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THERAPIES AND NEW TECHNOLOGIES IN THE TREATMENT OF DIABETES (M PIETROPAOLO, SECTION EDITOR)

Bariatric Surgery in the Treatment of Type 2 Diabetes

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Abstract

Purpose of Review We seek to characterize the impact of bariatric surgery on diabetes mellitus by recalling its history, examining the clinical data, exploring the putative mechanisms of action, and anticipating its future.

Recent Findings Results of clinical trials reveal that bariatric surgery induces remission of diabetes in 33–90% of individuals at 1-year post-treatment versus 0–39% of medically managed. Remission rates decrease over time but remain higher in surgically treated individuals. Investigations have revealed numerous actions of surgery including effects on intestinal physiology, neuronal signaling, incretin hormone secretion, bile acid metabolism, and microbiome changes.

Summary Bariatric surgery improves control of diabetes through both weight-dependent and weight-independent actions. These various mechanisms help explain the difference between individuals treated surgically vs. medically. They also explain differing effects of various bariatric surgery procedure types. Understanding how surgery affects diabetes will help optimize utilization of the therapy for both disease prevention and treatment.

Keywords Bariatric surgery · Metabolic surgery · Diabetes mellitus · Diabetes remission · Obesity

Introduction

"Diabesity" was coined in 1973 to emphasize the pathophysiologic interconnection between the diseases of type 2 diabetes and obesity [1, 2]. Since that time, the acceleration of diabesity's impact on health and economics has led Dr. Paul Zimmet to state that it "is likely to be the biggest epidemic in human history" [3]. Worldwide, 650 million individuals have the disease of obesity and over 400 million individuals have diabetes [4, 5]. The impact of these diseases on morbidity, mortality, quality of life, and healthcare costs have been well-described [6]. Treating individuals with diabetes and obesity results in health improvements and long-term reductions in healthcare costs [7–9]. Unfortunately, significant health improvements can be difficult to attain and/or maintain even with the best available dietary, behavioral, and medication therapies available [2]. As an illustration of this point, the results of a study examining the 2012 claims data from the 50 largest metropolitan areas in the USA revealed that 44% of insured patients diagnosed with diabetes and receiving medication therapy were classified as having "uncontrolled" diabetes [10]. Similarly, conventional, lifestyle-focused weight management strategies face challenges in terms of degree of weight loss, weight maintenance, and attrition [11, 12]. Furthermore, individuals with both obesity and diabetes tend to lose less weight and have more difficulty maintaining a reduced-weight state when compared to individuals without diabetes [13, 14]. As such, there has been a pressing need for therapeutic options beyond the traditional medical tools. Bariatric surgery has emerged as the most effective treatment for weight loss and maintenance. Unsurprisingly, it is also being recognized as a highly effective treatment for type 2 diabetes [15]. Interestingly, the mechanisms by which surgery impacts glucose homeostasis are much more extensive than

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originally expected and continue to be elucidated. In this review, we will describe the clinical problem, the impact of bariatric surgery on diabetes, the physiologic mechanisms for the glycemic effects of surgery, and emerging policy discussions.

