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Bariatric Surgery Versus Lifestyle Interventions In Managing Obesity In Patients With Type II Diabetes: A Systematic Review

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BARIATRIC SURGERY VERSUS LIFESTYLE INTERVENTIONS IN MANAGING OBESITY IN PATIENTS WITH TYPE II DIABETES: A SYSTEMATIC REVIEW

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ABSTRACT

Bariatric Surgery Versus Lifestyle Interventions
In Managing Obesity In Patients With Type II
Diabetes: A Systematic Review

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***Purpose**:* Obesity, with coexisting T2DM, is difficult to treat successfully for various reasons and carries enormous health risks and financial burdens. The purpose of this systematic review is to compare outcomes of conventional medical treatment to bariatric surgery for the treatment of T2DM, and determine which patients may be appropriate for referral.

Data Sources: An electronic search of the literature was conducted to identify studies from 2008 to 2014 in the following databases: CINAHL, National Library of Medicine PubMed®/MEDLINE®, EBSCO, SciVerse®, Springer Link®, and the Cochrane library.

Conclusions: Bariatric surgical options, even before weight loss occurs, positively affect glucose homeostasis and in some bariatric procedures and individuals with particular characteristics, produce considerable weight loss and remission of diabetes. Positive correlates were younger age, shorter disease duration, and BMI >30 kg/m2. Secondary outcomes are also improved. The same effects are seldom realized through conservative methods.

Results/Implications for Practice: All obese patients should be referred for intensive intervention, with the minimum goal of 10% weight loss. Under certain circumstances, referral for bariatric surgery should be considered, particularly for individuals with BMI >40 kg/m2, or BMI ≥35 kg/m2 and at least one obesity related co-morbidity. Others may be considered on a case-by-case basis.

Keywords: Type 2 Diabetes Mellitus, Bariatric Surgery, Lifestyle Intervention, Obesity, Systematic Review

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Introduction

In the United States, more than one-third of the population is obese, defined as a BMI >30 kg/m2, with an increasing number reaching severe obesity (BMI >40 kg/m2) (Centers for Disease Control and Prevention, 2012). A similar trend is occurring worldwide, particularly in urban areas and developing countries (Beaubien, 2014; Mathers & Loncar, 2006). There is an undisputable link between obesity and the development of chronic diseases, including type 2 diabetes mellitus (T2DM).

Obesity, with coexisting T2DM, is difficult to treat successfully for various reasons and carries enormous health risks and financial burdens. Sustained hyperglycemia is a risk factor for micro and macro vascular disease, including neuropathy, nephropathy, and retinopathy, and is a significant contributor to cardiovascular disease (Jeong & King, 2011; Paneni, Beckman, Creager, & Cosentino, 2013). It is estimated that the cost of care for obese individuals with diabetes is two to four times more expensive than their non-diabetic counterparts (Klein, Ghosh, Cremieux, Eapen, & McGavock, 2011). The American Diabetes Association (2013) reports the cost of diabetes, disease related complications, and lost productivity surged to more than $245 billion per year in 2012, an increase of 41% from 2007 estimates, and current projections indicate that prevalence and associated costs will continue to increase.

The relationship between weight loss and the amelioration of T2DM is not well understood, or if such a relationship exists. Numerous data suggest that even modest weight loss may be beneficial in reducing diabetes risk factors. Attaining weight loss through conservative measures, such as diet and exercise, is generally recommended first. Yet studies that compared conservative measures with surgical interventions demonstrate superior and more durable outcomes favoring bariatric surgery. Bariatric surgery, independent of weight loss, seems to drastically halt the progressive effects of diabetes. Hage and colleagues (2012) suggest that bariatric procedures may alter the release of adapokines and gut peptide hormones such as ghrelin and glucagonlike peptide-1 (GLP-1), which may account for improvements that are observed just days postoperatively, before significant weight loss has occurred.

Primary care providers, including nurse practitioners, are responsible for 80-90% of the surveillance and management of patients with diabetes (Morrison, Shubina, Goldber & Turchin 2012; Unger, 2012). This provides an opportunity for evaluation, aggressive management to avoid complications, and referral for T2DM complications when necessary. When non-surgical conservative measures such as diet, exercise, and pharmacotherapies are unsuccessful in the treatment of obesity related T2DM, the International Diabetes Federation recommends the consideration of evidenced based surgical interventions (Dixon, Zimmet, Alberti, Mbanya, & Rubino, 2011)

Despite numerous studies and trials verifying the efficacy and safety of bariatric surgery to treat T2DM, both practitioners and patients remain reluctant to consider surgery other than as a “last resort.” (Dixon et al., 2011; Sarwer et al., 2012a; Sarwer et al., 2012b). The purpose of this systematic review is to compare outcomes of conventional medical treatment to bariatric surgery for the treatment of T2DM, and determine which patients may be appropriate for referral. Clinical implications will also be identified.

