Metabolic-Bariatric Surgery for Type 2 Diabetes: Time(ing) for a Change

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COMMENTARY

We are fast approaching the 30th publication anniversary of Pories et al.'s provocatively entitled article, "Who Would Have Thought It? An Operation Proves to Be the Most Effective Therapy for Adult-Onset Diabetes Mellitus" (1). His group's intrepid assertion that, compared with gastric bypass, "no other therapy has produced such durable and complete control of diabetes mellitus" anticipated even more impressive reductions in cardiovascular events and total mortality following metabolic-bariatric surgery for type 2 diabetes (2–4). These benefits extend to the pediatric population, as recently acknowledged by the updated American Academy of Pediatric guidelines, which, for the first time, recommend consideration of metabolic-bariatric surgery for eligible adolescents (5).

This is a good time to take stock of the use of metabolic-bariatric procedures for the management of diabetes. The bottom line is that they remain woefully underused (6).

This poor showing could reflect metabolic-bariatric surgery's relatively late entry into the diabetes treatment portfolio. Shortly after its discovery 100 years ago, insulin quickly became a life-saving treatment for type 1 diabetes and then a supplement to the relative insulin deficiency in those with type 2 diabetes, when β-cell function does not keep up with the additional demands imposed by insulin resistance. Subsequent therapies for type 2 diabetes (e.g., metformin and sulfonylureas) improved glycemic control but did not slow what has proven to be a key linchpin in the pathogenesis of type 2 diabetes: a progressive decline in β-cell function (7). These medications were followed by newer therapies (e.g., α-glucosidase inhibitors, thiazolidinediones, glucagon-like peptide 1 receptor agonists, and others) that have demonstrated incremental benefits on glycemic control but with only a handful affecting islet cell responsiveness (8,9).

However, insulin resistance occurs in lockstep with adiposity in all of its manifestations: excess total fat mass, regional (visceral) adipose depot expansion, and ectopic lipid accumulation (liver and muscle) (10). So why has greater attention not been focused on weight loss as a primary therapy for type 2 diabetes? In part, it is because obesity historically has been viewed as a modifiable risk factor along the lines of a lifestyle choice. In this context, weight loss by intensive lifestyle intervention is acceptable despite this approach's limited long-term success for both weight loss amount and diabetes remission (11), pharmacologic obesity treatment is optional, and surgical procedures are a last resort when other therapies have failed and β-cell dysfunction is most advanced. This commonly held belief by patients and providers runs counter to the latest science of obesity as a chronic disease (12), and, along with insurance companies' reliance on a decades-old BMI threshold of $\geq$35 kg/m^2 for approval instead of a more recent evidence-based cutoff of a BMI $\geq$30 kg/m^2 (13), has resulted in only an estimated 1% of the eligible patients electing to undergo metabolic-bariatric surgery (6). This fact brings us back to what has happened since the 1995 Pories et al. (1) publication, where safely achieving 20% or more total weight loss with proportional improvements in insulin sensitivity following metabolic-bariatric surgery is now common (2,14,15). More specifically, what of the impact and timing of metabolic-bariatric surgery on β-cell function?

In this issue of *Diabetes*, Huang et al. (16) report the effect of approximately 35% total weight loss following sleeve gastrectomy on parameters of insulin sensitivity and β-cell function in patients with severe obesity. Insulin sensitivity and β-cell function were assessed by both intravenous and oral glucose challenges at several time points during a 1-year follow-up, and participants underwent detailed body composition measures by dual-energy X-ray absorptiometry, including an estimation of visceral adipose tissue.

Several features of the study design are notable compared with previous publications. First, participants were included who did (n = 36) and did not (n = 23) have type 2 diabetes, allowing study across a spectrum of islet cell function (or dysfunction). Second, in those with diabetes, the median

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duration of 2 years was relatively brief, 60% were not yet taking any diabetes medication, and only two participants were taking insulin. These patient characteristics all point to a stronger likelihood of recovering residual β-cell function and achieving diabetes remission after surgery, which indeed occurred in 94% of the participants (31 of 33) at follow-up.

Insulin sensitivity as measured by both oral and intravenous stimulation studies improved to similar extents in both groups, in strong association with the decline in total body weight, more specifically the reductions in percent body fat and visceral fat. β-Cell function also improved in both groups during both oral and intravenous glucose stimulation, even though stimulated insulin response increased in those with diabetes but counterintuitively declined in those without diabetes. To understand this seeming paradox, it is best to focus on the disposition index, which increased in both groups during follow-up. The disposition index is a simple mathematical relationship in which the product of the stimulated insulin response and insulin sensitivity is a constant (17). An increase in the disposition index indicates an improvement in β-cell function relative to the degree of insulin sensitivity, even if the β-cell function measurement declines. These findings are supported by in vivo and ex vivo data in mice (18) and are nearly identical to those of a recent publication using a similar study design in participants followed for 2 years after gastric bypass (19). In both the current and previous studies, however, even though the gains in β-cell function in those with diabetes were quite impressive, they still remained well below the benefits achieved by the group without diabetes after 1 year. Looking closer at the relative improvements in both groups, β-cell function and/or the disposition index in the group with diabetes after surgery had only recovered enough to reach a level at or below the baseline values in the group without diabetes prior to surgery (16,19). In other words, β-cell function originally lost in transitioning from normoglycemia or prediabetes to diabetes is improved but nowhere near close to being restored, leaving the patient in remission vulnerable to slipping back into diabetes.

Findings in the current (16) and previous studies (19,20) sharpen the focus for treatment options for patients with type 2 diabetes. Per recent American Diabetes Association guidelines (21), in patients in whom weight management is desirable, or roughly 90% of patients with diabetes (22), initial therapy should combine healthy lifestyle with diabetes medications that favor weight loss. It is possible that at some time in the future, newer antiobesity medications will meet or exceed the weight loss following metabolic-bariatric surgery in patients with diabetes (23,24). Until such time, and upon demonstration of long-term benefits on diabetes remission, complications, morbidity, and mortality comparable with those of metabolic-bariatric surgery (2–4) by these medications, the question is not whether metabolic-bariatric surgery should be offered to eligible patients with, or at risk for, diabetes. The question is when. Current American Diabetes Association guidelines imply that these procedures should be reserved until after other therapies have failed (25), effectively relegating surgical treatments to third- or fourth-tier options. However, that timing does not align with the data. If the goal is to preserve or recover β-cell function and give patients the best chance to achieve durable euglycemia, based on what Xin et al. (and others) have shown, a modification of the title of the Pories et al. publication is in order: "Who Would Have Thought It? The Most Effective Therapy for Adult-Onset Diabetes Mellitus Proves to Be an Operation in the Patient *Before They Get Diabetes*."

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