Obesity and Diabetes

The connection between obesity and type 2 diabetes has long been recognized [1]. Observationally, the rise in incidence and prevalence of diabetes has mirrored the rise in obesity prevalence rates [16, 17]. However, even though 90% of individuals with type 2 diabetes are obese, a substantially smaller fraction of individuals with obesity develop diabetes [4]. Yet, obesity is thought to be the strongest risk factor for development of type 2 diabetes [18]. This observation can be explained through an understanding of the biology of these diseases. Obesity is associated with various pathophysiologic changes that increase insulin resistance [19]. Despite the increase in insulin demand and decrease in insulin sensitivity, the pancreas can normally compensate by increasing insulin production to maintain glucose homeostasis. In contrast, when an individual with the genetic predisposition for type 2 diabetes is exposed to obesogenic environmental factors (increased fat/carbohydrate/caloric intake; decreased physical activity), pancreatic beta-cell dysfunction, altered adipose tissue function, and weight gain can occur [20]. The combination of progressively declining insulin production capacity and rising insulin resistance results in the inability of the body to maintain euglycemia. Eventually, this can be detected as impaired glucose tolerance and, later, clinical type 2 diabetes [19, 21]. Given the intersection between these processes, weight reduction has been the foundational treatment recommendation for individuals diagnosed with both obesity and diabetes [22]. Unfortunately, conventional methods to facilitate weight loss are unsuccessful for the majority of individuals [2]. Furthermore, many anti-diabetes medications such as insulin, sulfonylureas, meglitinides, and thiazolidinediones are associated with weight gain [23, 24]. Consequently, many individuals with diabetes remain in a vicious cycle where treatments for hyperglycemia can complicate long-term care by exacerbating obesity. Fortunately, weight-negative anti-diabetes treatment options such as glucagon-like peptide-1 receptor agonists (GLP-1 RA) and sodium glucose transporter-2 inhibitors have become available [25]. Yet, the magnitude of the weight loss seen with use of these medications is often insufficient to address severe obesity [26, 27].

After years of observing that shortened guts were associated with weight loss, surgeons in the 1950s started to develop surgical procedures to treat obesity [15]. Over the ensuing decades, surgical options have evolved in pursuit of the goal of optimizing both safety and efficacy. The types of bariatric surgery are reviewed in Table 1 [28–30].

As of 2019, the most commonly performed surgeries are sleeve gastrectomy (SG), Roux-en-Y gastric bypass (RYGB), laparoscopic adjustable gastric band (LAGB), and biliopancreatic diversion with duodenal switch (BPD/DS) [28]. As the techniques have changed and matured, the understanding of the mechanisms by which surgery facilitates weight loss and maintenance of a reduced-weight state has also evolved. At first, weight loss was thought to occur primarily through caloric restriction and/or malabsorption and surgical procedures were categorized based on these presumed mechanisms of action. It is now recognized that most of the current, commonly performed surgeries improve both obesity and its comorbidities (including type 2 diabetes) through pleiotropic effects on intestinal physiology, transcriptional programs in intestinal differentiation programs, neuronal signaling, incretin hormone secretion, bile acid metabolism, lipid regulation, microbiome changes, and glucose homeostasis. For this reason, many prefer to describe these procedures as types of "metabolic surgery" [31, 32]. These observations have led to intensified efforts to assess the impact of surgery on type 2 diabetes and better understand the mechanisms behind its effects.

Impact of Surgery on Type 2 Diabetes

Given the long-recognized association of type 2 diabetes and obesity, it was expected that glycemic control would improve as a result of surgically facilitated weight loss. However, the surprising observation of immediate, post-surgical glycemic improvement suggested short-term mechanisms of action that were distinct from (but complementary to) long-term mechanisms. These provocative anecdotal accounts and ensuing case reports paved the way for several cohort studies published in the 1980s that helped explore the impact of bariatric surgery on type 2 diabetes in both the short and long term. For example, one study of insulin-treated patients with type 2 diabetes recorded an improvement in glycated hemoglobin (HbA1c) from 11.8 to 7.9% following gastric bypass surgery and another study noted 139 of 141 patients were able to discontinue anti-diabetes medications by 4-month post-surgery [33, 34].

These early studies stimulated efforts to quantify the impact of bariatric surgery on type 2 diabetes. Consequently, metrics were needed as part of the assessment process. The chief metric that has emerged is the rate of inducing "diabetes remission." Unfortunately, there has not been consensus on the definition of the term and the ensuing variations complicate review of the data. For example, some early cohort studies defined remission as medication-free euglycemia (i.e., normal range fasting blood sugar and/or HbA1c) while others allowed for continued monotherapy with metformin [35–37]. In 2009,