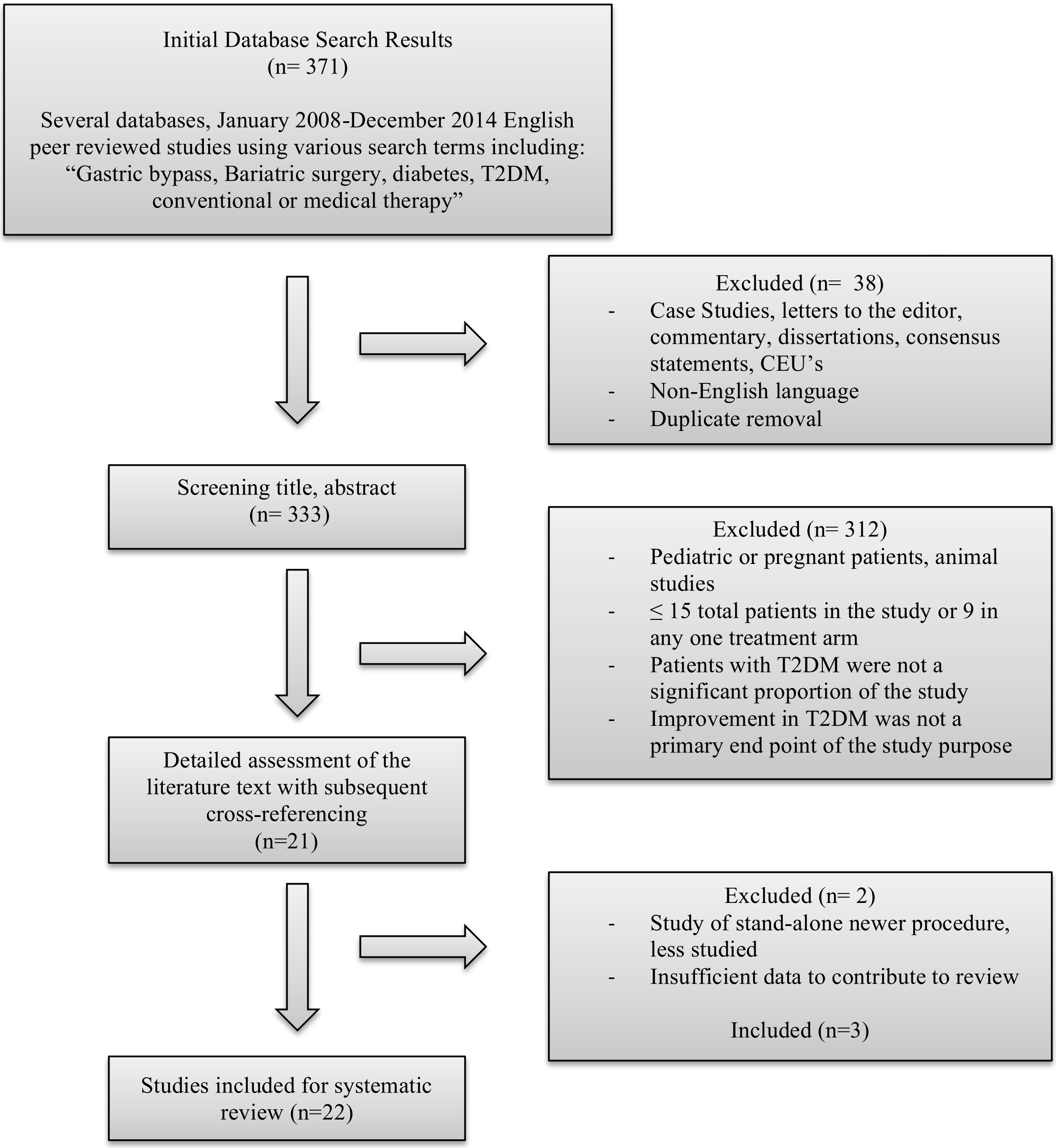
Methods

An electronic search of the literature was conducted to identify studies from 2008 to 2014 in the following databases: CINAHL, National Library of Medicine PubMed®/MEDLINE®, EBSCO, SciVerse®, Springer Link®, and the Cochrane library. Search terms included obesity, gastric bypass, bariatric surgery, Roux-en-Y, sleeve gastrectomy, laparoscopic adjustable gastric band, medical, conservative, treatment, management, and diabetes mellitus. Limits were set to identify peer reviewed research studies in the English language. The initial database search identified 371 articles for review. Duplicates, case studies, commentary, dissertations, consensus statements, and letters to the editor were excluded.

To be included, research was based on adult participants medically diagnosed with T2DM for any length of time prior to interventions and those patients comprising a significant proportion of the study population. Diabetes improvement after intervention was a primary end point of the study's purpose. Abstracts were scanned for suitability and references searched to identify other potential articles for inclusion. Studies were excluded if total participants numbered fewer than fifteen, if the focus was diabetes prevention or predicting surgical outcomes, prenatal or postpartum patient outcomes, or included pediatric patients. 312 studies were excluded based on the criteria, leaving twenty-one for more thorough review. A detailed assessment of the literature and cross-referencing of articles suggested three for inclusion. Ultimately, two were excluded leaving twenty-two studies that met the criteria for inclusion (See figure 1).

Due to the various study designs included, quality of the studies was assessed using the methodology described by Whittemore and Knafl (2005). Each study was coded on a 2-point scale, high or low, relative to two criteria pertinent to this review, methodological rigor and relevance of the data. Data relevance was rated high in all included studies, and methodological rigor in most. Identified limitations are presented in the discussion section.

Figure 1. Article Identification, Screening, and Selection Process.



Results

Study Characteristics

A total of 22 studies were evaluated. Nine were prospective studies, either cohort or comparative in nature, including one randomized control trial (RCT) (Kashyap et al., 2013). Seven were retrospective studies generally conducted as chart reviews, with one being a large cohort study (Arteburn, et al., 2013), and seven were RCTs, though only two were double blinded (Dunn et al., 2012; Lee et al., 2011). It would have been optimal to include more randomized double blind studies, however, the potential surgical intervention seldom permitted for this type of study design.

Data was published for 7,297 people who participated in the twenty-two studies; the smallest group consisted of 18 participants (Abbatini et al., 2012) and the largest evaluated 4,434 participants (Arteburn et al., 2013). Studies were conducted in the United States, Australia, Asia, Brazil, Chile, Italy, and Taiwan. Study duration and subsequent follow up time varied greatly, the shortest being one month in two studies (Dunn et al., 2012; Plum et al., 2011), and the longest 5-6 years in four studies (Adams, et al., 2012; Arteburn et al., 2013; Brethauer, Aminian, Romero-Talamas, Batayyah & Mackey, 2013; Lakdawala et al., 2013). The average duration of follow up was 12-24 months. The relative brevity of follow-up limits the ability to project longer-term outcomes such as weight regain and disease reoccurrence. Additional well-designed longitudinal studies may better define outcome durability.

