Success (but Unfinished) Story of Metabolic Surgery

Ali Aminian[1] *and Steven E. Nissen*[2]

Diabetes Care 2020;43:1175–1177 | https://doi.org/10.2337/dci20-0006

In patients with type 2 diabetes (T2D), evidence has evolved rapidly in recent years demonstrating major benefits of metabolic surgery on control of blood glucose (1–3) and a wide range of cardiovascular (CV) and renal outcomes (4–6). Historically, the relative risks versus benefits of surgical treatment of obesity remained controversial for two principal reasons: the complicated nature of the surgery and the absence of compelling evidence for meaningful clinical benefits. Both of these concerns have now been substantially clarified, but there remains considerable scientific work to be done.

Surgical treatment of obesity started more than half a century ago with complicated operations such as intestinal rerouting procedures (e.g., jejunoileal bypass). Severe adverse outcomes from these procedures, including malnutrition and liver failure, seemed to outweigh the benefits. Over the years, surgical innovations have resulted in the development of less complicated and less invasive, but metabolically effective, alternative procedures targeting the stomach (e.g., gastric bypass). In parallel, the growing epidemics of obesity and T2D and absence of effective and durable pharmacotherapy for severe obesity have resulted in increased demand for more effective treatments, which has fueled surgical innovations.

The increased acceptance of metabolic surgery has been enhanced by many advancements in minimally invasive surgical techniques, formal training of bariatric surgeons, a rigorous accreditation process for recognition of bariatric surgeons and bariatric centers, and emergence of less invasive procedures (e.g., sleeve gastrectomy). Evidence generated through collaboration between the medical and surgical communities has strongly suggested that the metabolic and CV benefits of surgical procedures extend beyond the effects of weight loss alone (7,8). As a consequence, extraordinary growth in surgical treatment of obesity has occurred during the last two decades, resulting in an estimated 250,000 metabolic procedures performed annually in the U.S. and 700,000 worldwide (9).

Obesity and hyperglycemia are associated with chronic inflammation, increased oxidative stress, ectopic lipid deposition, vascular endothelial dysfunction, and alterations in the metabolism, workload, and structure of myocardium and kidney. These cellular abnormalities can lead to atherosclerotic disease, cardiac arrhythmias, heart failure, and renal dysfunction. Current evidence suggests that the substantial and sustained weight loss with metabolic surgery, along with effects independent of weight loss, can prevent and reverse the detrimental effects of obesity and T2D on many body organs.

The study from Sweden published in this issue of *Diabetes Care* (4) focuses on the renal benefits of metabolic surgery but also reports on the CV effects of that surgery. The incidence of a composite of severe renal disease or a 50% reduction in glomerular filtration rate was significantly lower after Roux-en-Y gastric bypass (RYGB) (hazard ratio [HR] 0.56 [95% CI 0.44–0.71]). In the RYGB group, 305 individuals developed macroalbuminuria, as opposed to 575 in the control group, representing a 45% total risk reduction (4). Considering that T2D is the leading cause of end-stage renal disease in developed countries, these benefits are important and notable.

The Swedish data were extracted by merging four nationwide registries with almost full coverage of Swedish patients who have T2D. In total, 5,321 patients with obesity and T2D who underwent RYGB were matched to nonsurgical patients and followed nearly 4.5 years. Like all observational studies, there were important limitations to the current study. These include the potential for residual measured or unmeasured confounders, particularly since the matching of study groups was based on only four variables. The proportion of missing data was large for some variables. Furthermore, less than 5% of patients in the control group were taking new diabetes medications (e.g., glucagon-like peptide 1 receptor agonists and sodium–glucose cotransporter 2 inhibitors) that are associated with

[1]*Bariatric and Metabolic Institute, Department of General Surgery, Cleveland Clinic, Cleveland, OH*
[2]*Department of Cardiovascular Medicine, Cleveland Clinic, Cleveland, OH*

Corresponding author: Ali Aminian, aminiaa@ccf.org

See accompanying article, p. 1276.

well-documented CV benefits. Despite these limitations, the risk of developing diabetic nephropathy and progressive impairment in renal function was remarkably lower in the surgical group (4).

