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Utility of Bariatric Surgery in the Remission of Type 2 Diabetes Mellitus

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ABSTRACT:

Objective: Assess whether bariatric surgery is more effective than lifestyle modification and medication in the long-term reduction of hemoglobin A1c (HbA1c) and fasting plasma glucose among obese adults with type 2 diabetes mellitus. **Design:** Systematic literature review. **Methods:** A PubMed search was performed utilizing the terms bariatric surgery, type 2 diabetes and remission. In PubMed the following limits and terms were used: published in the last 10 years, humans, full text, clinical trial, randomized control trial, and English. **Results:** An analysis of three randomized control trials (RCTs) supports bariatric surgery as a modality to induce the remission of type 2 diabetes mellitus (T2DM) in overweight or obese adults, however the results show a decline in success after the first 12 months after surgery. **Conclusion:** While shown to be beneficial in the initial 12-month period, the long-term data does not support the utility of bariatric surgery alone in the induction of T2DM.

INTRODUCTION:

Obesity and type 2 diabetes mellitus (T2DM) are among the leading causes of preventable and premature deaths in the United States.¹ T2DM is a complex metabolic disorder that is caused by two primary factors: defective insulin secretion by pancreatic β -cells and the failure of insulin-sensitive tissues to respond appropriately to insulin.² As the disease progresses, insulin secretion is no longer able to maintain glucose homeostasis, resulting in chronic hyperglycemia that can eventually cause nervous system dysfunction. Patients with T2DM are often characterized by being obese or having a higher body fat percentage, distributed predominantly in the abdominal region. Obesity itself increases insulin resistance, leading to T2DM in those who previously did not have it, or worsens the disease course for those that do. Thus, the main factors of the T2DM epidemic are the nationwide rise in obesity which has skyrocketed by 26% since 2008 as well as sedentary lifestyles and high caloric diets. In fact, it is estimated that 85.2% of people with T2DM are overweight or obese.³

Weight loss is a key component in the management of diabetes; however, despite expanding pharmaceutical therapies and behavior modifications, 90% of patients with T2DM fail to achieve the treatment goals necessary to prevent long-term complications, including neuropathy, retinopathy, kidney disease, and more.⁴ Mounting evidence suggests the use of bariatric surgery, such as sleeve gastrectomy and the Roux-en-Y procedure, in the treatment of T2DM in patients whose body mass index (BMI) is 35 kg/m² or higher. The Roux-en-Y procedure involves creating a stomach pouch out of a small portion of the stomach and attaching it directly to the small intestine, bypassing a large part of the stomach and duodenum. The new stomach pouch is now too small to hold large amounts of food and by skipping the duodenum, fat absorption is also reduced.⁵ It is theorized that bariatric surgery may improve hyperglycemia, which is associated with reduction in mortality and diabetes-related complications.⁶ However, as with any surgery, there are potential associated risks.

Randomized control trials (RCTs) have been and are currently being used to assess the relationship between bariatric surgery and hemoglobin A1c (HbA1C) reduction among T2DM patients. Three RCTs are compared to further evaluate these outcomes of patients with T2DM following bariatric surgery compared to those who underwent lifestyle modification only.

CLINICAL QUESTION:

Among obese adults with type 2 diabetes mellitus, is bariatric surgery more effective than lifestyle modification & medication in the long-term reduction of HbA1c to $\leq 6.5\%$ and/or fasting plasma glucose (FPG) ≤ 125 mg/dl?

