COMMENTARY

Bariatric/Metabolic Surgery for Diabetes: Lessons From the Past and Present

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One of the most important breakthroughs in diabetes was announced in 1921 by a surgeon-led team working on the gastrointestinal tract. Frederick Banting, a general surgeon in Canada, partnered with a physiologist, John Macleod, and others to purify insulin from pancreatic extracts and demonstrated that this gut hormone could treat diabetes. Eighty years later, more than 30 gut-derived hormones have been described (1), many of which have also been shown to influence glucose as well as lipid metabolism, appetite control, and energy expenditure. And these are just the ones we know about.

Despite its gastrointestinal origins, research into the mechanisms of insulin's action and its use for the treatment of diabetes became the domain of endocrinologists, who to this day, it may be argued, have otherwise ignored the largest endocrine organ in the body to focus on the five or six hypothalamic-pituitary axes. As a result of these efforts, diabetes is now understood to be a chronic disease that manifests when too little insulin is secreted by pancreatic islets in response to the body's needs: an absolute deficiency in the case of type 1 diabetes and a relative insulin deficiency in type 2 diabetes. It is frustrating that, despite nearly 100 years of research since insulin's discovery, the specific causes of insulin resistance and impaired insulin secretion that lead to diabetes remain largely elusive.

Enter the surgeons again. Starting in the latter half of the last century, obesity became an increasingly prevalent medical problem in the U.S. and other developed nations. As obesity rates have risen, so has our understanding of the importance of excess fat storage in expression of insulin resistance and type 2 diabetes. In this issue of *Diabetes Care*, Buchwald and Buchwald (2) chronicle the history of surgical approaches to weight loss in patients with obesity and the subsequent, often dramatic improvement in hyperglycemia and type 2 diabetes these patients experience. In highlighting those surgeons whose key innovations led to today's effective procedures, they can make it seem, in retrospect, that these innovations occurred in an orderly fashion. However, anatomic variations, some minor and some major, were constantly proposed and tested by surgeons. Opinions differed regarding the optimal length of the Roux limb or common channel. The duodenal switch was added to the biliopancreatic diversion in an effort to preserve the pylorus and reduce dumping symptoms. Only recently have common standards for these procedures been widely accepted, thereby assuring patients that regardless of which surgeon they see, both the specifics of the procedure and the outcomes from bariatric procedures will align with published data. Acknowledgment should also be given to the countless numbers of patients with obesity who, through their willingness (some might say their desperation), volunteered to undergo these procedures and either suffered the consequences or helped to establish their benefits.

However, the medical community has historically been wary of bariatric/metabolic approaches to diabetes management, citing a lack of high-quality evidence (e.g., randomized controlled trials) and failure to properly define the mechanisms of diabetes improvement. Buchwald and Buchwald (2) nicely chronicle the initial observational studies from single sites, followed by large prospective cohort studies and the now more than 10 randomized controlled trials that have 3- to 5-year follow-up data consistently showing superior weight loss and diabetes control, or equivalent control with far less diabetes medication use, following bariatric/metabolic procedures compared with intensive medical diabetes management. Counterarguments are given, though, that if patients lose weight through other means, they will achieve the same result. Even the earliest improvements in glucose control have been attributed to the large postoperative drop in calorie intake (3). Buchwald and Buchwald highlight this conceptual issue early in their review. That is, are these procedures simply weight-loss inducing (hence "bariatric") or do they have weight-independent

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effects ("metabolic")? Further, do their mechanisms of action fit simply into either "restrictive" or "malabsorptive" descriptors? As the authors point out, depending on the procedure, it is all of these and more. Regardless of the heterogeneity in entry characteristics of participants and the definitions used for diabetes remission that have characterized surgical publications to date, glucose control improves through both weight loss (4) and weight loss–independent mechanisms (5). Candidate mechanisms abound, ranging from changes in adipokines to a rapidly expanding array of gastrointestinal factors that include not just the previously mentioned gut hormones (6) but also changes in bile acid levels (7,8), nutrient sensing (9), and the microbiome (10). The interface between the gastrointestinal tract and glucolipid metabolism is perhaps one of the most exciting areas of diabetes research today, calling for the integration of multiple disciplines including neuroendocrinology, nutrition, microbiology, hepatology, and metabolism.

Not covered in the review (2) are several areas of common ground shared by bariatric/metabolic surgery and medical management. For example, microvascular and macrovascular complications of diabetes have been shown to improve with medical management (11, 12) as well as bariatric/metabolic surgeries (13), and reductions in cardiovascular events and total mortality have been noted with both (14–18). And while the sleeve gastrectomy and gastric bypass procedures are effectively irreversible, so is committing a patient to lifelong treatment with metformin or insulin. In both cases, diabetes is not "cured" but managed. Finally, variable glycemic responses between individuals occur regardless of which treatment is chosen, as does progressive disease worsening in the long term. For those treated medically, first-line drugs give way to combination therapies over time (19). In the case of bariatric/metabolic surgery, diabetes recurrence after initial remission can approach 40% during long-term follow-up (20–22). Underlying this individual responsiveness and disease progression is, likely, an ongoing decline in β-cell function despite continued treatment (23–25). Similarly, recent data acquired after gastric bypass have shown this procedure (26,27) to now be among a handful of interventions (28) demonstrated to improve islet cell secretory response in patients with diabetes, although that capacity remains tenuous (26,29) and diabetes appears poised to recur with worsening insulin resistance, such as with weight regain. Ironically, if improvement in diabetes outcomes is the primary goal, then bariatric/metabolic surgery should probably be considered even earlier in the disease course, such as in patients with obesity and prediabetes, when the capacity to preserve or restore islet cell function is greatest. However, this would add considerable strain to an already contentious debate regarding health care resource allocation and utilization in the U.S.

The review by Buchwald and Buchwald (2) tends to pass lightly over the complications of bariatric/metabolic procedures, giving the impression that they were anticipated or have been resolved. Not mentioned is a major surgical innovation that led to dramatically improved patient safety, which was the widespread adoption of minimally invasive (laparoscopic) techniques in the 1990s (30). Since then, the immediate surgical risk has been lowered to acceptable levels and is on par with other routine gastrointestinal procedures, such as cholecystectomies (31). However, the determination of the prevalence and severity of longer-term complications, including gastrointestinal complications and bone health, remains a work in progress.

It is fitting that the scientific and clinical communities are returning to the gastrointestinal tract to better understand and manage type 2 diabetes. At many academic centers, surgeons are again partnering with physiologists to continue the tradition of Banting and Macleod. As Buchwald and Buchwald point out, we should not necessarily consider current procedures to be "the last word"; further refinements may lead to safer patient outcomes and even newer breakthroughs in the physiology and treatment of diabetes. Future procedures will still need to be guided by the best science, which will require rigorous training and multidisciplinary research that no doubt surgeons will continue to lead.

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