Although the primary focus of the study was renal outcomes, many other benefits of metabolic surgery were evident. The incidence of heart failure was 67% lower in the surgical group (HR 0.33 [95% CI 0.24–0.46]). Although the risk of developing atherosclerotic CV disease (fatal and not fatal) was lower in the surgical group compared with the control group (HR 0.74 [95% 0.61–0.89]), the benefit was less striking than for heart failure and nephropathy (4).

These findings are consistent with those of previous studies, including recently reported Cleveland Clinic experience. Our series reported that metabolic surgery was associated with a striking 62% lower risk of heart failure and impressive 60% lower risk of renal disease in 8 years. In addition, the risks of coronary artery disease, cerebrovascular disease, and atrial fibrillation were all significantly lower in the surgical group: 31%, 33%, and 22% risk reductions, respectively (5). More than 25 observational studies have now reported survival benefits of surgically induced weight loss (Table 1) (10). Although not tested in the setting of a randomized clinical trial (RCT), the consistency of the finding of lower risk of mortality following metabolic surgery is quite compelling.

It is important to emphasize that the current practice of metabolic surgery is very safe, 20-fold safer than 20 years ago. Early postoperative death occurs in 1 in 1,000 patients (it was 2 in 100 patients two decades ago), and risk of all complications has reached an all-time low of 2–5%. The safety profile of metabolic surgery is actually comparable to commonly performed procedures such as appendectomy, cholecystectomy, knee artheroplasty, and hysterectomy. Given the excellent safety profile of metabolic surgery, earlier intervention with metabolic surgery to treat T2D and metabolic disease may eliminate the need for some later higher-risk procedures to treat the CV and renal complications of T2D and obesity. Nonetheless, if obesity is simply viewed as a self-induced condition secondary to poor lifestyle and wrong choices instead of a progressive multifactorial physiological dysregulation, surgical intervention, even in the presence of solid data on its safety and efficacy, may be viewed an overly aggressive approach (11).

Table 1—Association of metabolic and bariatric surgery with risk of all-cause mortality in 29 comparative observational studies

First author (journal)	Publication year	Reduction in risk of death (%)
MacDonald KG (J Gastrointest Surg)	1997	68
Christou NV (Ann Surg)	2004	89
Flum DR (J Am Coll Surg)	2004	33
Adams TD (N Engl J Med)	2007	40
Busetto L (Surg Obes Relat Dis)	2007	60
Peeters A (Ann Surg)	2007	72
Sjöström L (N Engl J Med)	2007	29
Sowemimo OA (Surg Obes Relat Dis)	2007	82
Perry CD (Ann Surg)	2008	50
Marsk R (Br J Surg)	2010	30
Maciejewski MK (JAMA)*	2011	36
Johnson RJ (Am Surg)	2012	40
Scott JD (Surg Obes Relat Dis)	2013	55
Arterburn DE (JAMA)**	2015	53
Eliasson B (Lancet Diabetes Endocrinol)	2015	58
Guidry CA (Am J Surg)	2015	52
Davidson LE (JAMA Surg)	2016	40
Flanagan E (Am Surg)	2016	68
Lent MR (Diabetes Care)	2017	56
Pontiroli AE (Cardiovasc Diabetol)	2018	48
Reges O (JAMA)	2018	50
Fisher DP (JAMA)	2018	67
Moussa OM (Ann Surg)	2019	51
Kauppila JH (Gastroenterology)	2019	37
Ceriani V (Int J Obes)	2019	36
Aminian A (JAMA)	2019	41
Singh P (Br J Surg)	2020	30
Moussa O (Eur Heart J)	2020	75
Liakopoulos V (Diabetes Care)	2020	42

Table adapted and modified from Aminian et al. (10). *Not significant reduction after propensity matching. **The follow-up study to Maciejewski et al. (2011) reported significant mortality reduction after metabolic and bariatric surgery.

Despite all the advancements and findings in recent decades, the story of metabolic surgery is not finished yet. The mechanisms of action of these procedures have not been adequately characterized. Relentless efforts to further improve the safety of surgery are ongoing. Less invasive endoscopic metabolic procedures (e.g., endoscopic placement of a liner that covers the duodenum and proximal jejunum, or endoscopic burning of duodenal mucosa) are emerging (12). Tools for an individualized approach to match a patient to the right surgical procedure are under development (13–15). Access to care and insurance coverage for metabolic surgery remains problematic, which prevents many patients from gaining access to the most effective therapy for obesity and T2D.