Table 1 Types of bariatric surgery procedures

Surgery type	Description	Time introduced	Estimated % of total bariatric cases performed from 2011 to 2017
Jejunoileal bypass (JIB)	Bypass of most of the intestines with gastric preservation	1950s	0 (no longer performed)
Roux-en-Y gastric bypass (RYGB)	Gastric pouch creation with bypass of the remaining stomach and first segment of small intestine	Open: 1960s Laparoscopic: 1994	17.8
Mini-gastric bypass (MGB)	Similar to RYGB but with a longer gastric pouch and a longer biliary limb	1997	[a]
Biliopancreatic diversion (BPD) and duodenal switch (DS); (BPD/DS)	BPD: Distal gastrectomy (later: vertical sleeve gastrectomy) with creation of a gastrointestinal anastomosis involving a biliopancreatic bypass DS: BPD modification involving vertical gastrectomy, some duodenal preservation, and duodenal-intestinal anastomosis involving biliopancreatic bypass	BPD: 1979 DS: 1986	0.7
Vertical banded gastroplasty (VBG)	Partition of the stomach using staples and placement of a polypropylene mesh band or ring around the outlet of the pouch	1982	[a]
Gastric banding (GB) and laparoscopic adjustable gastric banding (LAGB)	Gastric partitioning with a ring to create a small upper pouch and the rest of the stomach. Later modified to an inflatable balloon ring	GB: 1978 LAGB: 1986	2.77
Sleeve gastrectomy (SG)	Resection of 80% of the stomach leaving a tube-shaped gastric pouch.	Open: 1988 Laparoscopic: 1999	59.39

[a] All other procedures comprise under 2.5% of total cases

the American Diabetes Association (ADA) published a consensus statement defining complete diabetes remission as demonstrating normal fasting blood glucose levels and/or HbA1c without the use of anti-diabetes medications for at least 1 year. Partial remission was defined as HbA1c < 6.5% and fasting blood glucose less than 126 mg/dL without medications for 1 year [38]. Since then, many of recent studies have used similar definitions [39–42•]. Of note, at the time of manuscript submission, the upcoming revised ADA consensus statement on diabetes remission was still under development.

Regardless of the definitions used, clinical studies have repeatedly demonstrated the significant ability of surgery to improve glucose homeostasis and induce remission. Several large cohort studies comparing bariatric surgery to conventional obesity management have confirmed that bariatric surgery patients are able to achieve diabetes remission more frequently than those who use conventional obesity therapy alone [35–37, 43•, 44•]. For example, in the Swedish Obesity Study (SOS), of 343 patients that underwent bariatric surgery (VBG, LAGB, and RYGB), 72.4% achieved diabetes remission at 2 years, compared to only 16.4% of control patients [35]. Similarly, in a 2019 study that included 1111 patients with diabetes who underwent RYGB, 74% of patients had diabetes remission at 1 year [44•].

While cohort studies provide evidence that bariatric surgery can induce diabetes remission, they may be confounded by factors inherent to the patients that choose bariatric surgery over medical therapy. Additionally, some cohort studies use conventional obesity therapy, which may not include a rigorous, validated weight loss program as the control group [35, 44•], leading to under-estimation of the effectiveness of medical therapy and inflation of the efficacy of bariatric surgery. To address these concerns and improve scientific understanding, randomized controlled trials (RCTs) were conducted. These have been designed to compare the effectiveness of bariatric surgery and lifestyle/medical management to induce diabetes remission. The results of significant trials (cohort and RCT) are summarized in Table 2.

As seen by the studies summarized, there is a wide range of remission rates reported after surgical therapy. The heterogeneity is likely due to the diversity of surgical procedures included, the varied populations studied, and the different definitions of diabetes remission used. Additionally, studies can vary with respect to reporting cumulative remission (counted as any individual who ever achieved remission) and/or prevalent remission (counted as only individuals who were in remission at the time of measurement). Furthermore, some studies correct for attrition while others do not [54]. Despite this variability, the RCTs consistently demonstrate that bariatric surgery has a superior diabetes remission rate when compared to medical therapy. For example, after 1 year of treatment, diabetes remits in a substantial proportion (33–90%) of surgically managed individuals but only in a small minority (0–39%) of medically managed individuals (Table 2). As further evidence of this, a meta-analysis of clinical trials available through 2013 (with follow-up ranging from 40 weeks to 2 years) concluded that the relative risk of attaining diabetes