Patient Characteristics

Study participants were between the ages of 18-72, with the mean age between 45-50. Overall, a greater number of participants were women, from 39% (Cohen et al., 2012) to 88% (Dunn et al., 2012), though gender varied between studies. Body mass index (BMI) was reported as either a range or a mean, or both. Six studies included participants with a BMI between 30-35 kg/m2, two studies 30-40 kg/m2, and four studies a BMI > 35 kg/m2. Three studies in Asia specifically investigated intervention impacts on patients with lower BMI's (25-35 kg/m2) (Huang et al., 2011; Lee et al., 2011; & Lee et al., 2012). One study (Brethauer et al., 2013) only included patients with a BMI over 40 kg/m2. The remainder of the studies reported a BMI range between 27-72.1 kg/m2, with an overall mean of 37.8 kg/m2. One study did not have

BMI data available for all participants and excluded BMI from the reported data (Arteburn et al., 2013). HbA1c, used as a biochemical measure of glycemic control and diagnostic tool for T2DM, was reported inconsistently. Only fifteen studies reported pre-intervention HbA1c, with a mean of 8.6%, and all but five studies reported the duration of diabetes. Average disease duration ranged from six months to 20 years, with an average mean of 8.9 years. Several studies considered intervention effects on individuals with disease duration less than five years, and one study duration less than two years (Dixon et al., 2008).

Intervention and Definitions

Of the 7,297 study participants, 1106 comprised the non-surgical control groups. 368 were part of conservative management groups, defined by any intervention that included dietary changes, exercise, pharmaceutical therapy, and counseling. The remaining 738 were free to pursue interventions independently, but did not receive an intervention as part of the study. The conservative management groups were described in numerous ways including routine medical management, intensive medical therapy, low calorie diets, or lifestyle changes. Surgical interventions included 104 patients who had laparoscopic adjustable gastric banding (LAGB), 27 had a duodenal switch (DS), and 20 had a biliopancreatic diversion (BPD). 5,884 had Roux-en-Y gastric bypass (RYGB) surgery, either open or laparoscopic, some in conjunction with lifestyle interventions; 20 of those also had an oomentectomy, and 30 had duodenum exclusion as a part of the surgical intervention. 156 patients had a sleeve gastrectomy (SG), generally laparoscopically, 30 with concurrent duodenum exclusion and 20 with concurrent lifestyle intervention. Forty obese, non-diabetic patients were included as a part of matched control groups for two studies; they are included in the above figures though not implicated in the outcomes or discussion.

Outcomes

Weight loss. All but one study addressed weight loss in some form, either total percentage lost, amount lost in kilograms, BMI changes, excess weight loss percentages, or waist circumference. Two studies had very brief follow up periods and primary end points related to changes in incretin and hormone production affecting glycemic control, and specific statistics regarding weight changes were not provided (Laferrere, et al., 2011; Plum et al., 2011). In the remainder, without exception, individuals in surgical intervention groups achieved greater weight loss than those in conventional treatment groups, although the outcomes varied between interventions. The greatest weight loss occurred in the groups having RYGB, BPD, or DS procedures. In two separate studies, BPD and DS were each compared with RYGB and no statistically significant difference was noted, however there were far more RYGB patients represented in this review (Dorman et al., 2012; Mingrone et al., 2012). Sleeve gastrectomy procedures produced the next greatest weight loss, followed by laparoscopic adjustable banding procedures. One study noted similar weight loss between two surgical groups, RYGB and SG (p =0.58), but observed a significant difference in reduced truncal fat in the RYGB group at twenty-four months (-16% vs. -10%, p =0.04) (Kashyap et al., 2013). In addition, greater improvements in A1c and beta cell function were noted, suggesting that decreased truncal fat may predict better outcomes.

Adams and associates (2012) and Brethauer and associates (2013), two of the longer term studies, documented durable weight loss of 27.7 ± 1.2% and 28.1±10.9% respectively at five or more years in RYGB groups. Brethauer et al. also included SG and LAGB treatment arms that experienced weight loss of 22.2 ± 9.3% and 13.2 ± 10.7%, respectively, at five or more years. Among the conventional treatment groups, weight loss varied from 0-7.9% at one and two years (Abbatini et al, 2012; Dixon et al, 2008; Dorman et al., 2012; Ikramuddin et al., 2013; Kashyap et al., 2013; Leslie et al., 2012; Mingrone et al., 2012; Schauer et al., 2012), and 0-0.2% weight gain at six years (Adams et al., 2012).

HbA1c. HbA1c (A1c) has become a standard diagnostic and monitoring tool for T2DM, along with fasting plasma glucose (FPG) and oral glucose tolerance testing (OGTT). Bonora and Tuomilehto (2011) report A1c testing has several advantages over FPG or OGTT including the ability to better chronicle chronic hyperglycemia, eliminate the need to fast, immune to outside stressors, and increase association with chronic complications. Diabetes remission, or resolution, is often a determinate of intervention success, yet may be subjective based on the goal study parameters. The 2013 American Diabetes Association (ADA) guidelines recommend maintaining A1c below 7% and fasting plasma glucose (FPG) ≤ 126 mg/dL in persons with T2DM to reduce vascular disease. T2DM is diagnosed in part after an A1c ≥ 6.5%, with A1c parameters for prediabetes established as 5.7-6.4%.

There was variance from study to study regarding desired A1c levels, with some authors subscribing to more stringent guidelines while others more liberal. Conservative, or non-surgical treatment for T2DM, was a part of thirteen studies. Seven studies reported no measurable change in glycemic control as monitored by A1c or FBG. The remainder described an average remission rate of 9% (range 5.9-13%), including one study that described remission rates of 6% and 8% from two non-surgical control groups that persisted at the six year follow up (Adams et al., 2012).

In the surgical treatment arms, two studies did not report specific outcomes relative to A1c or FPG (Laferrere et al., 2011; Plum et al., 2011). Four studies reported A1c goals of 7% per the ADA guidelines, each considering glycemic control as a part of a triple endpoint for patients with metabolic syndrome. In the studies, an A1c <7% is not identified as resolved diabetes, but improved glycemic control. Nine studies considered an A1c of <6.5% as a remission point, while others adopted more stringent guidelines of <6.2% (Dixon et al., 2008), and <6.0% in the remaining eight studies.

