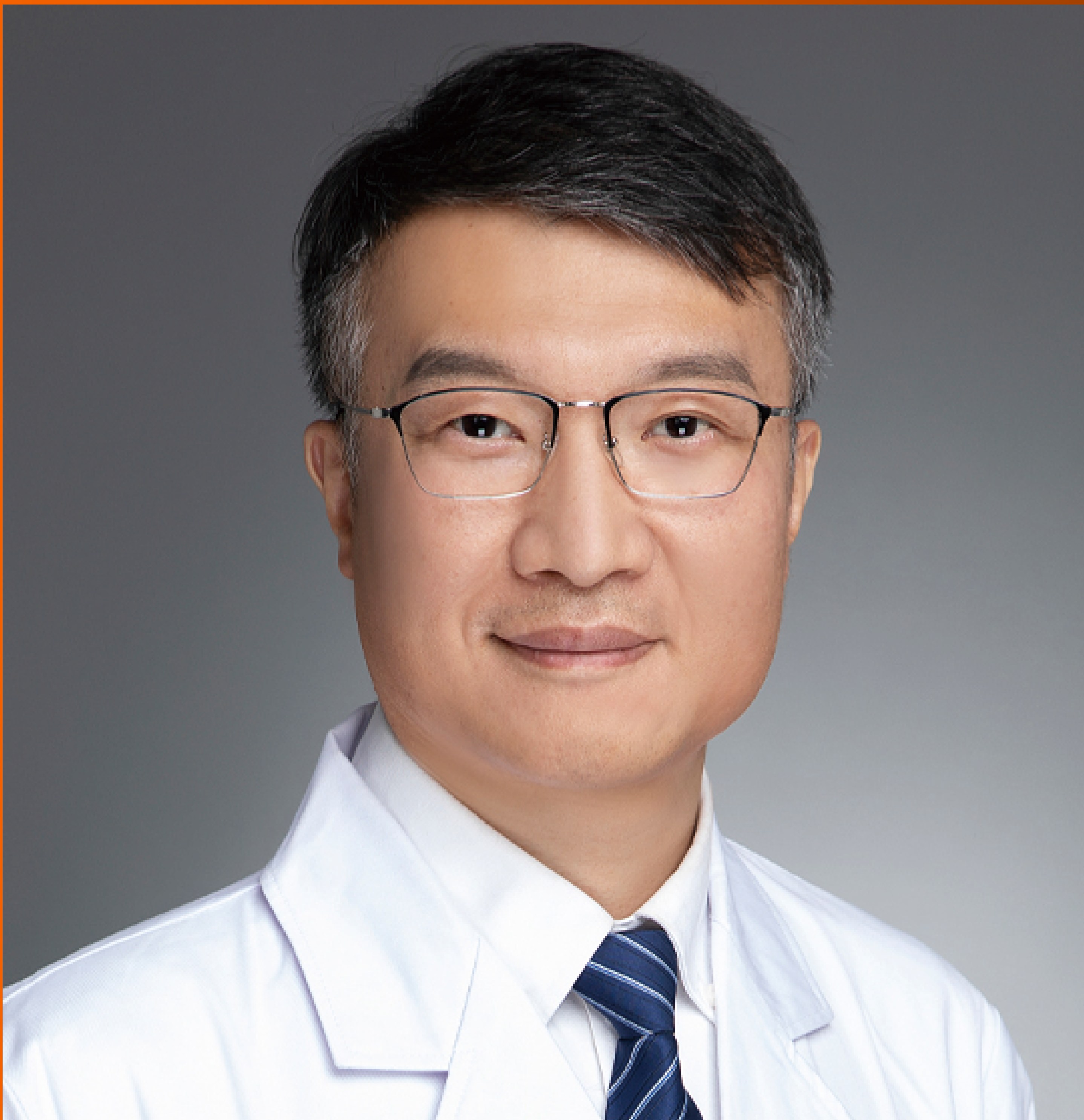
ISSN 1948-9358 (online)

World Journal of *Diabetes*

World J Diabetes 2021 July 15; 12(7): 916-1140



Published by Baishideng Publishing Group Inc

World Journal of Diabetes

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World Journal of Diabetes

Monthly Volume 12 Number 7 July 15, 2021

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RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Li-Li Wang*; **Production Department Director:** *Yu-Jie Ma*; **Editorial Office Director:** *Jia-Ping Yan*.