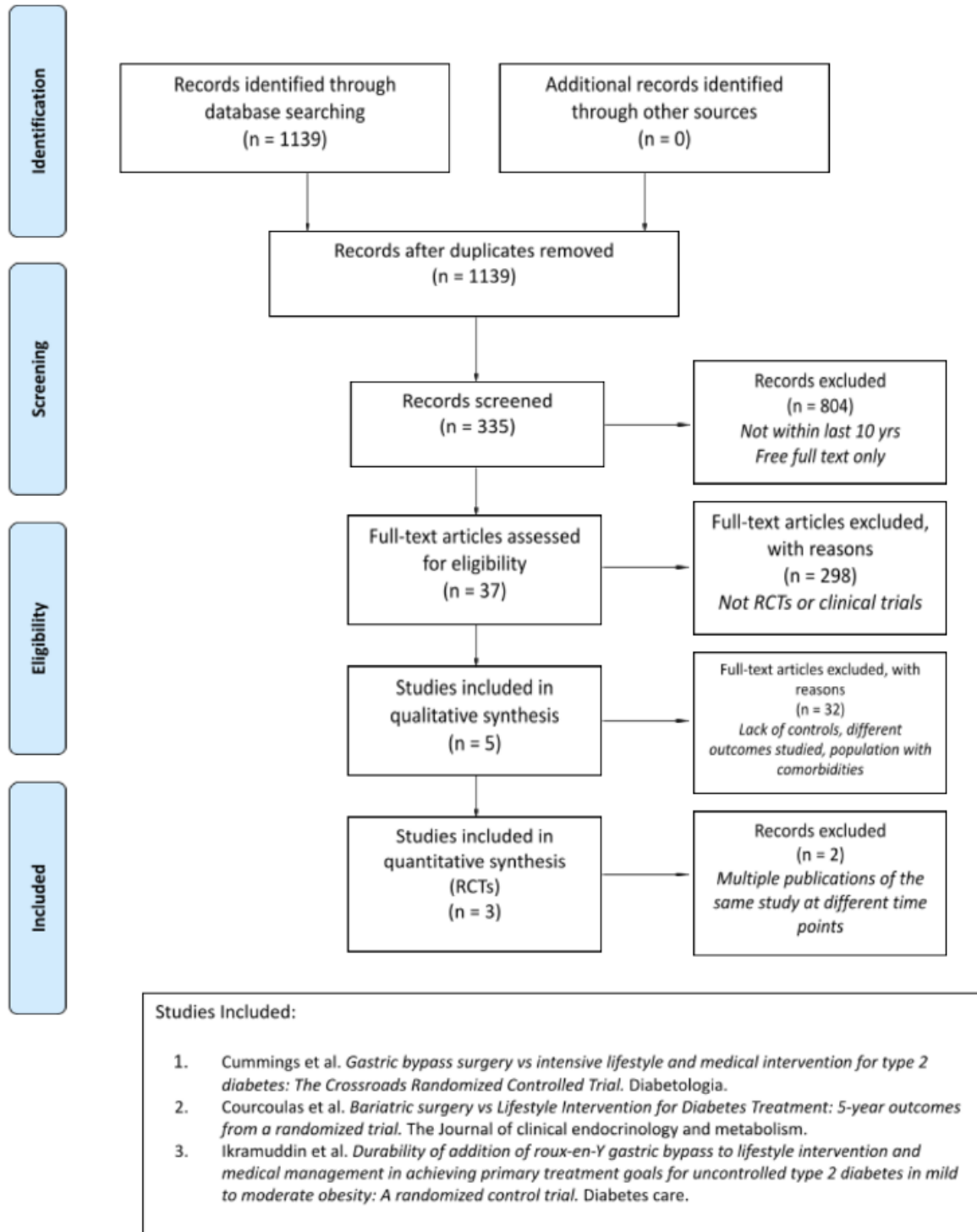
METHODS:

An initial search of PubMed was performed in September 2022 using the terms bariatric surgery, type 2 diabetes and remission. Limits included "published in the last 10 years, humans, full text, clinical trial, randomized control trial, English."

This yielded 37 articles. Of these, the majority of studies did not align with the current clinical question regarding their inclusion criteria or study outcomes and therefore were eliminated.