Table 2 Summary of studies assessing the impact of bariatric surgery on control of diabetes

Date	Reference: first author	Study design	Surgical patients		Control patients	Remission rate: surgical group		Remission rate: control group	Average follow-up (years)	Remission definition
2010	Pournaras [41]	Cohort study	109	RYGB	–	72%	RYGB	–	2–3	FBG < 126 mg/dl, 2 h. OGTT < 200 mg/dL, A1c < 6.0% w/o meds
			107	LAGB		17%	LAGB			
2012	Mingrone [44•]	RCT	20	RYGB	20	75%	RYGB	0%	2	ADA definition[a]
			20	BPD		95%	BPD			
2013	Arterburn [43•]	Retrospective cohort study	4434	RYGB	–	37.1%	1 year	–	3.1	ADA Definition
						63.3%	3 years			
						68.2%	5 years			
2013	Ikramuddin [45]	RCT	60	RYGB	60	44%		9%	1	A1c < 6.0% (secondary outcome)
2013	Liang [46]	RCT	31	RYGB	36 + 34[b]	90%	[c]	0%	1	Off diabetes medications
2014	Halperin [47]	RCT	19	RYGB	19	58%		16%	1	A1c < 6.5% off meds
2014	Sjostrom [48]	Cohort study	55	RYGB	260	30.4%	(composite)	6.5%	15	FBG < 110 mg/dL and no meds
			61	LAGB						
			227	SG						
2015	Courcoulas [49•]	RCT	18	RYGB	14	40%	RYGB	0%	3	ADA Definition
			20	LAGB		29%	LAGB			
2015	Ding [50]	RCT	23	LAGB	22	33%		23%	1	A1c < 6.5% on or off meds
2015	Mingrone [51•]	RCT	20	RYGB	20	37%	RYGB	0%	5	ADA Definition
			20	BPD		63%	BPD			
2016	Cummings [52•]	RCT	15	RYGB	17	60%		5.9%	1	A1c < 6.0%, off all meds
2017	Schauer [53•]	RCT	49	RYGB	38	29%	RYGB	5%	5	A1c < 6.0%
			47	SG		23%	SG			
2018	Courcoulas [54]	Observational Cohort	1738	RYGB	–	60.2%	RYGB	–	7	ADA Definition
			610	LAGB		20%	LAGB			
2018	Ikramuddin [55]	RCT	57	RYGB	56	7%		0%	5	A1c < 6.0% off meds (secondary outcome)
2018	Jacobsen [56]	Registry based cohort study	855	RYGB	956	57.5%	(composite)	14.8%	7.8	No diabetes drugs dispensed
			69	SG						
2018	Lager [57]	Retrospective cohort study	380	RYGB	–	32.1%	RYGB	–	4	A1c < 6.5% off meds
			334	SG		22.0%	SG			
2018	Salminen [58]	RCT	52	SG	–	12%	SG	–	5	ADA Definition (secondary endpoint)
			49	RYGB		25%	RYGB			
2018	Simonson [59]	RCT	19	RYGB	19	42%		0%	3	A1c <6.5% and FBG < 126 mg/dL on or off meds
2019	Madsen [60]	population based cohort	1111	RYGB	1074	74%	1 year	–	5	A1c < 6.5% off meds or A1c < 6.0% on metformin monotherapy
						54%	5 years			

[a] ADA definition: normal fasting blood glucose levels and/or HgbA1c without the use of anti-diabetes medications for at least 1 year

[b] Usual medical care plus exenatide

[b] Diabetes duration of > 10 years was an exclusion criterion

RCT randomized control trial, *RYGB* Roux-en-Y gastric bypass, *LAGB* laparoscopic adjustable gastric banding, *BPD* biliopancreatic diversion, *SG* sleeve gastrectomy, *ADA* American Diabetes Association, *FBG* Fasting blood glucose, *OGTT* oral glucose tolerance test

remission was at least 5 times higher in surgically treated individuals versus non-surgical groups and possibly as much as 22 times higher [55].