NAME OF JOURNAL
World Journal of Diabetes

ISSN
ISSN 1948-9358 (online)

LAUNCH DATE
June 15, 2010

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Timothy Koch

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/1948-9358/editorialboard.htm

PUBLICATION DATE
July 15, 2021

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World J Diabetes 2021 July 15; 12(7): 1093-1101

DOI: 10.4239/wjd.v12.i7.1093

ISSN 1948-9358 (online)

MINIREVIEWS

Diabetes remission after bariatric surgery

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Author contributions: Chumakova-Orin M, Vanetta C performed research and wrote the paper; Moris D and Guerron AD contributed critical revision of the manuscript for important intellectual content.

Conflict-of-interest statement: Authors have nothing to disclose.

Manuscript source: Invited manuscript

Specialty type: Surgery

Country/Territory of origin: United

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Abstract

Over the last decade, obesity rates have continued to rise in the United States as well as worldwide and are showing no signs of slowing down. This rise is in parallel with the increasing rates of type 2 diabetes mellitus (T2DM). Given the association between obesity and T2DM and their strong correlation with increased morbidity and mortality in addition to healthcare expenditure, it is important to recognize the most effective ways to combat them. Thus, we performed a review of literature that focused on assessing the outcomes of T2DM following bariatric surgery. Available evidence suggests that bariatric surgery provides better T2DM resolution in obese patients when compared to best medical management alone. Additionally, Biliopancreatic diversion with duodenal switch as well as Roux-en-Y gastric bypass have demonstrated higher rates of T2DM resolution when compared with other bariatric procedures.

Key Words: Bariatric surgery; Diabetes; Remission; Gastric Bypass; Obesity

Core Tip: Bariatric surgery is a safe and effective way to achieve diabetes remission in those with obesity *via* a variety of mechanisms, the majority of which are independent of weight loss. Available evidence suggests that bariatric surgery provides better type 2 diabetes mellitus resolution in obese patients when compared to best medical management alone.

Citation: Chumakova-Orin M, Vanetta C, Moris DP, Guerron AD. Diabetes remission after bariatric surgery. *World J Diabetes* 2021; 12(7): 1093-1101

URL: https://www.wjgnet.com/1948-9358/full/v12/i7/1093.htm

DOI: https://dx.doi.org/10.4239/wjd.v12.i7.1093

States

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

Received: January 28, 2021
Peer-review started: January 28, 2021
First decision: May 3, 2021
Revised: May 10, 2021
Accepted: June 25, 2021
Article in press: June 25, 2021
Published online: July 15, 2021

P-Reviewer: Marchesi F
S-Editor: Liu M
L-Editor: A
P-Editor: Li JH

INTRODUCTION

Obesity rates continue to rise in the United States as well as worldwide. In fact, obesity prevalence doubled from 15% to 33% between 1980s and 2004 and was estimated to be 37.7% from 2013 to 2014[1,2]. Interestingly, some of the recent reports project that nearly 1 in 2 United States adults will have obesity [defined as body mass index (BMI) ≥ 30 kg/m^2] by 2030 and nearly 1 in 4 adults will have severe obesity (defined as BMI ≥ 35 kg/m^2) by then[3]. These numbers are alarming as obesity has been linked to developing type 2 diabetes mellitus (T2DM), coronary artery disease, non-alcoholic fatty liver disease, malignancy, amongst others, as well as lower life expectancy. Obesity was also attributable to 365000 deaths in 2000, second to only tobacco smoking [4]. Insulin resistance has been described as the main culprit for the development of T2DM in obese patients[5]. In fact, there is a > 6-fold increase in risk of developing T2DM in those with morbid obesity or BMI ≥ 40 kg/m^2[6]. Diabetes remains one of the most prevalent chronic diseases in the United States affecting about 9% of the population in 2011, with rates continuing to grow in parallel with obesity[6].