Two separate randomized control trials were published at 1-, 3-, and 5-year intervals. One of these studies (Courcoulas et al) was listed for three of the 37 results, whereas the other study (Ikramuddin et al) had only one of its publications in the original results list.^{7,8} A PubMed listing of “similar articles” provided the other publications for Ikramuddin et al. The final publication of each study is used to answer the current clinical question.

PRISMA Flow Diagram



RESULTS:

Study #1

*Gastric Bypass Surgery vs. Intensive Lifestyle and Medical Intervention for Type 2 Diabetes: The CROSSROADS Randomized Control Trial*⁹

Objective

The objective of this study was to study how Roux-en-Y gastric bypass (RYGB) surgery compares against conventional lifestyle and medication management of type 2 diabetes in patients with a BMI of ≥ 35 . The study was completed by researchers at the University of Washington Group Health Research Institution and the Fred Hutchinson Cancer Research Center.

Study Design

1,808 participants were screened and met the researchers' inclusion criteria (ages 25-64, a diagnosis of T2DM with medication management, and a BMI between 35-45). Of these patients, 43 were randomized and assigned in a 1:1 ratio of RYGB or lifestyle modification. The lifestyle modification included ≥ 45 mins of aerobic exercise at least 5 days a week, a dietician-monitored glucose- and weight-lowering diet, and optimal diabetes management for 1 year. It is important to note that although the participants within each group were "equivalent" in baseline characteristics, the patients in the RYGB group had overall had diabetes for a longer period of time (average diagnosis of about 11 years, compared to that of 7).

Patients received all of the lifestyle modifications for free and those who underwent RYGB surgery had the cost covered by the research group. Participants of course were unable to be blinded to their treatment, so a blinded adjudicator was used to determine results. The primary outcome studied was the remission of diabetes (HbA1c of $< 6\%$) without the use of diabetes medications. Secondary outcomes included fasting glucose, insulin resistance, body weight, waist circumference, medication usage, blood pressure, and quality of life. These were not related to the clinical question thus were not pertinent. 11 participants dropped out of the study before undergoing intervention.

Results

15 patients underwent RYGB and 17 were assigned to the lifestyle modification. Data collection occurred at 6 months and 12 months. Data collected at in-person visits included height; weight; waist circumference; percent lean and fat mass determined by dual-energy x-ray absorptiometry (DEXA) and bioelectrical impedance plethysmography (baseline and 12 months only); blood pressure; heart rate; fasting plasma levels of glucose and insulin; levels of HbA1c and cholesterol; quality of life measured with the EQ-5D questionnaire; and adverse events. The total weight lost after 1 year was markedly higher in the RYGB group compared to the lifestyle modification group, with an average loss of 25.8% and 6.4% respectively. Diabetes remission as defined by the researchers was achieved in 60% of the RYGB group and only 5.9% of the lifestyle modification and medical management group, as illustrated in Figure 1. Adverse events of any kind were reportable at follow up appointments and there were no hospitalizations or deaths during the study. The most commonly reported adverse event was hypoglycemic events, and the lifestyle modification group reported this occurrence much more frequently than the RYGB group (43 and 16 events, respectively). The researchers concluded that even with rigorous lifestyle, diet, and medication management, RYGB may be a more effective option for diabetes remission within the studied population, as demonstrated over the course of 1 year.

