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Draft Comparative Effectiveness Review

Number XX

Comparative Effectiveness of Bariatric Surgery and Nonsurgical Therapy in Adults With Metabolic Conditions and a Body Mass Index of 30.0 to 34.9 kg/m²

Prepared for:
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Contract No.: XXX-XXXX-XXXXX-X

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AHRQ Publication No. xx-ECH-xx

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None of the investigators has any affiliations or financial involvement that conflicts with the material presented in this report.

Preface

The Agency for Healthcare Research and Quality (AHRQ) conducts the Effective Health Care Program as part of its mission to organize knowledge and make it available to inform decisions about health care. As part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Congress directed AHRQ to conduct and support research on the comparative outcomes, clinical effectiveness, and appropriateness of pharmaceuticals, devices, and health care services to meet the needs of Medicare, Medicaid, and the Children's Health Insurance Program (CHIP).

AHRQ has an established network of Evidence-based Practice Centers (EPCs) that produce Evidence Reports/Technology Assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care. The EPCs now lend their expertise to the Effective Health Care Program by conducting comparative effectiveness reviews (CERs) of medications, devices, and other relevant interventions, including strategies for how these items and services can best be organized, managed, and delivered.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about systematic reviews, see

http://www.effectivehealthcare.ahrq.gov/reference/purpose.cfm

AHRQ expects that CERs will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. In addition, AHRQ is committed to presenting information in different formats so that consumers who make decisions about their own and their family's health can benefit from the evidence.

Transparency and stakeholder input from are essential to the Effective Health Care Program. Please visit the Web site (http://www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an e-mail list to learn about new program products and opportunities for input. Comparative Effectiveness Reviews will be updated regularly.

We welcome comments on this CER. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by e-mail to epc@ahrq.hhs.gov.

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Comparative Effectiveness of Bariatric Surgery and Nonsurgical Therapy in Adults With Metabolic Conditions and a Body Mass Index of 30.0 to 34.9 kg/m²

Structured Abstract

Objectives: To systematically review the scientific evidence on efficacy, safety, and comparative effectiveness of various types of bariatric surgery for treating adult patients with a BMI of 30.0 to 34.9 kg/m² and metabolic conditions such as diabetes. Comparative effectiveness of surgery versus non-surgical interventions was also assessed.

Data Sources: Systematic reviews, case series, cohort, case control studies and controlled trials, found through searching PubMed®, Embase, CINAHL, Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Abstracts of Reviews of Effects (DARE), and Clinicaltrials.gov through September, 2011.

Review Methods: To be included, studies had to report on laparoscopic adjustable gastric banding (LAGB), Roux-en gastric bypass (RYGB), biliopancreatic diversion with duodenal switch (BPD), sleeve gastrectomy (SG), or conservative nonsurgical treatment, and had to include patients with BMI at least 30 kg/m^2 but less than 35 kg/m² with metabolic conditions such as type 2 diabetes. The following studies were excluded: 1) studies that did not report any outcomes of efficacy, effectiveness, or safety/adverse events; 2) non-surgical studies with less than one year followup; 3) non-surgical studies already included in previous systematic reviews; and 4) single case reports. Two reviewers, each trained in the critical analysis of scientific literature, independently reviewed and abstracted each study.

Results: We found only 28 studies reporting bariatric surgery results in this specific target population; only two were head to head trials comparing different procedures. In the 28 studies, surgery patients showed significantly greater weight loss at one year than reported in systematic reviews and RCTs on diet, exercise and other behavioral interventions. While both behavioral interventions and various medications lowered HbA1c levels significantly, the decreases reported in bariatric surgery patients were greater. In addition, improvements in diabetes outcomes were reported as early as one month post-surgery. Improvements in hypertension, LDL cholesterol, and triglycerides were also significant. Short term rates of adverse events associated with bariatric surgery were relatively low. Mortality rates, usually short-term in-hospital deaths, were relatively low (range: 0.0 to 0.3 percent). The more commonly reported complications, such as gastrointestinal related (overall: 31.9 percent), were minor and tended to not require major interventions. Due to the dearth of long-term studies of bariatric surgery in this particular target population, we found no evidence regarding major clinical end points such as all-cause mortality, cardiovascular mortality and morbidity, and peripheral arterial disease.

Conclusions: There is moderate strength evidence for RYGB, LABG, and sleeve gastrectomy for treatment of diabetes and metabolic conditions in patients with a BMI of between 30 kg/m^2 and 35 kg/m^2, in the short term. For BPD, both the number of studies and their sample sizes are much lower; thus the strength of evidence for this procedure is rated low. Evidence on comparative effectiveness of RYGB vs LABG vs sleeve gastrectomy is insufficient. Long term studies of bariatric surgery are needed to assess overall safety and effectiveness compared to non-surgical interventions.

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Appendixes cited in this report are available at http://ahrq.gov/XXXX (AHRQ will supply the rest of the information for this statement)

Comparative Effectiveness of Bariatric Surgery and Nonsurgical Therapy in Adults With Metabolic Conditions and a Body Mass Index of 30.0 to 34.9 kg/m²

Executive Summary

The Effective Health Program was initiated in 2005 to provide valid evidence about the comparative effectiveness of different medical interventions. The object is to help consumers, health care providers, and others in making informed choices among treatment alternatives. Through its Comparative Effectiveness Reviews, the program supports systematic appraisals of existing scientific evidence regarding treatments for high-priority health conditions. It also promotes and generates new scientific evidence by identifying gaps in existing scientific evidence and supporting new research. The program puts special emphasis on translating findings into a variety of useful formats for different stakeholders including consumers.