This association between obesity and diabetes has detrimental effects on morbidity and mortality and creates a significant economic burden as a result. The cost of diabetes in 2012 was reported to be 45 billion dollars, with 69 billion dollars attributed to reduced productivity and 176 billion dollars attributed to direct medical costs[7]. Additionally, the cost of diabetes is projected to reach nearly 500 dollars billion by 2030[8]. This has led to an increased interest in finding ways to successfully treat diabetes and maintain remission.

While lifestyle modifications such as diet and exercise along with pharmacotherapy can be successful in treating both obesity and T2DM, few achieve sustained weight loss and only 10% of those with T2DM achieve favorable disease control in order to minimize and prevent long-term complications[9]. This article will thus focus on reviewing the most current data on diabetes remission following bariatric surgery.

ASSOCIATION OF T2DM AND OBESITY

Obesity has been linked to the development of T2DM *via* insulin resistance. Several mechanisms have been described. One of such proposed mechanisms involves increased release of a variety of factors including non-esterified fatty acids (NEFAs), glycerol, leptin, adiponectin, proinflammatory cytokines among others from adipose tissue which in turn leads to insulin resistance[10]. This occurs *via* reduced phosphorylation of phosphatidylinositol-3-OH kinase in muscle and increased gluconeogenic enzyme expression in the liver[9]. While this leads to insulin resistance, not all obese patients will go on to develop T2DM as they are able to overcome this by increased insulin release from pancreatic β cells to correct for decreased insulin sensitivity[9]. Thus, those with β cell dysfunction are at the highest risk of developing T2DM *via* increased release of NEFAs as they not only reduce insulin sensitivity but also decrease pancreatic β cell function[9].

Standard treatment of T2DM focuses on achieving good glycemic control in order to minimize cardiovascular and other risks and is mainly achieved *via* medical management. However, this treatment modality can become challenging in patients with obesity as a variety of pharmacotherapy agents can in fact cause weight gain and thus further worsen insulin resistance[11]. This is when bariatric surgery comes into play. Though initially described as surgical treatment for weight loss, bariatric surgery has demonstrated significant effects on reducing rates of T2DM in addition to improving cardiovascular health and thus reducing morbidity and mortality[12]. These beneficial effects are achieved *via* a multitude of mechanisms beyond weight loss.

MECHANISMS OF T2DM REMISSION FOLLOWING BARIATRIC SURGERY

Weight loss

While the exact mechanism for T2DM remission following bariatric surgery is not fully understood, several have been proposed. One such mechanism involves reduced caloric intake which in turn leads to significant weight loss and subsequently improved glucose sensitivity. This was thought to be achieved *via* restrictive and/or malabsorptive properties of bariatric surgery. However, this does not explain some of the drastic effects seen on glucose control immediately following surgery, and thus the majority of glucose-lowering is achieved prior to weight loss[13]. Additionally, scintigraphy studies demonstrate that nutrient delivery through gastric pouch is actually increased rather than restricted following Roux-en-Y gastric bypass (RYGB)[14].

Insulin sensitivity

One of the most important factors contributing to improved glucose tolerance is a significant decrease in insulin resistance fairly early following bariatric surgery. In fact, insulin resistance decreases about 50% in 1 wk following surgery and into the normal range seen in glucose tolerant patients when measured homeostatic model assessment of insulin resistance[15-17]. In addition to improved liver insulin sensitivity, insulin clearance also increases and is thought to be due to decreased caloric intake which in turn leads to decreased liver fat content. This has been demonstrated using post-operative magnetic resonance imaging of the liver following RYGB[14]. These combined effects in turn lead to decreased basal glucose concentration and are thought to improve pancreatic β cell function by decreasing the toxic effect of glucose[18].