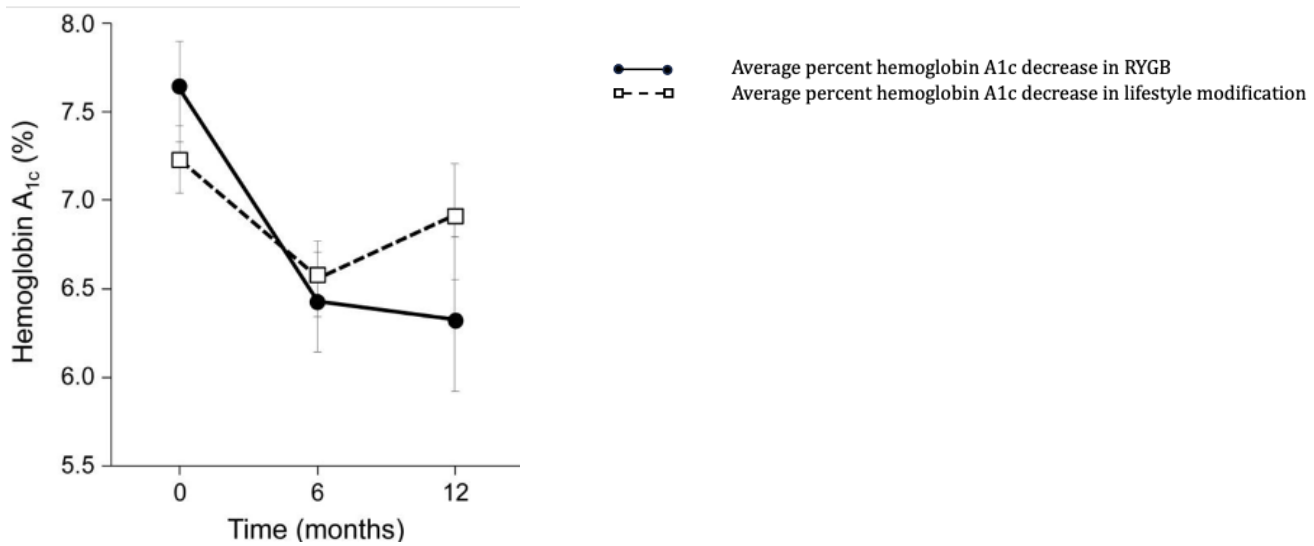


Figure 1. Average percent hemoglobin A1c decrease in RYGB (black line, circles) and lifestyle modification (dotted line, squares)

Researchers concluded that RYGB was a superior method of diabetes remission than even intensive lifestyle and diet modifications and the best available pharmaceutical treatments for patients with a BMI of ≥ 35 for at least 1 year after intervention.

Study Critique

Perhaps the greatest limitation of this study is the short term of study, ending at 1 year, although researchers claim they are following these patients to create longer duration research. It is important to note as well that the patients were unable to be blinded to intervention, and the sample size of the study was incredibly small. Due to the stringent inclusion criteria, the population studied may also not be representative of the entire patient population with type 2 diabetes, as many patients who have type 2 diabetes concurrently have other health conditions or may be pregnant, deeming them ineligible for this study.

Study #2

Bariatric Surgery vs Lifestyle Intervention for Diabetes Treatment: 5-Year Outcomes from a Randomized Trial. Courcoulas et al.

Objective

To compare the remission of T2DM in class I and class II obese adults at 5 years following surgical or nonsurgical treatments.

Study Design

This was a 3-arm prospective randomized control trial at the University of Pittsburgh, in the United States, of 61 participants with obesity and T2DM who were recruited from a variety of advertisement techniques (television, local media, and internet sources). Table 1 outlines inclusion criteria.

Table 1. Patient Inclusion Criteria

Adults 25 to 55 years old

BMI of 30 to 40 kg/m²

T2DM diagnosis confirmed by FPG level of >125 mg/dL and/or treatment with at least 1 glucose-lowering medication

*BMI = body mass index, T2DM = type 2 diabetes mellitus, FPG = fasting plasma glucose

The participants were initially randomized to either bariatric surgical treatments (Roux-en-Y gastric bypass [RYGB] or laparoscopic adjustable gastric band [LAGB]) or an intensive lifestyle weight loss intervention (LWLI) program for 1 year. Then, lower level lifestyle weight loss interventions (LLLI) were delivered for the next 4 years. The initial phase was defined at year 1, the second phase at year 2 and 3, and the third phase was year 4 and 5. The LLLI for all groups consisted of an in-person session (approximately 30-40 minutes) and a brief telephone call (less than 10 minutes) per month plus regular refresher group meetings where a specific behavior change concept related to weight loss was targeted.