The SG procedure was included as a part of six studies involving 156 patients, which reported remission rates of 46.7% (range 26-89%) at one year. Two studies had secondary analysis points at two and five years, indicating relapse rates of 15.8% and 17% respectively among those who had initially remitted. (Brethauer et al., 2013; Kashyap et al., 2013). Each of those studies defined remission as an A1c < 6.0%, indicating that patients who relapsed continued to have improved glycemic control relative to baseline values and were considered partial remitters. LAGB was performed in 96 diabetic patients and an average remission occurrence of 25% (range 0-50%) was reported at one to two years. Interestingly, Dorman and associates (2012) had the most liberal A1c requirements, but reported no significant change among LAGB patients at twelve months.

Twenty studies included RYGB procedures, alone or in conjunction with other interventions. All twenty reported considerable improvements in glycemic control among RYGB patients, including A1c and when reported, FPG. Of the eighteen studies that considered A1c as a marker for diabetes resolution, remission was reported in an average of 61.2% (range 27-93%) of patients at the first, or final end point. A1c improved markedly in RYGB, BPD, and DS, but when compared, BPD and DS achieved results superior to RYGB (p =0.001 and p < 0.001, respectively) and diabetes was deemed resolved in more patients (95% at two years for BPD, and 81.5% at 12 months for DS). Four studies with multiple analysis points reported diabetes reoccurrence among 13-35.1% of RYGB patients who had initially remitted.

Insulin sensitivity and beta cell function. T2DM is characterized by cellular resistance to insulin and impaired insulin secretion leading to sustained hyperglycemia, glucose toxicity, and eventual destruction of pancreatic beta cells. Twelve studies attempted to measure, in some way, the intervention effects on insulin resistance and beta cell function. None of the studies found significant improvement of insulin resistance, glucose tolerance, or beta cell function in conservatively treated populations when compared to surgical intervention groups.

Hyperinsulinemic-euglycemic clamps are considered the gold standard in evaluating insulin sensitivity, however this method is inconvenient, more costly, and time-consuming. Dunn and associates (2012), used this technique to evaluate diabetic patients following RYGB, with or without oomentectomy, and discovered that hepatic insulin sensitivity had improved at one month but muscle insulin sensitivity had not. In the same study, a lower preoperative hepatic glucose production (HGP) and hepatic insulin sensitivity index (HISI) were positively correlated to patients with early diabetes resolution when compared to patients who did not achieve remission.

Serum insulin and HOMA-IR were often used as measures of insulin resistance, occasionally in conjunction with fasting C-peptide. Eight studies used a combination of the three measures and found significant improvements in glucose tolerance and insulin resistance in both RYGB and SG populations alone and when compared to conventionally treated patients. In two studies, the results endured at the six-year analyses points (Adams et al., 2012; Cohen et al., 2012). Lee and associates (2011), found no significant difference in either fasting serum insulin or HOMA-IR twelve months after patients were surgically treated with RYGB or SG.

C-peptide levels were associated with likelihood of diabetes remission, as alternative markers of beta cell function, according to Lakdawala et al. (2013). Results from the study suggest that C-peptide levels >6 mg/dL were associated with 100% remission, while C-peptide between 3-6 and 1-3 were associated with remission rates of 75.8% and 31%, respectively. Kashyap and associates (2013) indicated that RYGB patients had near-normal glucose tolerance and a 5.8 fold increase in pancreatic beta cell function at one to two years. The phenomenon was not observed to the same degree in SG patients who were a part of the same study, despite comparable weight loss. Plum et al. (2011) reported improvements in the disposition index (DI), including measurements such as insulin sensitivity (SI) and HOMA-IR, in RYGB patients compared to a low calorie diet (LCD) group after comparable weight loss. Additionally, the acute insulin response to glucose (AIRG) was improved in both LCD (p =0.04) and RYGB (p =0.03), however overall SI and DI improvement was significantly greater in RYGB patients (p =0.02 and p =0.04 respectively).

Secondary outcomes. The International Diabetes Federations (IDF) consensus worldwide definition of metabolic syndrome (2006) has identified a cluster of risk factors that contribute to an increased risk of heart disease, specifically diabetes or prediabetes, abdominal obesity, abnormal cholesterol, and increased blood pressure. Numerous studies in this review considered secondary outcome measures of one or more of these risk factors post-intervention, including triglycerides, high-density lipoprotein (HDL), and blood pressure.

Ten studies reported decreased triglycerides post-intervention, with the most significant improvement in RYGB and BPD compared to conventional treatment, though there was some conflict among reports. Mingrone et al. (2012) indicated significant improvement in BPD patients compared to both RYGB and conventional treatment, which also improved, but not significantly from one another. Schauer and associates (2012) reported significant decreased triglycerides in RYGB and SG treatment groups compared to conventional therapy, with no significant difference from one another. However, Kashyap (2013) compared RYGB to SG and conventional groups and found an average decrease of 32.44 points with no significant difference between the three groups. Dixon et al. (2008) reported significant change in LAGB patients compared to conventional therapy (-69.6, 95 % CI: 125.3-13.6, p =. 02).

Changes in HDL were reported in eleven studies and results varied widely. Adams and colleagues reported an increase of 13.1 points and significant improvement between RYGB and two conventional groups at six years, while Serrot et al. (2011) appreciated no significant change at one year between RYGB group and conventionally treated patients. Three studies noted significant improvements in HDL in the surgical groups, either alone, or when compared to conservative treatment, however the results did not differ significantly between the surgical interventions (Kashyap et al., 2013 Lee et al., 2011; Schauer et al., 2012). One study found that 33% of patients previously requiring medication therapy for dyslipidemia were able to discontinue therapy before the one year follow up (Lakdawala, 2013). At five years, that number had dwindled to 13%, with 20% having resumed dyslipidemia medication.

