Bariatric Surgery Significantly Improves Rates of Diabetes Resolution Compared with Medical Therapy Alone

Schauer PR, Kashyap SR, Wolski K, et al. Bariatric surgery versus intensive medical therapy in obese patients with diabetes. N Engl J Med. Epub 2012 March 26.

Study Overview

Objective. To determine whether bariatric surgery increases the proportion of patients who achieve a hemoglobin A1c of 6% or less, with or without medications, as compared with intensive medical therapy alone.

Design. Randomized controlled trial.

Setting and participants. This study took place at the Cleveland Clinic. Patients were recruited and studied between March 2007 and January 2011. Patients were eligible for participation in the trial if they were between 20 and 60 years of age, had a diagnosis of type 2 diabetes and a BMI of 27–43. Exclusion criteria included a history of previous bariatric procedure or other "complex abdominal surgery" or any poorly controlled medical or psychiatric disorders.

Patients were block-randomized into 1 of 3 arms: intensive medical therapy (ADA guidelines, including lifestyle modifications and medication), laparoscopic gastric bypass plus medical therapy, or laparoscopic sleeve gastrectomy plus medical therapy. All surgeries were performed by the same surgeon at the same medi-

cal center. All patients were re-evaluated at 3-month intervals during the first year of follow-up, during which time they received lifestyle counseling and adjustments to their medical regimens with the treatment goals of achieving A1c 6% or less, blood pressure (BP) 130/80 mm Hg or less, and LDL 100 mg/dL or less. Also at these visits, patients had measurements of their body weight, waist and hip circumference, blood pressure and A1c, as well as fasting plasma glucose levels.

Main outcome measure. The proportion of patients achieving a hemoglobin A1c of 6% or less (with or without medications) at 12 months after randomization. The difference between groups was analyzed using chi-square testing.

The researchers also evaluated differences in fasting plasma glucose and insulin, lipids and C-reactive protein, the homeostasis model of insulin resistance index (HOMA-IR), weight loss, BP, adverse events, and changes in comorbid disease including medication changes. ANOVA testing was used to evaluate differences in continuous variables between groups, and a mixed model for repeated measures was used in cases

where multiple measurements were taken on the same people (eg, weight, A1c) during the follow-up period.

It is worth noting that the study was sponsored in large part by industry funding from a device company called Ethico Endo-Surgery.

Results. The randomized groups consisted of 50 patients receiving medical therapy (7 dropped out before the first follow-up and 2 did not attend all follow-ups, leaving 41 for analysis), 50 receiving gastric bypass, and 50 receiving sleeve gastrectomy (1 dropped out during the follow-up period, leaving 49 for analysis). At randomization, there were no significant differences between the 3 groups. Mean age at baseline was 48.6 years (with a range of 47.9 y in gastrectomy to 49.7 y in medical therapy group), mean BMI was 36, 44% used insulin, over half were female (ranging from 58% in the bypass group to 78% in the gastrectomy group, $P = 0.08$), and about three-quarters were white. In terms of comorbidities, between 80% and 90% of patients had dyslipidemia and 60% to 70% had hypertension at baseline.

The primary endpoint of an A1c of 6% or less was reached in just 12% of medical therapy patients, compared with 42% of bypass patients and 37% of sleeve-gastrectomy patients ($P = 0.008$ overall, $P = 0.59$ comparing the 2 surgical groups). One important difference between the 2 surgical types was that all bypass patients who achieved the target A1c did so with no medication, and while the majority of successful gastrectomy patients were without medications at 12 months, 28% remained on 1 or more glucose-lowering drugs. Because duration of diabetes and baseline insulin use are thought to be predictors of failure to achieve remission [1,2], the investigators stratified their results according to median age, use of insulin, and duration of diabetes. They report no significant heterogeneity with respect to achieving their primary endpoint between the strata. Patient A1c levels dropped more quickly in the surgical groups than they did in the medication group, often normalizing by 3 months postoperatively. Additionally, A1c levels were less likely to rebound upwards by the 12-month mark in surgical patients than in patients in the medical group. Whereas overall glucose-lowering medication use increased over the year of follow-up for the medical group (in an effort to meet target A1c), there was a significant reduction in the number of medications used for the surgical groups at 12 months ($P < 0.001$ comparing medication to either surgical type).

Nondiabetes outcomes were superior in the surgical groups as well. Medical therapy patients lost a mean (SD) of only 5.2% (7.7%) of their body weight during the 12 months of follow-up, whereas bypass patients lost 27.5% (7.3%) and gastrectomy patients 24.7% (6.6%) ($P < 0.001$ comparing medication to either surgical type). The median (interquartile range) change in triglycerides among medical patients was –14% (–40 to 3%), compared with –44% (–65 to –16%) for bypass patients and –42% (–56 to 0%) for gastrectomy. There was no significant difference in LDL change by group; however, the use of lipid-lowering therapy declined significantly among surgical patients as compared to those in the medical group.