The full report and this summary are available at www.effectivehealthcare.ahrq.gov. Ahrq.gov/reports/final.cfm

Background

Bariatric surgery, also known as weight loss surgery, refers to surgical procedures usually performed on people who are morbidly obese, for the purpose of losing weight and to treat, as well as prevent, obesity – related comorbidities. Bariatric surgery has evolved since its introduction in the 1950s, with some procedures that were popular initially (like jejunoileal bypass) having been abandoned due to unacceptable complication rates. The types of bariatric surgery that are most commonly performed now include laparoscopic adjustable gastric banding (LAGB), Roux-en gastric bypass (RYGB); biliopancreatic diversion with duodenal switch (BPD); and sleeve gastrectomy (SG).

Studies show that these procedures cause significant weight loss in morbidly obese patients. In addition, bariatric surgeries such as LAGB and RYGB in morbidly obese patients have been found to be far more effective than conventional non-surgical therapy at improving diabetes in the short term. Improvement in diabetes has been demonstrated to start rapidly after bariatric surgery, especially for patients undergoing RYGB, before significant weight loss has occurred. The mechanism of postoperative metabolic improvements has not been fully elucidated and may in part be independent from weight loss, suggesting that bariatric surgery may improve metabolic comorbidities even for patients who are not morbidly obese.

Bariatric surgery is an accepted practice for patients with a BMI of 40kg/m² or greater, and for patients with a BMI of between 35-40kg/m² who have significant obesity-related comorbidities such as diabetes, hypertension, cardiovascular disease, dyslipidemia, obstructive sleep apnea, and degenerative arthritis. The U.S. National Institutes of Health (NIH) criteria from 1991 state that patients should have undergone medically supervised weight loss attempts prior to bariatric surgery.

In the past few years bariatric surgery has been suggested as an option for lower BMI (at least 30 kg/m^2 but less than 35 kg/m²) patients as a way to treat diabetes and other metabolic conditions. Given a lack of consensus regarding the minimum BMI requirement and uncertainties regarding the comparative effectiveness of different bariatric procedures, especially in the long term, a review of the relative risks

and benefits of the various surgical and conservative approaches to treatment of metabolic conditions such as diabetes (e.g., LAGB, RYGB, and other new procedures) in patients whose BMI is <35 kg/m² was suggested by the Medicaid Medical Directors Learning Network (MMDLN). MMDLN nominated the topic to AHRQ in 2008; the topic was refined by the Southern California EPC in conjunction with key informants including bariatric surgeons, researchers, consumers, and payers.

Objectives

This systematic review aims to address the following key questions.

1. What does the evidence show regarding the comparative effectiveness of bariatric surgery for treating adult patients with a BMI of 30.0 to 34.9 kg/m² and metabolic conditions, including diabetes? Are certain surgical procedures more effective than others (LAGB, gastric bypass, or sleeve gastrectomy)?

2. What does the evidence show regarding the comparative effectiveness of bariatric surgery vs. conventional nonsurgical therapies for treating adult patients with a BMI of 30.0 to 34.9 kg/m² and metabolic conditions?

3. What are the potential short-term adverse effects and/or complications associated with bariatric surgery for treating adult patients with a BMI of 30.0 to 34.9 kg/m² who have metabolic conditions?

4. Does the evidence show racial and demographic disparities with regard to potential benefits and harms associated with bariatric surgery for treating adult patients with a BMI of 30.0 to 34.9 kg/m² and metabolic conditions? What other patient factors (social support, counseling, preoperative weight loss, compliance with recommended treatment) are related to successful outcomes?

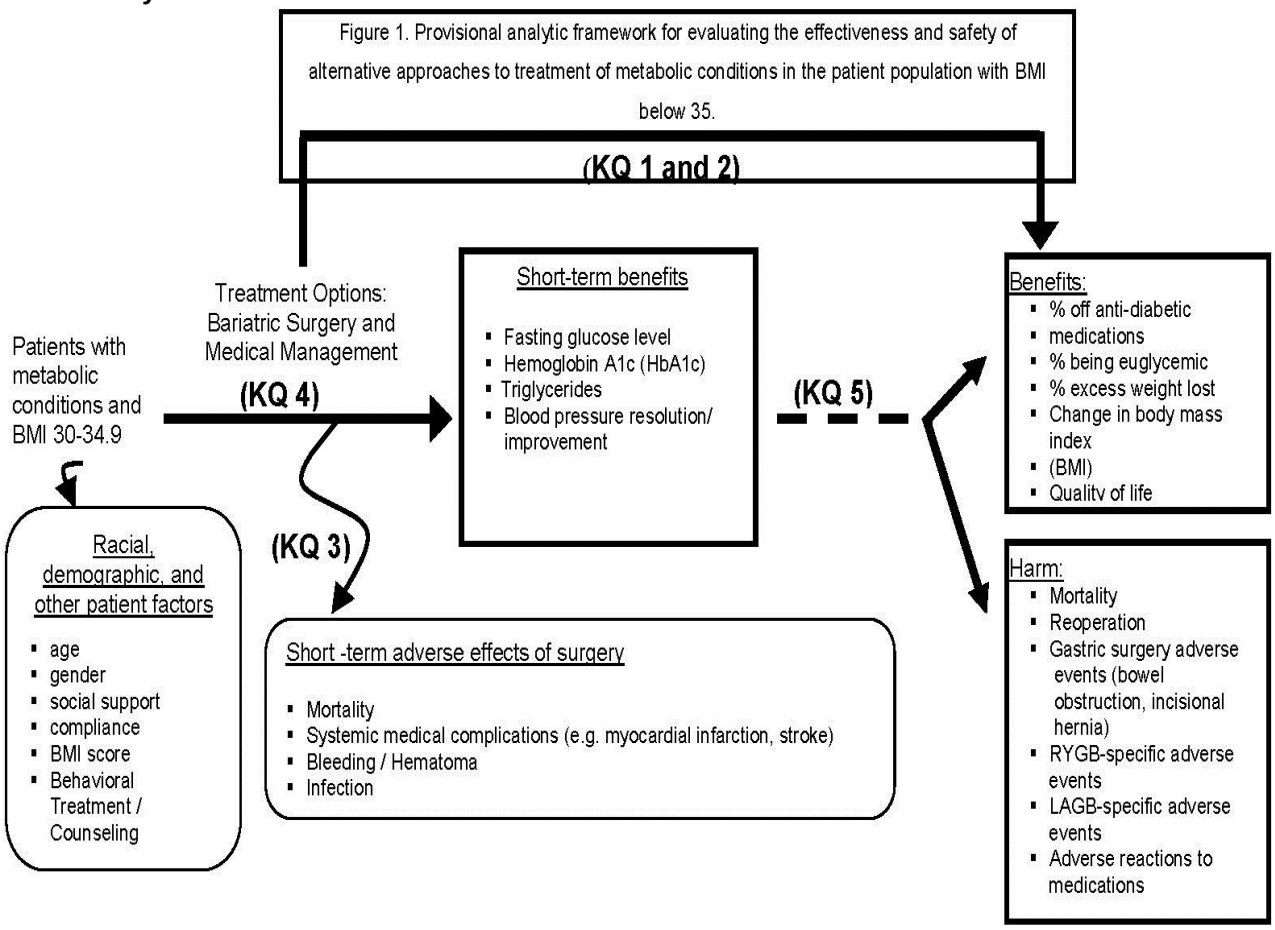
5. What does the evidence show regarding long-term benefits and harms of bariatric surgery for treating adult patients with a BMI of 30.0 to 34.9 kg/m² and who have metabolic conditions? How do the long-term benefits and harms of bariatric surgery compare to short-term outcomes (within 1 year after surgery)?