Thirteen studies related alterations in blood pressure, with generally modest decreases seen. One study reported no significant change (Dixon et al., 2008) and four studies reported significant improvement with no remarkable differences between surgical versus conventional treatment groups (Lee et al., 2011; Lee et al., 2012; Mingrone et al., 2012; Schauer et al., 2012). Two studies reported significant improvements in RYGB groups when compared to three separate conventional groups ($p < .001$, $p < 0.01$, and $p < 0.01$ respectively) (Adams et al., 2012; Leslie et al., 2012). In spite of improvements in secondary measures, medication therapy was still recommended in many patients. Interestingly, two studies mentioned inappropriate discontinuation of medication therapy (17%-41%) for hypertension and dyslipidemia or both, at the one or two year analysis points. (Leslie et al., 2012; Serrot et al., 2012)

Complications. In 2009, researchers for the Agency for Healthcare Research and Quality (AHRQ) released a study of more than 9,500 patients at 652 facilities who underwent bariatric surgery between 2001-2006 (Encinosa, Bernard, Du, & Steiner, 2009). Results indicated a reduction in postoperative complications during the first six months, from 42% to

33% at the conclusion of the study. In addition, post-operative infection rates had decreased by 58%. During this same time period, the incidence of bariatric procedures increased by 113% and included many older and sicker patients. Much of the improvement has been attributed to standardization of procedures including a significant increase in laparoscopic procedures, which increased by 62%, and specialized surgical centers that often include multidisciplinary teams.

Several of the studies in this review occurred during the same time period as the AHRQ study, as techniques and processes were evolving. Thirteen studies addressed complication rates and types, with an overall complication rate of 16.6% (range 3.8-40.7%) in the surgical population. Complications were categorized as major or minor, and early or late, and included risks inherent to surgery such as wound infections, deep vein thrombosis, and pulmonary events, as well as complications unique to gastrointestinal surgery such as anastomotic leaks, stenosis, strictures, bowel obstruction, intrabdominal bleeding, and incisional hernias. Other adverse effects included nausea and vomiting, cholecystitis, gout attacks, and dumping syndrome. Nutritional deficiencies have been reported as a common postoperative effect and vitamin supplementation after surgery is anticipated, particularly with procedures that exclude more of the stomach, duodenum, and ileum. Only one study mentioned nutrient deficiencies, most commonly in the surgical population, including iron or vitamin B deficiencies, hypoalbuminemia, or low Vitamin D (Ikramuddin et al., 2013). In the conventional treatment arm there was a 12.9% (range 9-26.6%) incidence of adverse events reported in four studies. The events were generally related to medication or meal substitution intolerances that resolved with discontinuation, or as a result of admissions for co-morbidities such as chest pain, hypoglycemia, or arrhythmias.

Discussion

Twenty-two studies met the criteria for inclusion in this review, resulting in systematic analyses to determine the efficacy of lifestyle interventions compared to bariatric surgery methods in treating obese patients with T2DM. Several factors were examined, including weight loss, HbA1c, insulin resistance and beta cell function, secondary outcomes, and complication rates. Some comparisons were also made between bariatric surgery types. In all the studies that measured weight outcomes, results were superior in surgical groups compared to conservatively treated groups. Weight loss, even if modest, is associated with improvement or elimination of metabolic syndrome and a decrease in cardiovascular risk factors (Heffron et al., 2013; Morton, Crowe, Leva, & Garg, 2013; Sjostrom et al., 2007). Seldom is the weight loss achieved through non-surgical measures sufficient to realize these benefits, particularly in extreme obesity. In this review, most studies identified a correlation between weight loss and improvement in diabetes measures, but not all. Cohen et al. (2012) stated that no correlation between weight loss and reductions in A1c occurred at any time point, and occurred between weight loss and FPG only at five and six years.

Biochemical measures of glycemic control and pancreatic beta cell function improved most in more aggressive restrictive/malabsorptive surgical procedures that altered the digestive tract, such as RYGB, BPD, and DS. In some cases, the endoluminal sleeve or SG, generated results that were similar or slightly less efficacious, and may be an appropriate surgical option for patients with a lower BMI or fewer co-morbidities. LAGB, or gastric banding, is a reversible procedure that resulted in modestly improved HbA1c in one study (Dixon et al., 2008) and no real improvement in another (Dorman et al., 2012). Several predictors of successful diabetes resolution emerged in four studies (Arteburn et al., 2012; Huang et al., 2011; Lakdawala et al., 2013; Lee et al., 2012). Positive correlations included disease duration <5-7 years, younger age, higher BMI (> 30 kg/m2) or percentage of EWL, and increased fasting C-peptide levels, specifically >6 mg/dL. These findings suggest that earlier recognition of candidates and referral for intervention is needed.

It is difficult to compare the risks of surgical intervention with the benefits of both weight loss and improved glycemic control. Though risks exist and the research demonstrates the potential for weight regain and a degree of diabetes relapse, we should consider the years of improved glycemic control and secondary effects following bariatric surgery and the impact on future health and reduced microvascular disease. Sjostrom et al. (2007), in referencing the observations from the Swedish Obesity Study (SOS), a prospective controlled cohort study involving 4047 obese subjects comparing bariatric surgery subjects (n=2010) with matched controls (n=2037), suggests that overall mortality was decreased in previously obese surgical subjects when compared to the controls after almost eleven years of follow up. At 10.9 years, mortality was 5.0% in the surgical group compared to 6.3% in the control group (95% CI: 0.59-0.99, p =0.04). The most common causes of death were related to myocardial infarction, nearly double in the control group versus the surgery group, and cancer, where incidence was one-third greater in the control group.

Limitations

Our systematic literature review identified several limitations in the research to date. First, most of the results were drawn from retrospective and prospective cohort studies with limited length of study, small population samples, and unequal or absent comparative groups. Additional well-designed randomized studies, particularly longitudinal studies, would verify or dispute existing literature and help define which populations would benefit from surgical intervention, specifically cost versus benefit in individuals with a lower BMI. Additionally, the risks and benefits of various surgical procedures may be further defined. Secondly, T2DM diagnosis and remission criteria and measures of glycemic control and pancreatic function vary widely between studies. Standardized evaluation, remission criteria, and reporting methods in future studies would greatly enhance the existing evidence base and permit sounder clinical decision-making.