Diabetes and Bariatric Surgery: Mechanisms

As the results of the numerous clinical studies have accumulated, many clinical and scientific questions have arisen. The most fundamental of these is: why does diabetes improve after surgery? In keeping with expectations, some degree of glycemic improvement after bariatric surgery is associated with weight loss. Indeed, 75% of patients who did not achieve diabetes remission had weight regain [47]. Insulin sensitivity, a crucial component of diabetes pathogenesis, improves in patients following bariatric surgery to a similar degree as in patients who have lost an equivalent amount of weight using caloric restriction [57, 59, 61]. The weight-dependence of improved insulin sensitivity is further supported in studies comparing SG and RYGB, which have differing effects on gut physiology. In patients that achieved 20% weight loss, both SG patients and RYGB patients achieved similar improvements in insulin sensitivity [62].

Somewhat less expected has been the discovery that the microbiome may contribute to improvement in glucose homeostasis following bariatric surgery. While it is unclear if changes in the gut microbiome cause metabolic improvement, or occur because of metabolic improvement, the gut microbiome is markedly altered following bariatric surgery with increased microbiome diversity within 3 months [63–66] in both RYGB and VBG. In rodents, fecal transplant from either mice or humans that have undergone RYGB into germ-free rats fed a high-fat diet results in weight loss and improvement in glycemic parameters, suggesting that, regardless of what causes the microbiome to change, the post-RYGB microbiome improves glycemic control [67, 68].

A striking feature of bariatric surgery is the rapid improvement in glycemic control that precedes weight loss. In some of the earliest case reports, authors remarked that some patients were insulin-free at the time of discharge despite having presurgical insulin requirements of hundreds of units [34]. What are the mechanisms that drive these rapid, weight-independent improvements in glucose homeostasis? The answer to this question is rather complex but starts with alterations in gut hormones which are worth reviewing here.

Glucagon-like peptide 1 (GLP-1) is a gut hormone secreted from intestinal neuroendocrine L cells which induces the "incretin effect" of increasing insulin secretion and glucose clearance in response to oral glucose. Following bariatric surgery, post-prandial GLP-1 levels are increased, leading to improved beta-cell glucose sensitivity and lower post-prandial blood glucose [69–72]. In mice lacking the GLP-1 receptor (GLP-1R KO mice), continued improvements in glucose homeostasis following SG and RYGB are observed [73–75], as occurs in patients treated with a GLP-1 receptor antagonist following bariatric surgery [76].

Other gut hormones that may contribute to improved glucose homeostasis include PYY and oxyntomodulin, both of which are increased following bariatric surgery. Indeed, a recent clinical trial of subcutaneous GLP-1, PYY, and oxyntomodulin combination therapy for 4 weeks demonstrated improved post-prandial glycemic control similar to that of RYGB patients [77].

As practice patterns evolved and as SG has superseded RYGB as the most commonly performed bariatric surgery [28], most recent studies have focused on comparisons between these two procedures. Based on these studies, it appears that patients who undergo "more" rearrangement of their GI tract have a small, but reproducible, improvement in long-term glycemic control compared to patients undergoing less drastic procedures. This is demonstrated by a recent meta-analysis that reviewed 16 RCTs comparing glycemic outcomes in patients who underwent SG versus RYGB and found that patients who underwent RYGB had lower fasting blood sugar and lower A1c at 3 years following surgery [78•]. In further support of this hypothesis, the lowest remission rate is reported for LAGB, which does not alter the gut anatomy, with a 1-year diabetes remission rate of 33% [79].

Why do some procedure types affect glycemic control more than others? Historically, two competing (but not mutually exclusive) hypotheses have emerged to explain how gut rearrangement leads to improvements in glycemic control: the hindgut hypothesis and the foregut-exclusion hypothesis.