Despite the numerous positive outcomes among surgical patients, there were also higher rates of adverse events in the surgical group. For example, 11 (22%) bypass patients required hospitalization for an adverse event during 12 months of follow-up compared with 4 (8%) gastrectomy patients and 4 (9%) medical therapy patients.

Conclusion. In this randomized trial of surgery versus medical therapy for diabetes in an obese population, surgical patients were significantly more likely to achieve an A1c of 6% or less, and to do so without the use of medications, as compared with patients in the medical group.

Commentary

In the past several decades, the prevalence of obesity and type 2 diabetes have skyrocketed in the United States, leaving clinicians struggling to treat their patients despite important advances in the medical therapy for both conditions. Many diabetics in the United States have poorly controlled disease, which leads to micro- and macrovascular complications with a profound impact on morbidity, mortality, and quality of life [3,4]. Although bariatric surgery has traditionally been used as a treatment of obesity, there is a growing realization that it often results in the resolution of diabetes, even before patients achieve any significant weight loss [5].

To date, most of the evidence looking at diabetes resolution after bariatric surgery has been observational, but the existing studies show powerful effects of surgery on normalization of glucose and A1c levels and likelihood of coming off of all diabetes medications after surgery [6]. On the other hand, studies of intensive medical therapy for diabetes, even coupled with lifestyle interventions, have shown more modest effects [7].

With this landmark study, Schauer and colleagues have performed a randomized trial of bariatric surgery versus medical therapy and generated evidence similar to that from existing observational studies. The randomized design helps to circumvent many of the issues that could have affected these previous studies. For example, observational studies comparing surgical to medical patients are subject to confounding by indication—are patients who self-select (or are selected for) bariatric surgery somehow sicker (or healthier?) than those who do not get it? Are they more motivated to lose weight or control their diabetes? Another positive aspect of this study design is the use of block randomization. Given that enrollment went on over a 4-year period, during which there were advances in the medical and surgical therapy of diabetes, block randomizing helped to guard against confounding by secular trends that could have been observed had, for example, a majority of patients in one group been from 2007 as opposed to 2011. Furthermore, rather than limiting entry into the study to patients with newer or milder cases of diabetes, the investigators enrolled those with fairly advanced disease, often with evidence of vascular complications already present at baseline. These patients were clearly not the "best case scenario" patients often enrolled in randomized trials.

Although the use of a single medical center and single surgeon for all procedures were likely good ways of standardizing treatment, they also somewhat limit the generalizability of the study. Further studies using multiple centers from different geographic areas might be more representative of the actual predicted effects of wide-scale use of bariatric surgery to treat diabetes.

The number of patients in this trial was relatively small, so while the overall follow-up rate was excellent, differential dropout by group could have affected the measurement of outcomes. There were 9 patients who were randomized but not analyzed in the medical therapy arm, representing an 18% loss rate in that group versus 0% lost in the bypass group and only 2% in the gastrectomy group.

One fact that received little mention by the authors was the somewhat surprising lack of effect of baseline insulin use and duration of diabetes on the primary outcome of A1c improvement. This negative finding may also be reflective of the smallish sample, leading to tiny numbers of patients in some strata, thus limiting the ability of the investigators to find significant differences in their exposure–outcome relationship according to these probably very important factors.

The quick resolution of diabetes among surgical patients (often by 3 months postop) is consistent with data from observational studies, but one of the remaining unknowns about bariatric surgery is the durability of that resolution. The major existing study with prolonged follow-up of bariatric patients comes from Sweden. It revealed a 50% relapse rate at 10 years among patients who had achieved an initial remission of diabetes after their surgeries [8,9]. The current study presents only 12 months of follow-up time, and it will be interesting to see if and how the results change at the termination of the planned 4-year extension study.

Finally, although the effects of bariatric surgery on diabetes are profound, they must be weighed against the health costs of the procedures themselves and the potential long-term consequences (known and unknown) of significantly altering the human digestive pathway. The rate of adverse events requiring hospitalization was particularly high among gastric bypass patients in the year after surgery, and, as stated above, it will be important to see what happens with these and other patients during the planned 4 years of follow-up mentioned by the authors.

Applications for Clinical Practice

In this randomized trial of bariatric surgery versus medication for diabetes, Schauer et al found that surgery was significantly more likely to help patients achieve target A1c levels than comprehensive medical therapy alone. While this is a promising finding, clinicians may want to await results of longer-term follow-up studies before referring diabetic patients for irreversible bariatric procedures.

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