Finally, the majority of the research seems to be founded and conducted in surgical centers by surgical staff and may include some bias towards surgical intervention. Several studies included conventional treatment arms with no specific interventions, serving only as matched comparison groups. Other studies vaguely described conservative interventions; few included intensive conservative measures equal to those of surgical intervention. To avoid scientific bias, more studies should include truly intensive multi-component interventions including possible inpatient therapy, psychological evaluation and counseling, and consistent outpatient follow up and dietary counseling.

Conclusion

Obesity and T2DM are increasing in prevalence and a leading cause of morbidity and mortality in the United States. Unfortunately, conservative methods have proven ineffective in generating consistent and sustainable weight loss outcomes and diabetes regression in morbidly obese individuals with T2DM. Research regarding patients with BMI 30-35 kg/m2, or Class I Obesity, and T2DM appears promising but currently lacks sufficient evidence to recommend unequivocal surgical referral.

PCP's, as gatekeepers, should recommend all obese patients engage in an intensive, multi-component intervention with the minimum goal of 10% weight loss. For patients who have participated in one or more intensive programs for a minimum of six months and been unsuccessful, referral for surgical consult should be considered in those with a BMI >40 mg/k2, or BMI ≥35 mg/k2 and at least one obesity related co-morbidity. Patients with BMI ≥30 kg/m2, T2DM, and at least one obesity related co-morbidity should be managed aggressively and surgical referral carefully considered. More invasive and aggressive surgery methods, like the RYGB, BPD, and DS, are generally reserved for patients with a higher BMI and more co-morbidities, however, early research suggests that patients with Class I obesity and any co-morbidity, particularly diabetes, may benefit from earlier intervention. The gastric sleeve, an emerging procedure with results nearly equivalent to more invasive procedures, may also be an option.

We recommend further research to elucidate the mechanisms of diabetes improvement following bariatric surgery. Additional understanding and validation of surgical effects may help overcome reluctance among providers and patients to consider bariatric surgery options when conservative methods have not produced meaningful clinical results. In the meantime, PCP's should evaluate patients on an individual basis, considering cost and weighting complications associated with surgery against those associated with uncontrolled T2DM, and utilize available behavioral, medical, psychological, and as determined, surgical interventions in managing obese patients with T2DM.

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Table 1. Study Characteristics and Outcomes.

Study	Study Design	BMI	Intervention	Diabetes Remission Criteria – A1c	Outcomes	Analysis Points
Abbatini *et al.* (2012) Italy	Prospective	30-35	LSG (n=9) CMT, undefined (n=9)	<6.5%	Significant weight loss in LSG group (*p*<.05), measured by BMI, as well as decrease in A1c (*p*<.05) and FPG (*p*<.05). Diabetes resolved in 8/9 patients. No significant changes in CMT group.	1, 3, 6, 9, 12 mo.
Adams *et al.* (2012) USA	Prospective	≥ 35	RYGB (n=418) NSC 1 (n= 417) NSC 2 (n=321)	<6.5%	RYGB group maintained 27.7% weight loss at 6 years, decreased from 34.9% at 2 years. NSC 1 weight gain 0.2% at year 6, and NSC 2 unchanged. Diabetes remission in RYGB patients 75% at year 2, decreasing to 62% (95% CI, 49-75%) at year 6 vs 8% NSC 1 (*p*<.001), and 6% NSC 2 (*p*<.001	2 years 6 years
Arteburn *et al.* (2013) USA	Retrospective Cohort	NR	RYGB, open (n=2461) LRYGB (n=1973)	<6.0%	No data regarding weight loss. 68.2% (95% CI, 66-70%) diabetes remission within 5 years. 35.1% of those redeveloped diabetes within 5 years. Median duration remission 8.3 years.	Mean 3.1 years
Brethauer *et al.* (2013) USA	Retrospective Cohort	>40	RYGB (n=162) LSG (n=23) LAGB (n= 32)	<6.0%	Mean EWL 55% at 5+ years. RYGB EWL 11% higher than LSG (*p*=0.047) and 20% higher for LSG than for LAGB (*p*=0.004). 24% cohort achieved diabetes remission at 5 years, 26% partial remission (A1c 6-6.4%). Results best in RYGB vs LSG (*p*<.006), RYGB vs LAGB (*p*<0.001), and LSG vs LAGB (*p*=0.04). 27% of RYGB group who achieved complete remission maintained at 5 years. Among participants that initially remitted (n=127), there was a 19% relapse rate at 5 years for entire cohort.	2 years, 5+ years
Boza *et al.* (2011) Chile	Retrospective	30.4-35	LRYGB (n=30)	<6.5%	At 2 years, average BMI 23.9 ±2.4 kg/m2, representing a 28.4% decrease (*p*<0.001). At 12 mo., 83.3% patients achieved remission of	12 mo. 2 years

Study	Study Design	BMI	Intervention	Diabetes Remission Criteria – A1c	Outcomes	Analysis Points
					diabetes, decreasing to 65% at year 2. Ten patients with early or late complications, most often gastro-jejunal stenosis in 23.3% (13.3% early, 10.0% late) and one incidence of early pulmonary atelectasis.	
Cohen *et al.* (2012) Brazil	Prospective	30-34.9	RYGB (n=66)	<6.5%	Significant decreases in total body weight and waist circumference (p<0.001). HbA1c and FPG decreased significantly (p<0.001 for both), seen primarily in the first 6 months. Remission of diabetes occurred in 88% of patients with no reoccurrence during follow up (100% retention). No correlation between weight loss and HbA1c at any point, and correlation between weight loss and FPG only at 5 and 6 years (p=0.001 and 0.017 respectively). Minor complication rate of 15% (not requiring reoperation), no major morbidity or mortality.	7, 30, 90 days 6, 12 mo. 2, 4, 5, 6 years
Dixon *et al.* (2008) Australia	RCT nonblinded	30-40	LAGB (n=30) CMT (n=30)	<6.2%	LAGB group achieved mean 20% weight loss at 2 years, compared to mean 1.4% loss in CMT group (p<.001). 43% of LAGB group and 13% of CMT group achieved remission at 2 years (p<.001). HbA1c and FPG were significantly improved at 2 years in LAGB group (p<.001 for both) and positively correlated with greater percentage of weight loss. 13% adverse effects first year in LAGB, 26.6% adverse effects in conventionally treated group.	2 years
Dorman *et al.* (2012) USA	Retrospective	>35	DS (n=27) LAGB (n=30) RYGB (n=86) NSC (n=29)	<6.5%	Both DS and RYGB patients experienced substantial weight loss over one year, though the difference was not statistically significant. HbA1c was also markedly decreased, though 1.2% less in DS patients than	1 week, 1, 3, 6, 9, and 12 mo.

