incidence rates were 28.4 case per 1,000 person-years for the nonoperative group and only 6.8 cases per 1,000 person-years in the gastric bypass group. The postoperative mortality was 0.2%, and 90-day re-operative rate was <3.0%.

Conclusion

Bariatric surgery seems to prevent the onset on T2DM in obese patients without T2DM.

Comment

This study's novel approach to proactively follow obese patients for the development of T2DM is unique. Results suggest that bypass can also be an effective way to prevent the onset on T2DM in obese patients. In 2012, Schauer *et al.* received a significant amount of media attention with the *NEJM* article. Schauer concluded that gastric bypass is a safe and effective way to achieve glycemic control and yielded statistically better results when compared to intensive medical therapy (9). This study goes one step further and suggests that bypass is also an effective way to prevent the onset of T2DM in obese patients without preexisting diabetes. Despite this novel approach, there are severe limitations to the study and how it translates to diabetes care. First, a majority of the patients in the study underwent a vertical band gastroplasty for their weight loss procedure (70%). This now represents a very small portion of gastric bypass procedures in the United States, and it would be difficult to interpret results from these data. In the future, it would be beneficial to do a subset analysis on the specific bypass procedures and their rates of diabetes prevention. The second shortcoming was the low participation rate at the 15-year mark; 36.2% of the patients had dropped out of the study and 30.9% had not reached the follow-up examination. Despite this percentage of patients lost to follow-up in the study, there were still 502 participants ($n=392$ control group and $n=110$ bypass group) who were available for analysis. It will be interesting to see if this protective strategy of gastric bypass continues as the remaining third of the study group reaches the 15-year follow-up examination.

Conclusion

It was an exciting year not only for metabolic surgery but also for T2DM, hypertension, dyslipidemias, and NASH, among others. These are no longer hopeless diseases but illnesses that can, finally, be treated successfully with marked improvements in mortality and morbidity. The discipline has also provided great hope for the prevention of solid cancers, with the demonstration that the prevalence of malignancies of

the breast, colon, prostate, and ovary fall by >70% within 5 years after the surgery.

These studies highlight some of the important milestones that have taken place in the evaluation of diabetes and gastric bypass surgery over the last year. We still face major challenges in our fight against diabetes and obesity. Unfortunately, key stumbling blocks still remain, such as access to care, response to care, and cost containment. Samuel Johnson said, "Great works are performed not by strength but by perseverance."

Author Disclosure Statement

No competing financial interests exist.

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