Analytic Framework

Figure S1 presents the analytic framework for this comparative effectiveness review (CER). Using data from controlled trials, cohort studies, and case series, evidence of the benefits and harms of different types of bariatric surgeries and conventional nonsurgical therapies in treating targeted patients (those with metabolic conditions and a BMI of 30 kg/m^2 =< 35 kg/m²) will be documented. The evidence for both short- and long-term outcomes will be assessed. Planned comparisons include: a) a) among different surgical procedures such as gastric bypass, LAGB, sleeve gastrectomy, BPD to answer KQ1, and b) of surgical procedures to conventional nonsurgical therapies (diet, exercise, pharmaceuticals, etc.) to answer KQ2. Documented short- and long-term benefits and harms of surgical procedures will also be compared to answer KQ3 and KQ5.

Benefits and harms for specific subpopulations (by gender, age, and race/ethnicity) and other patient factors (social support, counseling, preoperative weight loss, compliance with recommended treatment) will be examined and summarized to answer KQ4.

Figure S1. Analytic framework



Methods

We searched the electronic databases PubMed®, Embase, CINAHL (Cumulative Index to Nursing and Allied Health Literature), Cochrane library of systematic reviews, Cochrane Central Register of Controlled Trials (CENTRAL) and the Cochrane Database of Abstracts of Reviews of Effects (DARE) for studies addressing our key questions. Other sources included Clinicaltrials.gov, references of included studies and relevant reviews, and personal files from projects with related topics. The original search was conducted in March, 2010; electronic search updates were conducted monthly through September, 2011. We used various search terms for each type of procedure and non-surgical interventions. Further details and surgery strategies are included in the full report. There were no limits on publication date or language.

We searched the literature for systematic reviews, case series, cohort, case control studies and controlled trials. To be included, studies had to report on one of the surgical procedures listed above or conservative nonsurgical treatment, and had to include patients with BMI at least 30 kg/m^2 but less than 35 kg/m^2 with metabolic conditions such as type 2 diabetes. The following studies were excluded: 1) studies that did not report any outcomes of efficacy, effectiveness, or safety/adverse events; 2) non-surgical studies with less than one year followup; 3) non-surgical studies already included in previous systematic reviews; and 4) single case reports.

We reviewed the studies retrieved from the various sources against our exclusion criteria. Items included specific surgical procedure or nonsurgical treatment, study design, sample size, and type of outcomes reported (i.e. metabolic conditions, mortality, adverse events). Two reviewers, each trained in the critical analysis of scientific literature, independently reviewed each study and resolved disagreements by

consensus. The lead investigator resolved any disagreements that remained after discussions between the reviewers. Results from controlled trials, case-control studies, cohort studies, and cases series were abstracted by researchers using Distiller® software. Because of study heterogeneity, pooling was not possible; thus, we summarize the data qualitatively. Data abstracted included metabolic outcomes (glucose, blood pressure, lipids) and weight loss, mortality, and other adverse events. Other details included trial name (if applicable), setting, population characteristics (including sex, age, ethnicity, and co-morbidities), eligibility and exclusion criteria, any cointerventions, other allowed medication, comparisons, and results for each outcome. Intent-to-treat results were recorded if available.

We note here that we are dealing with two concepts, weight and disorders of glucose metabolism, that are a continuum physiology, but in the key questions are treated as dichotomous. In other words, we expect the risk of weight to be similar for a person with a BMI of 29.5 kg/m² and a person with a BMI of 31.5 kg/m², yet our key questions deal with the latter and not the former. Indeed, the published literature does not always conform to the same threshold specified in the key questions. We judged that studies that included substantial number of patients within the threshold of our key questions, but perhaps also some outside the range, were still informative, and were included. Thus, if a study included patients with a BMI of 29 kg/m² - 37 kg/m² we judged that it would be more informative to the key questions to include rather than exclude it. Similar decisions were made about the presence of impaired glucose tolerance and the clinical diagnosis of diabetes.