Study	Study Design	BMI	Intervention	Diabetes Remission Criteria – A1c	Outcomes	Analysis Points
					RYGB (p=0.001). LAGB patients lost even less weight than RYGB, and had an average 8.9 kg/m^2 higher BMI than case-matched RYGB patients post-intervention. LAGB patients HbA1c did not change. No significant change in weight or HbA1c was seen in NSC group. Diabetes was considered resolved at one year in 81.5% of DS patients, 58.1% of RYGB patients, 20% of LAGB patients, and 3.4% of NSC patients.	
Dunn *et al.* (2012) USA	RCT Double blinded	48 (mean)	RYGB (n=20) RYGB with oomentectomy (n=20)	<6.5%	Both groups lost considerable weight at one month, with no clear effect of additional oomentectomy on weight loss or insulin sensitivity. Of the 17 participants with diabetes, 59% were considered remitted at 1 month. Those with diabetes had a higher baseline hepatic glucose production (HGP) than those without (p=0.003), which improved to a greater extent after RYGB (p=0.006). At 1 month, overall hepatic insulin sensitivity improved but skeletal muscle insulin sensitivity did not.	1 mo.
Huang *et al.* (2011) Taiwan	Prospective	25-35	LRYGB (n=22)	<6.0%	Significant weight loss, decreased mean BMI from 30.8 ± 2.9 preoperatively to 23.7±1.6 by 12 months (p<0.001). At 12 months, 63.6% achieved remission of T2DM, 27.3% glycemic control (A1c < 7% with no diabetic medications), and 9.1% had improved. Positive correlation between those who remitted and younger age (p=0.002), higher BMI (p=0.001), and shorter disease duration (p=0.001). No major morbidity or mortality, minor complications within first year 9%.	12 mo.
Ikramuddin *et al.*	RCT nonblinded	30-39.9	LRYGB + Lifestyle (n=60)	<7.0% &	At 1 year, LRYGB participants lost 26.1% total body weight	12 mo.

Study	Study Design	BMI	Intervention	Diabetes Remission Criteria – A1c	Outcomes	Analysis Points
(2013) USA/Taiwan			LMM (n=60)	<6.0%	compared to 7.9% in the LMM group. In addition, 49% of LRYGB achieved the triple endpoint (A1c<7%, LDL<100 mg/dL, and SBP< 130 mm Hg) and 44% had a A1c<6.0%. In the LMM group, the triple endpoint and A1c<6% were only realized 19% and 9%, respectively. 36% total complication rate in RYGB group, thought only 20% of those were GI related, including 4 early serious postoperative complications, and 5 late postoperative. LMM group 25% adverse events, though only 6% directly GI related.	
Kashyap *et al.* (2013) USA	Prospective RCT	36.1 (mean)	IMT (n=20) RYGB / IMT (n=20) VSG / IMT (n=20)	<6.0%	Greatest weight loss in the RYGB group, though the VSG group statistically similar at 24 months (p=0.30), however truncal fat reduction was significantly greater in RYGB than VSG group (p=0.006). A1c reduced most in RYGB group at 12 mo. vs VSG (p=0.25) and IMT (p=0.02). At 24 months, 33.3% of RYGB had diabetes remission vs 10.5% of VSG (p=0.12) and 5.9% of IMT (p=0.09). A 5.8 increase in B-cell function was noted from baseline in RYGB group, with only negligible changes in IMT and VSG groups. Leptin decreased most significantly compared to IMT (p<0.001) and VSG (p=0.01). Complications included reoperation on 3 persons from surgical group, no morbidity.	12, 24 mo.
Lakdawala *et al.* (2013) India	Prospective	30-35	LRYGB (n=52)	<7%	Median EWL of 72.2% (66-92%) at one year, and 8/52 patients had weight regain leading to %EWL of 67.% (48-88%) at 5 the end of 5 years. At 1 year, 73.1% achieved remission for T2DM, 23.1% partial remission, and 3.8 unchanged. At 5 years, 15.4% who remitted initially relapsed	12 mo., 5 years

Study	Study Design	BMI	Intervention	Diabetes Remission Criteria – A1c	Outcomes	Analysis Points
					and were considered partially remitted. Positively correlated with diabetes remission were shorter disease duration (<5 years), higher percentage EWL (>75%), and higher fasting C-peptide levels (>6 mg/dL 100% remission, 3-6 mg/dL 75%). 3.8% minor complications in the early postoperative period including seromas/nausea. No late complications, significant dumping or malnutrition at 1 or 5 years. No mortality.	
Laferrere *et al.* (2011) USA	Prospective	>35	RYGB (n=10) LCD, 10 kg loss (n=11)	NR	RYGB achieved 10 kg weight loss faster than LCD group (*p*=0.003) and FBG and HOMA-IR decreased similarly, however, all RYGB patients were able to discontinue glucose lowering medications at one month while only half of LCD was able to. Glucose tolerance, measured by OGTT, improved more in RYGB group than LCD. Total amino acids (TAAs) and branched chain amino acids (BCAAs) decreased significantly after RYGB. Lower concentrations of TAAs/BCAAs are associated with leaner, non-diabetic individuals.	1, 2 mo.
Lee *et al.* (2011) Taiwan	RCT Double-blind	25-35	LRYGB + duodenum exclusion (n=30) VSG (n=30) without duodenum exclusion	<6.5%	At one year, BMI, EWL, and waist circumference improved more in the RYGB vs VSG group as follows (*p*=.009 BMI, .06 EWL, and .002 waist circumference). 70% of participants achieved remission T2DM, with greater proportion of RYGB than VSG (93% vs 47%; *p*=.02). 10% minor complication rate, 5% from each surgical group. No major complications or mortality.	3, 6, 9, 12 mo.