The primary outcome was the assessment of diabetes remission achieved at 5 years. Partial remission of T2DM was defined by the absence of any diabetes medications with a hemoglobin A1c (HbA1c) level < 6.5% and a fasting plasma glucose (FPG) ≤ 125 mg/dL. Complete remission of T2DM was defined by the absence of any diabetes medications with a HbA1c < 5.7% and FPG ≤ 100 mg/dL. Secondary outcomes included glycemic control and medications, weight change, lipid profile changes, blood pressure, and adverse events.

The intention-to-treat approach was used in statistical analyses of the primary endpoint assuming no remission for participants that did not return for follow-up.

Study Results

Overall, surgical treatments were found to be more effective than lifestyle interventions alone for T2DM treatment. Partial or complete remission was achieved by 6 RYGB participants (30%), 4 LAGB participants (19%) and no LWLI participants (Figure 2). At the 5-year follow-up, those in the RYGB group had the largest percentage of individuals (56%) not requiring any medications for T2DM compared to those in the LAGB (45%) and LWLI (0%) groups. No participant in the LWLI group experienced remission at any of the annual time points.

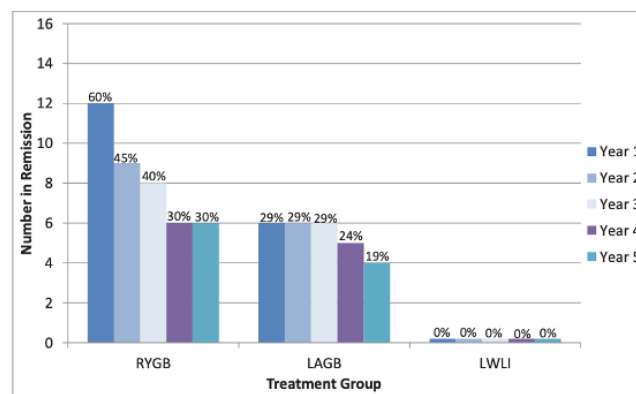


Figure 2. Prevalence of remission (partial or complete) by treatment group and year.

Secondary outcomes, including glycemic control, body weight, blood pressure, and lipids also demonstrated the greatest improvements in the RYGB group followed by LAGB then LWLI.

Study Critique

Strengths include the large sample size of participants with class I obesity, a subset of individuals with previously minimal research regarding bariatric surgery and T2DM. This study allowed for a broader enrollment for people with varying diabetes severity, with an initially lower average baseline HbA1C in the current cohort compared to previous studies, which allowed the investigators to expand the evidence within this population. As a result, the results of the study may be more generalizable to people with obesity and various degrees of T2DM severity.

The study is hampered by the behavioral approach undertaken in the LWLI group, which included modest energy restriction, behavioral counseling and physical activity. This approach may not be effective for all participants undertaking a LWLI, thus other dietary or physical activity approaches focused on other factors may warrant examination for comparison with bariatric surgery. Another limitation is the relatively small sample size in a single center, which may affect generalizability.

Additionally, previous RCTs with 5-year results comparing surgical with non-surgical treatments of T2DM differ in their definition of remission, making direct comparisons difficult and limits the extent to which these results can be applied clinically. It is important to note that remission rates for T2DM declined over the 5 years but still remained greatest for the RYGB group. This calls into question the long term benefit of bariatric surgery on T2DM and the factors contributing to diabetes relapse.

Study #3

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

Objective

To compare achievement of T2DM remission after two years of intensive lifestyle modification with and without gastric bypass surgery and three subsequent years of standard medical care follow-up.