The overall strength of evidence for intervention effectiveness was assessed by using guidance suggested by the U.S. Agency for Healthcare Research and Quality (AHRQ) for its Effective Health Care Program. This method is based loosely on one developed by the Grade Working Group, and classifies the grade of evidence according to the following criteria:

- **High** = High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence on the estimate of effect.
- **Moderate** = Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.
- **Low** = Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of effect and is likely to change the estimate.
- **Insufficient** = Evidence is either unavailable or does not permit a conclusion.

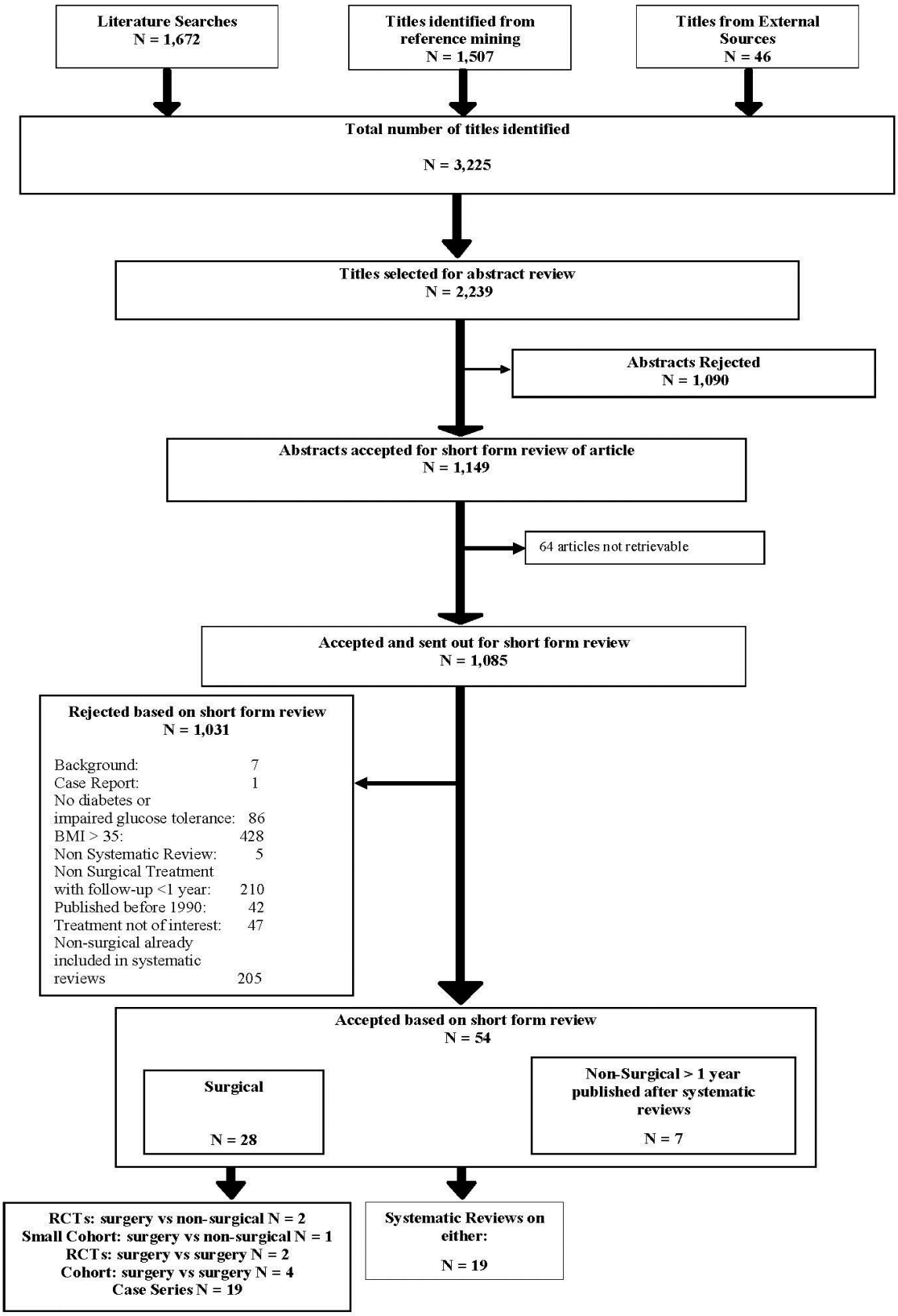
The evidence grade is based on four primary (required) domains and four optional domains. The required domains are risk of bias, consistency, directness, and precision; the additional domains are dose-response, plausible confounders that would decrease the observed effect, strength of association, and publication bias. For this review, global implicit judgment about “confidence” was used in the result.

Results

Figure S2 displays the results of our literature search. We identified 3,225 titles through our electronic database searches, reference mining, Scientific Information Packets received from device manufacturers, and expert panel suggestions. Our researchers selected 2,239 for further review; almost half were rejected upon abstract review. Of the 1,085 studies that underwent full-text review, we included 28 surgical studies, 19 systematic reviews, and seven non-surgical studies published after those reviews. The most common reasons for exclusion of surgical studies were focus on patients with higher BMI (428 studies) or the study did not report on diabetes or other metabolic outcomes (86 studies). The most common reasons for excluding non-surgical studies were followup of less than one year or inclusion in the previous systematic reviews that we summarized.

Of the 28 studies reporting bariatric surgery results in patients with diabetes or impaired glucose tolerance (IGT) and BMI of less than 35 kg/m², two were head to head trials comparing surgical procedures, four were cohort studies comparing surgical procedures, two were controlled trials with a non-surgical comparison arm, one was a small matched trial with a non-surgical arm, and the rest were observational studies with no comparison. Four of these studies included only a portion of patients with diabetes or impaired glucose tolerance (IGT); in the rest, all patients had diabetes.