Foregut/hindgut hypothesis

According to the foregut-hindgut hypothesis, there is an increased amount of incompletely digested food delivered to the distal intestine due to bypassed foregut. This in turn stimulates specialized L cells which facilitate the release of glucagon-like-peptide-1 (GLP-1) and peptide YY, both of which have been implicated in achieving weight loss. Additionally, both provide a favorable effect on pancreatic β cells leading to increased insulin sensitivity[18,19]. Interestingly, GLP-1 Levels rise dramatically within days of bariatric surgery stimulating pancreatic β cells. This effect of β cell stimulation is further amplified by a temporary early increase in plasma glucose levels eventually leading to increased insulin release[17]. While this hypothesis may explain the benefits seen following RYGB and biliopancreatic diversion with duodenal switch (BPD-DS), it does not explain the beneficial effects on glucose metabolism seen following sleeve gastrectomy (SG) as the intestinal tract remains in continuity[16].

Bile acids

Circulating bile acids (BA) levels also increase following bariatric surgery and are correlated with improved glucose sensitivity. This is thought to occur following reduced mixture of partially digested nutrients with BAs following surgery thus leading to higher concentration of free circulating BAs. This, in turn, leads to reduction in hepatic glucose production as well as glucogeogenesis within gut segments that are devoid of BAs[20].

METHODS

A comprehensive search of the published literature in PubMed, PubMed Central (PMC), EMBASE, Medline, and the Cochrane Register of Controlled Trials databases was conducted until January 2021. We used the guidelines of 2015 Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P). Randomised controlled trials with at least 12 mo of follow-up and prediction models of diabetes remission after bariatric surgery were included. Keywords containing "obesity", "metabolic [or] bariatric surgery", "type 2 diabetes", "diabetes remission", "predict", "prediction models" and "score" were constructed for inclusion. Only studies in english language were included.

TRIALS COMPARING T2DM REMISSION FOLLOWING BARIATRIC SURGERY

Mingrone *et al*[12] designed a randomized clinical trial (RCT) looking at 60 patients who were randomly assigned to one of the 3 groups: Conventional medical therapy, RYGB or BPD-DS. Their primary endpoint included diabetes remission which was defined as fasting glucose level < 100 mg/dL and glycosylated hemoglobin (HbA1c) < 6.5mmol/L without the use of pharmacotherapy. Fifty-six patients completed their 2 year follow up and at that time no patients in the medical group achieved remission while 75% in the RYGB and 95% in the BPD-DS were able to achieve remission (P < 0.05). Additionally, while the HbA1c levels did decrease significantly in all 3 groups from average baseline of 8.65% ± 1.45%, the 2 surgical groups had greater degree of lowering with average numbers at 2-year follow up being the following: 7.69% ± 0.57% for the medical group, 6.35% ± 1.42% in the RYGB group and 4.95% ± 0.49% in the BPD-DS group. The authors of this study concluded that bariatric surgery was able to achieve higher rates of remission in patients with severe obesity (BMI ≥ 35 kg/m^2), and HbA1c < 6.5 mmol/L without the use of pharmacotherapy[12].

Calorie reduction or surgery: Seeking to Reduce Obesity and Diabetes Study was an RCT that assigned patients with obesity (BMI ≥ 30 kg/m^2) and T2DM to either RYGB (*n* = 23) or intensive lifestyle and medical management (*n* = 20). Patients were followed for 1 year with primary outcome measured being T2DM resolution (defined as HbA1c <6% and being off medications). During this follow up, 60% of patients following RYGB achieved remission while nearly 6% of the medical group were able to do so (*P* < 0.05). This study reported no life-threatening complications in the surgical group. The authors concluded that RYGB yielded higher rates of T2DM remission at 1 year when compared to medical therapy alone[21].