In conclusion, the global intertwined epidemics of obesity and diabetes profoundly threaten global CV health. In patients with obesity, metabolic surgery can reliably achieve two established goals in management of T2D: remarkable glycemic control with strong observational evidence for CV and renal risk reduction. However, despite all the observational data, changing medical practice almost always requires a properly designed and powered RCT. A large well-designed RCT is essential to definitively evaluate the effectiveness of metabolic surgery in reducing CV morbidity and mortality in patients with obesity and T2D. We hope that recent advancements and findings in the field of metabolic surgery bring obesity specialists, diabetologists,

cardiologists, and bariatric surgeons to work closely together for better care of patients.

Duality of Interest. A.A. reported receiving research grants from Medtronic. S.E.N. reported receiving research support from Amgen, AbbVie, AstraZeneca, Cerenis, Eli Lilly, Esperion Therapeutics, Novo Nordisk, The Medicines Company, Orexigen, Pfizer, and Takeda and consulting for a number of pharmaceutical companies without financial compensation (all honoraria, consulting fees, or any other payments from any for-profit entity are paid directly to charity, so neither income nor any tax deduction is received).

References

1. Schauer PR, Bhatt DL, Kirwan JP, et al.; STAMPEDE Investigators. Bariatric surgery versus intensive medical therapy for diabetes—5-year outcomes. N Engl J Med 2017;376:641–651
2. Ikramuddin S, Korner J, Lee WJ, et al. Lifestyle intervention and medical management with vs without Roux-en-Y gastric bypass and control of hemoglobin A1c, LDL cholesterol, and systolic blood pressure at 5 years in the diabetes surgery study. JAMA 2018;319:266–278
3. Mingrone G, Panunzi S, De Gaetano A, et al. Bariatric-metabolic surgery versus conventional medical treatment in obese patients with type 2 diabetes: 5 year follow-up of an open-label, single-centre, randomised controlled trial. Lancet 2015;386:964–973
4. Liakopoulos V, Franzén S, Svensson A-M, et al. Renal and cardiovascular outcomes after weight loss from gastric bypass surgery in type 2 diabetes: cardiorenal risk reductions exceed atherosclerotic benefits. Diabetes Care 2020;43:1276–1284
5. Aminian A, Zajichek A, Arterburn DE, et al. Association of metabolic surgery with major adverse cardiovascular outcomes in patients with type 2 diabetes and obesity. JAMA 2019;322:1271–1282
6. Fisher DP, Johnson E, Haneuse S, et al. Association between bariatric surgery and macrovascular disease outcomes in patients with type 2 diabetes and severe obesity. JAMA 2018;320:1570–1582
7. Batterham RL, Cummings DE. Mechanisms of diabetes improvement following bariatric/metabolic surgery. Diabetes Care 2016;39:893–901
8. Chondronikola M, Harris LL, Klein S. Bariatric surgery and type 2 diabetes: are there weight loss-independent therapeutic effects of upper gastrointestinal bypass? J Intern Med 2016;280:476–486
9. Angrisani L, Santonicola A, Iovino P, et al. IFSO worldwide survey 2016: primary, endoluminal, and revisional procedures. Obes Surg 2018;28:3783–3794
10. Aminian A, Aleassa EM, Bhatt DL, et al. Bariatric surgery is associated with a lower rate of death after myocardial infarction and stroke: a nationwide study. Diabetes Obes Metab 2019;21:2058–2067
11. Aminian A, Brethauer SA, Kirwan JP, Kashyap SR, Burguera B, Schauer PR. How safe is metabolic/diabetes surgery? Diabetes Obes Metab 2015;17:198–201
12. Brunaldi VO, Galvao Neto M. Endoscopic techniques for weight loss and treating metabolic syndrome. Curr Opin Gastroenterol 2019;35:424–431
13. Aminian A, Zajichek A, Arterburn DE, et al. Predicting 10-year risk of end-organ complications of type 2 diabetes with and without metabolic surgery: a machine learning approach. Diabetes Care 2020;43:852–859
14. Aminian A, Brethauer SA, Andalib A, et al. Individualized metabolic surgery score: procedure selection based on diabetes severity. Ann Surg 2017;266:650–657
15. Aminian A, Vidal J, Salminen P, et al. Late relapse of diabetes after bariatric surgery: not rare, but not a failure. Diabetes Care 2020;43:534–540