Figure S2. Study/Literature flow diagram



Of the 28 surgery studies, there were eight studies with a RYGB arm, five with a LABG arm and six with a BPD arm. There were at least three studies on sleeve gastrectomy. (We found seven publications on sleeve outcomes by DePaula and colleagues. It was unclear how the populations overlapped; we were not able to ascertain clarification from the authors. One DePaula article reported one month outcomes for 420 consecutive patients; the six other articles reported on various subsets of these 420.) We also included nineteen systematic reviews on diet, exercise, medication, or bariatric surgery in our target population. Table A presents a summary of our findings.

Short term outcomes. There is moderate strength evidence that bariatric surgery is an effective way to treat diabetes in patients with BMI of at least 30 kg/m² but less than 35 kg/m² in the short term. At one year, surgery patients have shown significantly greater weight loss than can be expected from diet, exercise, or other behavioral interventions. And with the exception of exenatide, diabetes medications do not cause significant weight loss. While both behavioral interventions and various medications have been shown to lower HbA1c levels significantly, the decreases reported in bariatric surgery patients at one year are greater. In addition, improvements in diabetes outcomes have been reported as early as one month post-surgery. Improvements in hypertension, LDL cholesterol, and triglycerides have also been reported at one year in surgery patients.

Long term outcomes. There are few long-term data on patients with diabetes in this weight class who have undergone bariatric surgery. We found only four studies with follow-up of more than two years. One of these studies, a case series of LAGB patients in Italy, reported follow-up at five years. Unfortunately, five-year data were reported for only 29 of the 210 initial patients in this study, for a follow-up rate of only 13.8 percent. Another very small case series (N=7) of BPD followed patients for a mean of 13 years. Thus, the evidence that bariatric surgery is an effective way to treat diabetes in patients with BMI of at least 30 kg/m² but less than 35 kg/m² in the long term is insufficient. In contrast, behavior and medication interventions have been studied extensively in recent decades; several large long-term RCTs have found improved HbA1c continues for ten years. Whether these interventions improve micro- and macrovascular outcomes from diabetes is still being debated; we found mixed results in the literature. Long-term trials and meta analyses have reported clinically significant improvements in microvascular and macrovascular outcomes.

Specific bariatric procedures. We found two head to head trials comparing bariatric procedures. One average size trial (N=60) conducted in Taiwan compared RYGB to sleeve gastrectomy; the RYGB group had better weight and diabetes outcomes at one year post surgery. The other trial (N=38) compared two variations of sleeve gastrectomy: diverted versus non-diverted. At two years, this Brazilian study found similar weight loss among groups, but greater diabetes improvements using the diverted procedure.

We also found four cohort studies that compared procedures. Three were by the same Brazilian surgical group mentioned above; they compared the two types of sleeve gastrectomy. (It is unclear whether the three studies have overlapping populations; we received no response to several queries to the authors.) They found that both procedures led to significant weight loss and improved diabetes outcomes; they concluded that the diverted sleeve gastrectomy may be slightly more effective at improving metabolic outcomes. The other cohort study, conducted in the U.S. compared RYGB to LABG. This study was larger (N = 235) than the others, and had an adequate followup rate (61.9 percent for RYGB, 69.2 percent for LABG) at 6 to 12 months. Some patients were followed for two years. Weight loss was similar among groups; diabetes outcomes were generally better for RYGB patients.

We also examined observational studies of surgical procedures. Results at less than a year show clinically meaningful decreases in BMI for all types of bariatric surgery. Clinically meaningful diabetes outcomes were also reported at less than a year for all surgery types. At a year or more, decreases in BMI continued in all groups; RYGB patients had the greatest decrease. Clinically meaningful improvements in metabolic outcomes were present in all surgery groups.

Taking into consideration the entire body of evidence, we rate the strength of evidence as moderate for RYGB, LABG, and sleeve gastrectomy for treatment of diabetes and metabolic conditions in patients with a BMI of between 30 kg/m^2 and 35 kg/m^2, in the short term (up to two years). For BPD, both the number

of studies and their sample sizes are much lower in this population; thus the strength of evidence for this procedure is rated low. Evidence on comparative effectiveness of RYGB vs LABG vs Sleeve gastrectomy is insufficient.

Table A. Summary of data on interventions and outcomes in patients with diabetes or impaired glucose tolerance

Outcome	Behavioral changes (data almost entirely from systematic reviews of RCTs)	Intervention Medications (data almost entirely from systematic reviews of RCTs)	Bariatric Surgery (data almost entirely from observational studies)
Weight loss at one year:	2.8 kg for diet, exercise, behavioral vs usual care	Weight gain from 1 to 5 kg with some drugs. 2 kg weight loss with exenatide. No weight change with metformin.	BMI loss of 2 to 4 kg/m^2 (about 10 kg for someone 5 foot 6 inches tall)
Weight loss at two years:	2.7 kg for diet, exercise, behavioral vs usual care	Data unavailable	BMI loss of 4 to 8 kg/m^2 (about 18 kg for someone 5 foot 6 inches tall)
Long term weight loss (five years and more):	1.7 kg for diet, exercise, behavioral vs usual care at 5 years	Little data; the US Diabetes Prevention Program Outcomes Study (DPPOS) found no significant change with metformin at 10 years	BMI loss of 5.7 kg/m^2 at 5 years one study of LAGB
HbA1C at one year:	Decrease of 0.3 to 2.2 points	Decrease of 0.5 to 1.0 points	Decrease of 1.6 to 4.0 points
HbA1C at two years:	No significant change	Data unavailable	Decrease of 2.6 to 3.4 points
HbA1C at five years and more:	Little data; the US Diabetes Prevention Program Outcomes Study (DPPOS) found HbA1C concentrations lower in behavioral group at 10 years (vs. placebo)	Little data; the US Diabetes Prevention Program Outcomes Study (DPPOS) found HbA1C concentrations lower in metformin group at 10 years (vs. placebo)	Data unavailable
Other metabolic outcomes at one year:	Diet improved fasting glucose (1.3%-36.6% reduction) and triglycerides (11.3% - 58.9% reduction); the Spain PREDIMED study found Mediterranean diet reduced metabolic syndrome prevalence by 13.7% at 1 year; the Finnish Diabetes Prevention Study (DPS) found behavioral change reduced metabolic syndrome prevalence at 3.9 years (odds ratio: 0.62)	Most medications had minimal effects on systolic & diastolic blood pressure (< 5 mmHg change) Metformin and second generation sulfonylureas generally decreased LDL cholesterol levels	Decrease in triglycerides of 20 to 120 mg/dl
Other metabolic outcomes at five years and more:	Data unavailable	Data unavailable	Of 7 BPD patients followed, all had normal serum cholesterol and triglycerides.