Surgical Treatment and Medications Potentially Eradicate Diabetes Efficiently (STAMPEDE) RCT published by Schauer *et al*[22] in 2017 provides some of the longer-term data shedding light on the effectiveness of bariatric surgery on T2DM resolution. The study randomized 150 patients with obesity and T2DM to intensive medical therapy alone *vs* medical therapy and either RYGB or SG.One hundred and thirty-four patients completed 5 year follow up with primary endpoint being achievement of HbA1c level of ≤ 6%. Of those who underwent intense medical therapy alone, 5% were able to achieve this endpoint *vs* 29% of those who also underwent RYGB (adjusted *P* < 0.05) and 23% of those who underwent SG (adjusted *P* = 0.07). In the surgical group, this endpoint was achieved without the need for hypoglycemic medications in the majority of patients, whereas none of the patients in the medical group were able to achieve that endpoint without pharmacotherapy. Additionally, 89% of patients in the surgical group were off insulin during a 5 year follow up compared to 61% of patients in the medical group[22].

Hofsø *et al*[23] designed a triple blind RCT that was conducted in Norway comparing 109 patients with morbid obesity and presence of T2DM who were randomly assigned to SG (55/109) or RYGB (54/109). The primary outcome measured during their 1 year follow up was diabetes remission defined as having HbA1c ≤ 6% while being off pharmacotherapy. 107/109 patients completed 1 year follow up demonstrating that 47% of SG patients had diabetes remission and 74% of RYGB patients had diabetes remission (*P* < 0.05). This study also reported 57 adverse reactions during a follow up period with 1 patient returning back to the operating room following an intra-abdominal bleed following SG, 1 patient needing blood transfusions 10 days following RYGB. No deaths were observed in this study. Thus, the authors concluded that even though pancreatic β cell function improved after both types of surgery, RYGB was found to have greater effect on T2DM resolution when compared to SG at 1 year[23].

Another recent 3-arm RCT assigned 61 patients with obesity and T2DM to one of the 3 groups: RYGB, adjustable gastric banding (AGB) or intense medical therapy and were followed for 1 year initially. After 1 year follow up, the patients were assessed for additional 4 years following introduction of lower-level lifestyle interventions. Primary endpoint of this study was T2DM remission rates (partial: Fasting plasma glucose (FPG) ≤ 125 mg/dL, HbA1c < 6.5% and off medications and complete: FPG ≤ 100 mg/dL, HbA1c < 5.7% and off medications). At 5 years, partial or complete T2DM remission was achieved in 30% of RYGB group, 19% of AGB group and 0% of medical management group (*P* < 0.05). Additionally, 56% of RYGB patients were off medications at 5 years as compared to 45% of AGB group and 0% of medical management group (*P* < 0.05). Thus, the authors concluded that their surgical management was more effective in T2DM resolution than best medical management alone[11].

More recently, a study by Mingrone *et al*[24] published their 10 year follow up results comparing metabolic surgery and medical management for T2DM at a single center in Italy. This RCT included 3 treatment arms: BPD-DS, RYGB and medical management. They had 20 patients in each arm group with 60 patients total, 57 of which completed follow up. Remission was defined as FPG ≤ 100 mg/dL, HbA1c ≤ 6.5% and being off medications. Ten-year remission rates in the intention-to-treat analysis demonstrated that 5.5% [95% confidence interval (CI) 1.0-25.7] of medical group achieved remission when compared to 50% in BPD-DS [95%CI 29.9-70.1] group and 25% in RYGB [95%CI 11.2-49.9] group (*P* < 0.05)[24] (Table 1).

Table 1 Bariatric surgery *vs* medical management for type 2 diabetes mellitus remission

Ref.	Pts w/ follow up/enrolled pts	Study duration, years	Medical management T2DM resolution %	RYGB T2DM resolution %	SG T2DM resolution %	BPD-DS T2DM resolution %	AGB T2DM resolution %	T2DM resolution definition	*P* value
Mingrone *et al*[12], 2012	56/60	2	0	75	N/A	95	N/A	FPG < 100 mg/dL + HbA1c < 6.5 mmol/L + no pharmacotherapy	< 0.05
Cummings *et al*[21], 2016	43/43	1	6	60	N/A	N/A	N/A	HbA1c < 6% + no pharmacotherapy	< 0.05
Schauer *et al* [22], 2017	134/150	5	5	29	23	N/A	N/A		< 0.05
Hofsø *et al* [23], 2019	107/109	1	N/A	74	47	N/A	N/A		< 0.05
Courcoulas *et al*[11], 2020	50/61	5	0	30	N/A	N/A	19		< 0.05
Mingrone *et al*[24], 2021	57/60	10	5	25	N/A	50	N/A		< 0.05