Study	Study Design	BMI	Intervention	Diabetes Remission Criteria – A1c	Outcomes	Analysis Points
Lee *et al*. (2012) Asia	Prospective	<35	RYGB (n=172), specifically LRYGB (53) and LMGBP (119) LSG (n=24) LAGB (n=4)	<6.0%	Greatest reductions in BMI and waist circumference (P=0.027 and 0.002 respectively) seen in RYGB patients. Remission of diabetes was realized in 72.4% patients, highest in RYGB group vs LSG and LAGB groups (79.3%, 55.0%, and 50.0%, *p*=0.062). Disease duration <5 years, and baseline BMI >30 kg/m2 correlated with higher incidence of remission (*p*=0.006 and *p*=0.027). 1% serious postoperative complication in RYGB group and 8% minor complications in all groups. No mortality.	12 mo.
Leslie *et al.* (2012) USA	Retrospective	40.7-47.3	RYGB (n=152) RMM (115)	<7.0%	RYGB group achieved significant weight loss and had reduced BMI (*p*<0.01 for both) compared to RMM group, which had no change at 2-year end-point. 38.2% of RYGB group and 17.4% RMM group met triple end point (A1c<7%, SBP<130 mm Hg, and LDL<100 mg/dL) at 2 years (*p*<0.01), with the most significant change in HbA1c in RYGB group vs RMM group, though medications were still needed in some patients. 13.8% of serious complications 90 days postoperatively, 4% inherent risks of any surgery, and at least 5% requiring reoperation. 14.4% readmitted and 6.3% ED visits with no admission in first 90 days. Follow up related to complications in RMM not permitted by IRB.	2 years
Mingrone *et al.* (2012) Italy	RCT nonblinded	>35	RYGB (n=20) BPD (n=20) CMT (n=20)	<6.5%	Both RYGB and BPD groups realized significant weight loss compared to the CMT group (*p*<0.001 for both), though the difference wasn't significant between the two (*p*=1.00). At 2 years, diabetes remitted for none of the CMT group, compared to 75% of the RYGB and 95% of the BPD groups	2 years

Study	Study Design	BMI	Intervention	Diabetes Remission Criteria – A1c	Outcomes	Analysis Points
					(*p*<0.001 for both comparisons). Complications included 1 (5%) minor requiring reoperation at 9 months in BPD group, 1 (5%) requiring reoperation at 6 months in RYGB, and 2 (10%) with adverse reactions to medication in CMT. No mortality.	
Plum *et al.* (2011) USA	Prospective	43-48	RYGB (n=7) LCD (n=7) *No diabetes* RYGB (n=9) LAGB (n=8)	NR	RYGB and LCD groups lost an equivalent amount of weight in the specified time period, though loss occurred in half the time for RYGB patients. At second time check, diabetes medications were discontinued in all RYGB diabetic patients, but in none of the LCD group. Improvements in insulin sensitivity (Si), HOMA-IR, and decreases in HDL cholesterol, Leptin, and Adiponectin were significant only in RYGB population (p =0.002, p <0.01, p <0.05, p <0.05, and p <0.01 respectively) compared to LCD patients.	NR, referred to 1 mo.
Schauer *et al.* (2012) USA	RCT Non-blinded	27-43	RYGB (n=50) VSG (n=50) IMT (n=50)	<6.0%	Decreases in weight and BMI were greater after RYGB than VSG (p =0.02 and 0.03, respectively), but both were significantly greater than those in the IMT group (p <0.001 for both comparisons). Glycemic control improved in all three groups, with resolution of T2DM occurring in 42% RYGB group vs 37% of VSG group (p =0.008), and 12% of IMT group (p =0.002) by 1 year. HOMA-IR, HDL, and CRP improved significantly in both surgical groups compared to IMT at 1 year. 22% of RYGB had complication within 12 months requiring hospitalization including 6% reoperation, 8% of SG including 2% reoperation, and 9% in IMT group for various conditions. No mortality.	12 mo.

Study	Study Design	BMI	Intervention	Diabetes Remission Criteria – A1c	Outcomes	Analysis Points
Serrot *et al.* (2011) USA	Retrospective	30-34.9	RYGB (n=17) NSC (n=17)	<7.0%	Weight loss, EWL, and BMI changes were significantly greater in RYGB cohort (*p* <0.001 for all comparisons), with only marginal changes in the NSC group. HbA1c improved greatly in RYGB group compared to NSC *(p* <.001). No significant changes were seen in BP or LDL in either group. Complications in RYGB requiring 18% readmission rate in first year, 2 (12%) requiring reoperation. Issues in NSC group not addressed. No mortality.	12 mo.
Tavares de Sa *et al*. (2011) Brazil	Retrospective	30-35	RYGB (n=27)	<6.0%	Significant changes in BMI and weight loss (*p* <0.001 for both) at 12 months. FPG was reduced by 46% and HbA1c by 27%. 48% of patients were considered to have remission of T2DM, with significant improvement in 74%. Disease duration <7 years positively correlated with better glycemic control (*p* =.03).	20 mo. (mean)

Surgical Procedures referenced, all considered forms of Gastric Bypass Surgery
("L" before any procedure indicates a laparoscopic approach)
RYGB= Roux-en-Y Gastric Bypass, DS=Duodenal Switch, BPD= Biliopancreatic Diversion SG= Sleeve Gastrectomy, AGB= Adjustable Gastric Banding,

Non-surgical interventions
NSC= Non-surgical control, LMM=Lifestyle Medical Management Group, CMT = Conventional Medical Therapy, IMT-Intensive Medical Therapy, RMM= Routine med