Outcome	Behavioral changes (data almost entirely from systematic reviews of RCTs)	Intervention Medications (data almost entirely from systematic reviews of RCTs)	Bariatric Surgery (data almost entirely from observational studies)
Microvascular outcomes: (Renal disease, neuropathy, retinopathy, etc)	Data unavailable	UK Prospective Diabetes Study (UKPDS) found patients taking sulfonylurea, insulin, or metformin had 24% risk reduction for microvascular disease at 10 years Decision analysis models suggest that glucose control has a strong effect on microvascular outcomes.	In a two-year gastric sleeve study, macroalbuminuria resolved in all 4 patients who had it at baseline. Of 14 patients with microalbuminuria, it had resolved in all but 3. In another gastric sleeve study by the same research group (N=69), retinopathy was diagnosed in 26.1% of patients preoperatively. Objective improvement of the retinopathy was seen in 44.4% of these patients at 7 to 42 months.
Macrovascular outcomes: (Cardiovascular disease, stroke, heart attack)	Little data; the China Da Qing Diabetes Prevention Study (CDQDPS) found no significant difference in first CVD event, CVD mortality and all-cause mortality between intervention and control group	Meta-analysis of 5 trials with 33,040 participants found that on an average A1C reduction of 0.9% there was a 19% reduction in non-fatal myocardial infarction and a 15% reduction on coronary heart disease, and no statistically significant effect on stroke or all cause mortality.	Data unavailable
Prevention of diabetes:	Hazard ratio 0.51 for behavioral interventions vs standard advice at 1 to 5 years; the US Diabetes Prevention Program (DPP) found diabetes incidence in 10 years reduced by 34% by behavioral change vs. placebo, and the China Da Qing Diabetes Prevention Study (CDQDPS) found it was 43% lower in behavioral group over 20 years	Hazard ratio 0.70 for oral medications vs control at 1 to 5 years; the US Diabetes Prevention Program (DPP) found diabetes incidence in 10 years reduced by 18% in the metformin group vs. placebo	Data unavailable

Adverse Events. Unfortunately, we found no long-term studies of post-surgical adverse events in our target population. As displayed in Table B, short term (one-year post surgery) rates of adverse events for patients with BMI of at least 30 kg/m² but less than 35 kg/m² with diabetes are relatively low. As displayed in Table B, mortality rates, usually short-term in-hospital deaths, are relatively low (range: 0.3 percent to 0 percent).

The more commonly reported complications, such as gastrointestinal related (overall: 31.9 percent), were minor and tended to not require major interventions. Medical complications (overall: 3.8 percent) and metabolic disorders (1.6 percent) were also reported infrequently.

Rates of major surgical complications were uncommon (range: 1.8 percent to 7.4 percent), but these often required a significant intervention or reoperation. LAGB related complications were reportedly low at 4.7 percent for all events, 1.7 percent band slippage, 2.0 percent port or tubing leak, and 3.3 percent removal rate, although these are surgeon-reported data that mostly come from studies not specifically designed to assess complication rates. Studies of particular procedures reported consistent results, with

fairly precise ranges for each category of adverse events. Thus the strength of evidence for short term adverse events is considered moderate.

Table B. Incidence of Adverse Events Bariatric Surgery in patients with BMI 30 kg/m^2 to 34.9 kg/m^2