T2DM: Type 2 diabetes mellitus; RYGB: Roux-en-Y gastric bypass; SG: Sleeve gastrectomy; BPD-DS: Biliopancreatic diversion with duodenal switch; AGB: Adjustable gastric banding; FPG: Fasting plasma glucose; HbA1c: Glycocylated hemoglobin.

PREDICTORS OF DIABETES REMISSION AFTER BARIATRIC SURGERY

Several prediction models have been developed in order to assess diabetes remission following bariatric surgery. The models used are either scoring systems, in which each variable is given a specific score and the addition of scores gives the probability of diabetes remission; or a logistic regression model in which higher odds means a higher probability of diabetes remission[25]. Relevant scoring systems include the DiaRem, age, bmi, c-peptide level and duration of diabetes score (ABCD), and individualized metabolic surgery scores (IMSS).

DiaRem and DiaRem2

This model described by Still *et al*[26] in 2014 is based on a retrospective study of 690 diabetic obese patients who underwent RYGB. The preoperative factors which demonstrated to be independent predictive factors of diabetes remission were: Age, insulin use, HbA1c measurement, and type of antidiabetic medications. Preoperative insulin use was associated with the higher severity of diabetes and lower percentage of remission and was given the highest score of 10 points. The score range goes from 0 to 22, and the patients fall into one of five groups. The higher the score, the lowest the probability of diabetes remission.

Additionally, in 2019, the DiaRem2 score incorporated the duration of diabetes to the already validated DiaRem[27]. The association between “early remission” (defined as remission within the first 2 mo after surgery) and duration of diabetes, as well as early remission and score was analyzed. Patients were allocated into one of three remission groups according to their score: High (0-5), Intermediate (6-12) or Low (13-25). A highest score was associated with a decreased percentage of early remission.

ABCD

In this score proposed by Lee *et al*[28] in 2013, a first cohort of 63 patients who underwent either RYGB or mini-gastric bypass in Asia was analyzed. The four preoperative factors identified as independent risk factors for remission were: Age, baseline BMI, C-peptide level, and duration of diabetes. Patients with higher scores had higher remission rates. A modified scoring system was then tested in 510 patients, including SG patients. It showed lower remission levels after SG than those correlated to RYGB. One of the limitations of this score was that insulin and other antidiabetic medications used were not taken into account.

IMSS

IMSS was designed by Aminian *et al*[29] with the objective to guide procedure selection based on long-term diabetes remission. A sample of 659 patients who underwent RYGB or SG was analyzed. Duration of diabetes, number of diabetes medications, insulin use, and HbA1c were the four independent predictors used to develop this score. Patients were allocated into one of three stages of diabetes severity. This study included recommendations on what type of surgery to perform: RYGB for mild disease and moderate disease, and SG for severe disease. In severe diabetes, the rate of remission is lower, so the least demanding technique is preferred. Unfortunately, biliopancreatic diversion with duodenal switch was not included in this score even though this procedure has been associated with higher remissions of associated comorbidities.

Improved DiaRem model

The general limitations of the scoring systems commented is that they were based on one or two procedure types, with RYGB as the leading procedure, and they are usually limited to a population with a defined race/ethnicity. That is why Duke Group developed a logistic regression model including a diverse racial/ethnicity and a large BPD/DS sample[30]. This model was based on a retrospective review of 602 patients who underwent RYGB, SG, LAGB or BPD/DS. The objective was to analyze the relation of remission to procedure type. DiaRem score was used to assess the performance of this model in their cohort. The results showed BPD/DS patients have an approximately 229% increase in odds of having remission at 1 year compared with RYGB patients (adjusted OR 3.29; 95%CI: 1.27, 8.5).