Study Design

This is a randomized clinical trial with observational follow up of 120 participants who underwent lifestyle-intensive medical management (LMM) for two years with or without gastric bypass surgery and subsequent standard medical care for three years. Of the 120 total participants randomized, 56 were included in the primary analysis for LMM only and 57 participants were selected for a Roux-en-Y procedure in addition to LMM. 9 of the LMM participants elected to have gastric bypass and 2 participants randomized to have gastric bypass opted out of surgery but remained in the study. 7 participants did not complete the study. Inclusion criteria consisted of adults 35-67-years-old with T2DM and HbA1c of $\geq 8.0\%$ despite 6 months of clinical care, BMI 30-39.9, and willingness to accept and follow randomized treatment protocol.

LMM was characterized by 325 minutes of moderate physical activity per week and a drug-therapy protocol for control of hyperglycemia, cholesterol, and hypertension. Additionally, participants had monthly visits with an endocrinologist for 6 months, then quarterly through the second year. For the group that underwent gastric bypass surgery, all participants had a standardized Roux-en-Y procedure. After two years, study interventions were discontinued and participants resumed standard care with their primary care provider.

A triple endpoint was used to measure outcomes, defined as HbA1c $<7.0\%$, low-density lipoprotein (LDL) <100 mg/dL, and systolic blood pressure <130 mmHg. These measurements were collected at baseline and then annually for 5 years.

Primary data was evaluated on an intention-to-treat model and secondary analyses were performed as-treated to identify relationships between variables. Another post-hoc analysis was completed on crossover participants.

Study Results

In year 1, the triple endpoint was achieved by 28 participants (~50%) in the gastric bypass group and 9 (16%) in the LMM group (Table 2). Reduction in the number of participants who achieved the triple endpoint was observed between years 1 and 2 and years 2 and 3. From year 3 to 5, the number of participants who achieved the triple endpoint was stable. At year 5, 13 gastric bypass participants (23%) had sustained these results and 2 participants (4%) in the LMM group.

Secondary outcomes were also assessed. These included each component of the primary outcome considered individually (i.e., HgbA1c, LDL cholesterol, and systolic blood pressure) as well as FPG, weight loss, number and type of medications taken, triglyceride levels, and others.

In relation to the current clinical question, it was observed that HbA1c of $\leq 6.5\%$ was sustainably achieved at year 5 by 16% of gastric bypass participants as compared to 5% of LMM participants. Additionally, 25% of the gastric bypass participants and 4% of the LMM participants had a FPG <100 mg/dL at year 5.

Table 2. Outcomes Measured in Percent Success for Years 1, 3 and 5						
	Year 1		Year 3		Year 5	
	LMM	Roux-en-Y	LMM	Roux-en-Y	LMM	Roux-en-Y
Triple Endpoint	16%	50%	6%	23%	4%	23%
HbA1c \leq 6.5%	<i>Unspecified</i>	<i>Unspecified</i>	0%	35%	5%	16%
FPG <125	11%	44%	7%	20%	4%	25%

Table 2. Outcomes measured at year 1, year 3, and 5.

Study Critique

A strength of the study is its greater generalizability to the diabetic population as compared to other similar studies. Its larger sample size, inclusion of participants with a broader range of BMI, and use of participants from four different study sites are factors that contribute to its application to the general population. Additionally, the study analyzed a range of treatment goals (e.g., SBP, weight, number of insulin and non-insulin medications) for diabetic patients rather than evaluating HgbA1c and/or FBG, which have been the primary endpoints in other similar studies.

Limitations of this study include an average baseline HbA1c of 9.6%, which infers the participants had poorly controlled diabetes prior to beginning the study. It is unknown whether the outcomes of the study would be different for patients with better or more poorly controlled diabetes. In addition, the average duration of T2DM for participants was 9 years, therefore it cannot be determined what effects would be seen in patients who have had T2DM for a lesser duration. Lastly, 28% of participants were lost to follow-up.

DISCUSSION:

Obesity and T2DM are two related and modifiable causes of premature death in the United States. Weight loss plays a key role in the management of diabetes, but has proven to be difficult to attain for diabetics despite lifestyle modification and pharmacologic therapies. Recent literature suggests that bariatric surgery may significantly improve HbA1c in T2DM patients with obesity, allowing many patients to eventually discontinue all pharmacologic therapies (McGlone). To date, little evidence exists regarding the extent to which bariatric surgery induces sustainable remission. The purpose of this review is to identify whether bariatric surgery is more effective than lifestyle modification and medication in the long-term reduction of HbA1c and FPG.