Adverse Event[a]	Overall	LAGB	Gastric Sleeve	RYGB	BPD
Mortality	0.3% (3/1131)	0.2% (1/531)	0.4% (2/484)	0% (0/235)	0% (0/20)
	n=11 studies	n=5 studies	n=2 studies	n=5 studies	n=1 study
MEDICAL COMPLICATIONS					
CV/Respiratory					
Arrhythmia	0.9% (5/563)	---	0.9% (4/454)	0.9% (1/109)	---
Pneumonia	2.0% (11/563)	---	2.0% (9/454)	1.8% (2/109)	---
Pulmonary embolus	10.0% (1/10)	---	---	---	10.0% (1/10)
Any CV/Respiratory complication	3.8% (22/573)	---	3.7% (17/454)	3.7% (4/109)	10.0% (1/10)
	n=3 studies	---	n=1 study	n=1 study	n=1 study
Renal					
Acute Renal Failure	0.4% (2/454)	---	0.4% (2/454)	---	---
Urinary Tract Infection	1.1% (5/454)	---	1.1% (5/454)	---	---
Any Renal Complication	1.5% (7/454)	---	1.5% (7/454)	---	---
	n=1 study	---	n=1 study	---	---
GI					
Anorexia/Excessive wt loss	20.5% (96/469)	---	21.2% (96/454)	0% (0/15)	---
Diarrhea	2.0% (9/454)	---	2.0% (9/454)	---	---
Feeding difficulties	8.7% (17/196)	3.8% (2/53)	20.0% (2/10)	9.8% (13/133)	---
GERD	10.2% (50/491)	---	11.0% (50/454)	0% (0/37)	---
Nausea/Vomiting	7.5% (44/587)	0.9% (1/109)	7.3% (33/454)	7.5% (10/133)	---
Acute cholecystitis	0.9% (1/109)	---	---	0.9% (1/109)	---
Any GI complication	31.9% (254/795)	3.1% (8/255)	47.8% (222/464)	13.0% (24/185)	---
	n=8 studies	n=3 studies	n=2 studies	n=4 studies	---
Metabolic					
Hyperuricemia/ Gout	0.9% (4/454)	---	0.9% (4/454)	---	---
Hypoglycemia	9.8% (5/51)	---	---	12.5% (3/24)	7.4% (2/27)
Any metabolic complication	1.6% (10/614)	---	0.9% (4/454)	3.0% (4/133)	7.4% (2/27)
	n=4 studies	---	n=1 study	n=2 studies	n=1 study
Constitutional / Other[b]	0.6% (4/622)	---	0.2% (1/454)	1.8% (3/168)	---
	n=4 studies	---	n=1 study	n=3 studies	---
Readmission	3.3% (2/60)	---	3.3% (1/30)	3.3% (1/30)	---
	n=1 study	---	n=1 study	n=1 study	---
SURGICAL COMPLICATIONS					
Major Surgical Complications					
Bleeding/Hematoma	3.2% (19/590)	3.7% (1/27)	3.7% (17/454)	0.9% (1/109)	---
Pouch/Anastomosis	2.6% (21/793)	5.2% (11/210)	1.1% (5/454)	4.6% (5/109)	0% (0/20)
Other[c]	2.5% (17/672)	---	2.9% (14/484)	1.2% (2/161)	1.8% (1/57)
Any major surgical complication	6.5% (57/882)	5.1% (12/237)	7.4% (36/484)	5.0% (8/161)	1.8% (1/57)
	n=9 studies	n=2 studies	n=2 studies	n=4 studies	n=3 studies
Minor Surgical Complications NOS	10.0% (6/60)	---	10.0% (3/30)	10.0% (3/30)	---
	n=1 study	---	n=1 study	n=1 study	---
Wound	2.0% (12/587)	---	2.0% (9/454)	2.3% (3/133)	---
	n=3 studies	---	n=1 study	n=2 studies	---
Band-Related					
Slippage	---	1.7% (9/531)	---	---	---
Port/Tube Leak	---	2.0% (7/356)	---	---	---
Removal	---	3.3% (7/210)	---	---	---
Any band-related complication	---	4.7% (25/531)	---	---	---
	---	n=5 studies	---	---	---

Percentage (Number of patients with adverse event / Total number of patients)

[a] Studies may have reported on >1 adverse event category and the majority reported on >1 surgical weight loss treatment. Some patients had >1 adverse event. The total number of adverse events was counted for each category.
[b] Other includes rhabdomyolisis, major morbidity, and not otherwise specified.
[c] Other surgical complications include abscess, bladder or stomach perforation, internal hernia, ischemia, intraabdominal complications, reoperation, and not otherwise specified.

Discussion

The literature on bariatric surgery in patients with BMI of at least 30 kg/m² and less than 35 kg/m², has many limitations. Most importantly, very few studies have long term followup. There are only four studies that follow patients for more than two years, and only two studies report data at five years; one has a followup rate of only 13.8 percent and the other includes only seven patients. Thus, we have almost no data on long-term efficacy and safety. No evidence was found on major clinical end points such as all-cause mortality, cardiovascular mortality or morbidity, or peripheral arterial disease. Importantly, the available evidence from the diabetes literature indicates it may be premature to assume that controlling glucose to normal or near normal levels completely mitigates the risk of microvascular and macrovascular events.

Randomized controlled trials (RCTs) are considered the highest level of medical evidence. We found only two RCTs of surgery versus non-surgical treatment and only two RCTs comparing surgical procedures in this population. We acknowledge the difficulty in conducting randomized trials of surgery; however, we also identified only four cohort studies comparing procedures. The rest of our data comes from case series reports primarily submitted by the practicing surgeons. The sample sizes in most studies, regardless of methodological design, are far smaller than those of most trials of diet, exercise, and medications.

Applicability of research to the larger treatment population is important in interpreting the results of the included studies. The participation rate, the intended target population, representativeness of the setting, and representativeness of the individuals are used to assess applicability. The two RCTs of LAGB versus non-surgical interventions were conducted in Australia. The RCT comparing LAGB to sleeve gastrectomy was conducted in Taiwan, while the RCT comparing two types of sleeve gastrectomy was conducted in Brazil. This Brazilian team was also responsible for three of the four cohort studies comparing procedures. The other cohort study was conducted in the U.S. Of the remaining observational studies (case series) only three were conducted in the U.S. The other studies were conducted in Western Europe, South America, and India. Diet, behavior and culture may differ dramatically from country to country. The results seen in these populations may not be directly applicable to American patients.

Data reported on adverse events have several limitations. Most studies were not primarily designed to assess these outcomes and all studies reflect surgeon or surgery-team reported events. Additionally, follow-up times and rates were variable, and many studies did not state exactly where adverse events occurred, other than “within a year post surgery.” As such, the rates of adverse events may be biased and lower than actual. Comparisons between procedure types are limited for the same reasons. We found no studies reporting adverse events in the long term.

Finally, although our literature search procedures were extensive and included canvassing experts regarding studies we may have missed, the possibility of publication bias still exists. For example the Los Angeles Times has run a series of news articles reporting on five deaths following LAGB surgery. Whether there is any causal relationship between the surgery and the deaths has not yet been assessed in a peer-reviewed publication, so no conclusions can be drawn. Still, it illustrates the potential for there to exist adverse events and/or beneficial outcomes in as-yet-undescribed populations.

Future Research

Future research should focus on long-term outcomes of bariatric surgery in U.S. patients with diabetes and BMI of 30 kg/m^2 to 34.9 kg/m^2. There is insufficient evidence that bariatric surgery is effective in preventing the clinical consequences of diabetes – microvascular and macrovascular endpoints such as diabetic retinopathy, kidney failure, and myocardial infarction. Studies with followup of five or eight, or even 10 years will be needed.