Independent of the predictive model used, the procedure type is an independent risk factor for diabetes remission. Our results indicate BPD/DS as the procedure with a higher percentage of diabetes remission (Table 2). We believe that this procedure should be taken into account in future tools that include a recommendation of the procedure of choice.

CONCLUSION

Bariatric surgery is a safe and effective way to treat T2DM in those struggling with obesity. The effects can be seen fairly early prior to any substantial weight loss, thus highlighting the interplay of hormonal factors that leads to increased insulin sensitivity *via* activation of pancreatic β cells.

Several efforts have been made to prove the effectiveness of bariatric surgery in diabetes remission, including randomized clinical trials with 1, 3, 5 and even 10 years of follow-up. A variety of bariatric surgical procedures have demonstrated to be more effective than medical management for T2DM control, and BPD-DS and RYGB have shown some of the highest remission rates.

The literature available up to date still encounters certain limitations. For instance, in the STAMPEDE trial, patients had a relatively low BMI (mean 37 ± 3.5 kg/m^2) with 37% of them having a BMI value < 35 kg/m^2. This leaves aside the morbid and super obese population, but opens the discussion to lower the current indication guidelines to serve patients with T2DM and lower BMI.

In addition, remission was achieved in 23%-29% of patients submitted to surgery, but nothing is said about the remaining 70% who did not benefit from RYGB or SG. Could these patients benefit from another type of surgery such as biliopancreatic diversion with duodenal switch? Even the most recent information from a RCT by Mingrone *et al*[24] with the largest follow-up (10 years), exhibited maintained diabetes remission in only 37,5% of the patients when compared to conventional medical therapy.

BPD/DS is an under-utilized surgical procedure which has been associated with enhanced weight loss and resolution of comorbid disease[31], though postoperative complications are increased when compared to RYGB or SG[32]. Numerous studies, including our predictive model, have demonstrated that this procedure is related to increased weight loss and remission of diabetes and other comorbidities. Yet, its low implementation fails to show its benefits on a wide scale.

The discussion is no longer whether metabolic surgery achieves remission of diabetes or not, as this has broadly been demonstrated. Debate arises on which procedure is best for each individual patient. Predictive models are warranted to be improved once they succeed in including a large, diverse population, addressing duration of diabetes and insulin use, who are submitted to any of the surgical

Table 2 Predictors of diabetes mellitus remission following bariatric surgery

	Diarem	Diarem2	IMS	ABCD	Duke diabetes remission
Procedure	Rygb	RYGB	RYGB or SG	RYGB or mini-gastric	RYGB, SG, AGB, BPD/DS
Number of patients (*n*)	690	307	659	63	602
Variables	Insulin use	Insulin use	Insulin use	Diabetes duration	Age
					Sex
	Age	Age	Duration of diabetes	Age	Race
					Insulin use
	Hba1c	Hba1c	Hba1c	Baseline BMI	Hba1c
					BMI
	Type of antidiabetic drugs	Duration of diabetes	Number of diabetic medications	C-peptide level	Preop asthma, GERD, hypertension, hyperlipidemia, anticoagulation medication status
					Type of antidiabetic drugs
Scale	0-22 (5 groups)	0-25 (High-Intermediate-Low remission)	3 stages (Mild-Moderate-Severe)	0-10	Odds of remission according to preoperative variables and type of surgery
Recommendation on procedure of choice	No	No	Yes	No	No

RYGB: Roux-en-Y gastric bypass; SG: Sleeve gastrectomy; BPD-DS: Biliopancreatic diversion with duodenal switch; AGB: Adjustable gastric banding; HbA1c: Glycosylated hemoglobin; GERD: Gastroesophageal reflux disease.

procedures available (AGB, SG, RYGB, distal bypass, BPD-DS *etc*.).

The following steps are yet to be determined. Large multicentric studies are awaited to test and improve the existing scores, in order to ultimately develop a calculator able to predict individualized surgical outcomes. Yet, there is still a feeling of uncertainty and apprehension surrounding the fate of patients who experience diabetes relapse or weight regain after metabolic surgery.

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