An overview of the three studies is provided (Table 3). Inclusion criteria was slightly variable between the three reviewed studies. In general, each study included participants of adult age with an overweight or obese BMI classification. All participants had T2DM, but the particular inclusion criteria related to their diabetes differed amongst the three studies. Specifically, Cummings et al. and Courcoulas et al. both required their participants be on at least 1 glucose-lowering medication, whereas Ikramuddin et al. did not have this parameter. Furthermore, Courcoulas et al. and Ikramuddin et al. each had one additional defining criteria pertaining to T2DM, which was a FPG > 125 mg/dL and HbA1c \geq 8.0% respectively. Lastly, Ikramuddin et al. required participants to be under the care of a physician for their T2DM for a minimum of 6 months prior to entry into the study.

Bariatric surgery is a common procedure performed in the United States that can greatly aid in weight loss efforts of obese patients. The Roux-en-Y gastric bypass (RYGB) is the most commonly performed bariatric bypass procedure that decreases the amount of food a patient can eat as well as decreases absorption of nutrients from the food eaten. This surgery is completed by removing a large segment of the stomach to decrease its capacity, then the digestive tract is rerouted so the food bolus can bypass the duodenum and directly enter the jejunum. Gastric juices are still able to move through the duodenum to aid in the breakdown of larger particles. The Laparoscopic Adjustable Gastric Band (LAGB) procedure is another common method of

weight loss surgery that physically reduces the size of the stomach pouch by using a laparoscopically placed band around the anterior portion of the stomach. This allows the patient to feel fuller faster, thus reducing the urge to eat.

As with any procedure, bariatric surgery carries risks to the patient. Perisurgical risks include infection, adverse reactions to anesthesia, formation of blood clots, and perforations. Long-term complications are related to the mechanisms by which these procedures work. These include gastrointestinal disorders such as dumping syndrome, bowel obstruction and ulcerations. Formation of gallstones and hernias have also been reported, but these are less commonly reported. As many patients who qualify for bariatric surgery are also type 2 diabetics, there has been substantial research on the safety of these procedures for this patient population.

All three studies evaluated similar primary outcomes of diabetes remission, however the specific endpoints of each were marginally different. While all three of the studies utilized HbA1c levels to define remission, Ikramuddin et al. allowed for the highest HbA1c value of lower than 7% while Cummings et al. capped the HbA1c value at a value lower than 6%. Additionally, Courcoulas et al. combined partial and complete remission values as HbA1c less than 6.5%. While these HbA1c parameters are similar, it should be noted that they are not the exact same values and make a direct comparison between the studies slightly more difficult. Ikramuddin et al. and Courcoulas et al. both implemented additional parameters in the definition of diabetes remission. Specifically, Ikramuddin et al. used low-density lipoprotein levels and systolic blood pressure to define diabetes remission while Courcoulas et al. utilized FPG levels. The different parameters and cut-off values used in each of the three studies are possible limitations to the generalizability of this literature review.

Of the three studies, Cummings et al. examined participants for the least amount of time compared to Courcoulas et al. and Ikramuddin et al. Specifically, Cummings et al. examined participants for 12 months after the initiation of intervention, whereas Courcoulas et al. and Ikramuddin et al. evaluated participants for 5 years following intervention, but both published data for 12 months, 3 years, and 5 years. However, it should be noted that Cummings et al. intends to publish further data on their study at years 3 and 5. Thus, this review is limited to two studies in the comparison of data for years 3 and 5.