The hindgut hypothesis states that bypassing the proximal small bowel causes rapid transit of nutrients into the distal bowel, increasing secretion of gut hormones such as GLP-1 and PYY. This is supported by rodent studies in which anastomosing the ileum to the proximal bowel increases gut transit time [80], while post-surgical GLP-1 levels are higher in rats that underwent RYGB than in those that underwent SG [81].

The foregut-exclusion hypothesis posits that exclusion of nutrients from the duodenum and proximal jejunum decreases secretion of an as-yet unidentified signal that increases insulin resistance. This hypothesis has been tested in rodent studies as well. Rats received either duodenojejunal bypass, which completely excludes nutrients from the duodenum and proximal jejunum, or gastrojejunostomy, in which nutrients are able to rapidly reach the distal jejunum, but still have access to the duodenum. Rats that underwent duodenal-jejunal bypass had a significant improvement in their glucose tolerance, while the gastrojejunostomy rats did not, leading to the proposal of "anti-incretin" factors secreted from the duodenum [82]. Based on these findings, less invasive metabolic surgeries are now under investigation that simply ablates the duodenal mucosa, known as duodenal mucosal resurfacing [83].

Another metabolic pathway that is altered following rearrangement of the gut is bile acid signaling. Serum bile acid concentrations and composition change following RYGB and SG, but not following LAGB. Bile acids act as hormones that bind to the hormone receptor FXR and lead to improvements in glucose tolerance [84–89]. In rodent studies, improvements in glucose tolerance following VSG are reduced in mice lacking FXR or its binding partner TGR5 [88, 89]. However, pharmacologic studies in rodents have also shown that both inhibition and activation of FXR result in improved metabolic phenotypes accompanied by weight loss, thus the specific effect of activating FXR-signaling is unclear.

Failure to Achieve Diabetes Remission and Relapse of Diabetes

While bariatric surgery clearly demonstrates a high ability to induce remission of type 2 diabetes, the clinical trial data also reveal that remission is not attained in all individuals. Understanding the factors that predict glycemic response to surgery is critical in determining which patients are most likely to achieve diabetes remission. Several studies have addressed this question and the factors that are most associated with diabetes remission include shorter duration of diabetes prior to surgery (< 4 years), higher C-peptide, younger age, and use of only oral agents or diet to control diabetes [90–93]. While these collective data demonstrate the short-term efficacy of bariatric surgery, the durability of diabetes remission remains a pressing clinical question. Even though the majority of individuals will have long-term improvements in diabetes metrics (i.e., HbA1c < 7%, reduction in anti-diabetes medications, and reduction in complication rates), sustained remission is experienced by only a minority. Studies evaluating long-term outcomes have demonstrated an almost 50% relapse rate for patients who achieve diabetes remission [39, 44•, 47, 48, 50]. For example, 15-year follow-up data from the SOS revealed that rates of diabetes remission (defined as blood glucose levels under 110 mg/dL without anti-diabetes medication use) drop from 72.4% at 2 years post-surgery to 38.1% at 10 years and further to 30.4% at 15 years [60]. This is replicated in RCTs, as well. In a 2015 study conducted by Mingrone and colleagues in which individuals were randomized to medical therapy ($n = 20$), RYGB ($n = 20$), or BPD ($n = 20$), ADA partial remission was achieved at 2 years in 0, 75%, and 95% of individuals in these respective groups. By 5 years, the rates were 0, 37%, and 63% [47]. The factors that predict remission also contribute to achieving sustained remission. Predictors of relapse include insulin use and a longer duration of diabetes prior to surgery, with an HR of 1.13 for every additional prior year of having a diabetes diagnosis [39].

Impact of Bariatric Surgery on Diabetes-Related Complications and Prevention

While diabetes remission rates are an important metric for assessing bariatric surgery's impact on type 2 diabetes, health benefits are not exclusively conferred to individuals attaining remission. Multiple cohort studies and RCTs demonstrate that patients who undergo bariatric surgery experience a significant reduction in the use of both oral anti-diabetic medications and insulin. In one study, there was an 87% reduction in oral medication use and a 79% reduction in patients who continue to require insulin [36, 41, 47, 49•]. Our own data from a real world setting suggest 68.7% vs 56.0% reduction in diabetes medication usage after GB versus SG [52•]. Moreover, the years spent in good control are known to have a legacy effect for the subsequent decade in terms of fewer diabetes complications. Therefore, it is not surprising that bariatric surgery is also associated with a decreased incidence rate of both diabetes-related microvascular and macrovascular complications and decreased mortality. In the 15-year follow-up of the SOS, microvascular complications were 20.6 per 1000 person-years in the surgical patients as compared to 41.8 per 1000 person-years in controls (HR of 0.44 for the surgical patients). Additionally, macrovascular complications were also lower in the surgical group (31.7 per 1000 person-years) as compared to the control group (44.2 per 1000 person-years) with an HR of 0.68 for surgical patients. Perhaps most importantly, this study and several others have also shown decreased long-term mortality in surgical patients [60, 94, 95].

Studies have also examined the effect of bariatric surgery on prevention of diabetes development. In the SOS trial, bariatric surgery reduced the risk of developing diabetes by 96% at 2 years post-intervention and 78% at 15 years [60, 96]. Given the data on complications and prevention, bariatric surgery is being recognized as a valuable tool for disease and complication prevention, not just treatment [97].

Bariatric Surgery: Diabetes Treatment Guidelines

Globally, consideration for bariatric surgery generally occurs for individuals that meet the 1991 National Institutes of Health (NIH) criteria [98]. Qualifying individuals must have a body mass index (BMI) $\geq$ 40 kg/m^2 or BMI $\geq$ 35 with a serious weight-related comorbid health condition (such as diabetes). Yet, studies such as the STAMPEDE trial have included participants with lower BMIs than the NIH criteria and provided evidence of benefit for these patients [49•].

Based on the growing body of evidence and the expanded understanding of the mechanisms of actions of metabolic surgeries, there has been a growing movement to expand the eligibility criteria for surgery. In 2016, the

2nd Diabetes Surgery Summit (DSS-II) was convened which led to a consensus statement for the use of surgery as a primary treatment method for type 2 diabetes. A joint statement of the partner societies (including the ADA, the International Diabetes Federation, Diabetes UK, the Chinese Diabetes Society, and Diabetes India) was released and called for bariatric surgery to be "considered in patients with class I obesity (BMI 30.0–34.9) and inadequately controlled hyperglycemia despite optimal medical treatment by either oral or injectable medications (including insulin)" [99]. This statement falls short of acknowledging the racial and ethnic differences of adiposity and the resulting metabolic complications across populations of the world. It will be interesting to see if the improved understanding of these differences will lead to recommendations for surgical interventions at lower adiposity ranges in populations where metabolic consequences of increased adiposity are noted at much lower BMI levels.

Conclusion

Diabetes and obesity pose individual and global health challenges to a scale that is unprecedented. While many conventional medical therapeutic options are available, they are not universally effective due to myriad physiological, behavioral, and financial barriers. Bariatric surgery has emerged as the single most effective treatment option for type 2 diabetes and obesity. It must be acknowledged that surgery does not address the fundamental problem of overabundance of energy availability. Yet, though not a panacea for the environmental challenges, or a cure for these diseases, surgery significantly decreases their burden through weight-dependent and weight-independent mechanisms. Furthermore, elucidating these mechanisms improves the understanding of the diseases, themselves. Consequently, bariatric surgery serves as both an illuminating scientific model and an effective treatment tool to address the diabesity crisis.

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Compliance with Ethical Standards

Conflict of Interest Alison H. Affinati, Nazanene H. Esfandiari, and Andrew T. Kraftson declare that they have no conflict of interest.

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- • Of importance
- •• Of major importance

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