At 12 months, all 3 studies showed dramatic weight reduction compared to lifestyle interventions, and showed promising declines in HbA1c. In Cummings et al., diabetes remission as defined by the researchers was achieved by 60% of the RYGB group and only approximately 6% in the lifestyle modification and medication (i.e., non-surgical) group. Courcoulas et al.'s study included 2 different surgical interventions, RYGB and LAGB, and one lifestyle modification intervention. In one year, 60% of the RYGB achieved remission, 29% of the LAGB group, and 0% of the non-surgical group, proving RYGB to be the best option at the one-year mark. Finally, Ikramuddin et al. focused on a triple endpoint with HbA1c, LDL, and systolic BP, as described in Table 3. Based on these parameters, only 16% of the non-surgical group met the desired outcome, whereas 50% of the RYGB achieved the triple end point (as Ikramuddin et al. did not specify HbA1c levels at the 1-year mark).

To date, only Courcoulas et al. and Ikramuddin et al. have published data at year 3. These studies found a decline in diabetes remission rates at the third year as compared to 12 months. Courcoulas et al. noted a partial or complete T2DM remission of 40% of RYGB participants, 29% of LAGB, and 0% for the non-surgical group at 3 years. Ikramuddin et al. found achievement of the triple endpoint for 23% of RYGB participants compared to 6% of the non-surgical participants.

Similarly, only Courcoulas et al. and Ikramuddin et al. obtained data for diabetes remission at year 5. Both studies demonstrated a further decline in remission rates at 5 years compared to 3 years. Specifically, Courcoulas et al. found that 30% of RYGB participants, 19% of LAGB participants, and 0% of the non-surgical participants achieved diabetic remission at year 5. Ikramuddin et al. found that 4% of the non-surgical participants achieved remission and 23% of the Roux-en-Y participants achieved remission at year 5.

CONCLUSION:

Among obese adults with type 2 diabetes mellitus, is bariatric surgery more effective than lifestyle modification and medication in the long-term reduction of HbA1c to $\leq 6.5\%$ and/or FPG ≤ 125 mg/dl?

Bariatric surgery has recently been implicated in inducing remission of T2DM in overweight or obese adults. Three RCTs have demonstrated achievement in helping type 2 diabetic patients attain remission as compared to those undergoing lifestyle

modification and medication, but this success was not sustained over time. There was a significant decline in remission rates from the first 12 months to the fifth year. Without further research into its utility and result sustainability, bariatric surgery cannot yet be deemed a more effective modality in the remission of diabetes compared to lifestyle modification and medication, which is the primary treatment recommendation to date.

Table 3. Overview of Studies			
	Cummings et al	Courcoulas et al	Ikramuddin et al
Patients, N	43	61	120
Population (inclusion criteria)			
Age	Adults 25 - 64 years	Adults 25 - 55 years	Adults 30-67 years
BMI	30 - 45 kg/m ² <i>RYGB required BMI 35-45 kg/m²</i>	30 - 40 kg/m ²	30-39.9 kg/m ²
T2DM Criteria	Currently taking diabetes medications	FPG > 125 mg/dL and/or treatment with at least 1 glucose-lowering medication	T2DM under physician care for ≥ 6 months, HbA1c ≥ 8.0%
Primary Outcome	<i>Diabetes remission at 12 months:</i> HbA1c of < 6%	<i>Diabetes partial remission at 5 years:</i> HbA1c < 6.5% FPG ≤ 125 mg/dL <i>Diabetes full remission at 5 years:</i> HbA1c < 5.7% FPG ≤ 100 mg/dL	<i>Triple End Point at 5 years:</i> HbA1c < 7.0%, LDL < 100 mg/dL SBP < 130 mmHg
Surgical Procedure	RYGB	RYGB or LWLI	RYGB
Assessment Points	Month 12	Year 1, 2, 3, 4, and 5	Year 1, 3, and 5

Abbreviations: HbA1C = hemoglobin A1C, LDL = low-density lipoprotein cholesterol; SBP = systolic blood pressure; RYGB = Roux-en-Y gastric bypass; LAGB = laparoscopic adjustable

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