We found only one U.S. cohort study comparing procedures; this study used the BOLD (Bariatric Outcomes Longitudinal Database), a resource created by the Surgical Review Corporation to monitor outcomes from the Bariatric Surgery Center of Excellence (BSCOE) program. As of June 2009, there were 235 patients with diabetes within our BMI range in the BOLD database. The study we identified

reported outcomes at 6 to 12 months. Outcomes at 12 to 24 months were reported for only a small number of patients (6.8 percent) presumably because that followup time had not expired for most of the patients. Continued followup of these patients will be needed to assess the degree to which bariatric surgery mitigates long-term sequelae of diabetes.

Due to the lack of long-term studies, we found no evidence regarding major clinical end points such as all-cause mortality, cardiovascular mortality and morbidity, and peripheral arterial disease.. These outcomes should be tracked in any long-term study of bariatric surgery in patients with diabetes, as they are in long term studies of diet, exercise, and medication.

Glossary

Bariatric surgery: Surgery on the stomach and/or intestines to help an obese person lose weight.

Biliopancreatic Diversion (BPD): Surgery which involves removing 70 percent of the stomach along with bypassing a significant proportion of small intestine.

Body mass index (BMI): An individual's weight in kilograms divided by his or her height in meters squared. It is used to define normal weight, overweight, and obesity.

Roux en Y gastric bypass (RYGB): A surgical weight-loss procedure that involves the creation of a small stomach pouch to restrict food intake and construction of bypasses of the duodenum and other segments of the small intestine to cause malabsorption (decreased ability to absorb nutrients from food). Often referred to as gastric bypass

Gastroesophageal reflux disease (GERD): A condition commonly referred to as acid reflux, in which the liquid content of the stomach regurgitates (backs up or refluxes) into the esophagus.

Laparoscopic adjustable gastric banding (LAGB): A surgical weight-loss procedure that involves the placement of an adjustable belt around the upper portion of the stomach, restricting the size of the stomach and the amount of food it can hold.

Metabolic condition: A constellation of syndromes including impaired fasting glucose (prediabetes) and diabetes mellitus that increase the risk of cardiovascular disease.

Sleep apnea: A disorder characterized by a reduction or pause of breathing (airflow) during sleep.

Sleeve gastrectomy: A surgical weight-loss procedure in which the stomach is reduced to about 15 percent of its original size by surgical removal of a large portion of the stomach. There are variations on the sleeve gastrectomy that involve the addition of intestinal bypasses.

References

Please refer to the reference list in the full report for documentation of statements contained in the Executive Summary.

Internet Citation

{Provided by AHRQ} Authoring EPC, Title, Comparative Effectiveness Review: Number ##. AHRQ Publication Number No. 0#-###, Month 200#. Agency for Healthcare Research and Quality, Rockville, MD. http://www.effectivehealthcare.ahrq.gov/xxxxxxx

Introduction

In 2010, diabetes affected 25.8 million people in the U.S., or 8.3 percent of the population. About 1.9 million people aged 20 years or older were newly diagnosed with diabetes in 2010. In 2005-2008, based on fasting glucose or hemoglobin A1c levels, 35 percent of U.S. adults (79 million people) aged 20 years or older had prediabetes (50 percent of adults aged 65 years or older).[1] Among adults with diabetes, the prevalence of individuals considered as overweight or higher (BMI $\geq$ 25 kg/m²) was 80.3 percent; and the prevalence of obesity or higher (BMI >= 30 kg/m²) was 49.1 percent.[1]

Diabetes is considered a chronic, progressive disease. Traditional medical therapy focuses on glycemic control and control of long-term complications such as retinopathy, renal failure, and cardiovascular disease. Management may involve injecting insulin daily or using oral medications for a life time.

Studies show that bariatric surgeries such as LAGB and RYGB in morbidly obese patients have been found to be far more effective than conventional non-surgical therapy at improving diabetes in the short term.[2] Improvement in diabetes has been demonstrated to start rapidly after bariatric surgery, especially for patients undergoing RYGB, before significant weight loss has occurred. The mechanism of postoperative metabolic improvements has not been fully elucidated and may in part be independent from weight loss, suggesting that bariatric surgery may improve metabolic comorbidities even for patients who are not morbidly obese.

Bariatric surgery is an accepted practice for patients with a BMI of 40 kg/m² or greater, and for patients with a BMI of between 35-40kg/m² who have significant obesity-related comorbidities such as diabetes, hypertension, cardiovascular diseases, dyslipidemia, obstructive sleep apnea, and degenerative arthritis.

In the past few years bariatric surgery has been suggested as an option for lower BMI (at least 30 kg/m^2 but less than 35 kg/m²) patients as a way to treat or prevent diabetes and other metabolic conditions. Given a lack of consensus regarding the minimum BMI requirement and uncertainties regarding the comparative effectiveness of different bariatric procedures, especially in the long term, a review of the relative risks and benefits of the various surgical and conservative approaches to treatment of metabolic conditions such as diabetes (e.g., LAGB, RYGB, and other new procedures) in patients whose BMI is <35 kg/m² was suggested by the Medicaid Medical Directors Learning Network (MMDLN). MMDLN nominated the topic to AHRQ in 2008; the topic was refined by the Southern California EPC in conjunction with key informants including bariatric surgeons, researchers, consumers, and payers.

Conventional Therapy for Obesity and Diabetes

Conventional non-surgical therapy for overweight patients with diabetes or impaired glucose tolerance (IGT) includes diet, exercise, education, and medications (summarized below). Most interventions combine multiple modalities such as diet and exercise and must be sustained long-term to prevent weight regain.

Diet. A variety of diets have been proposed to assist obese patients in losing weight. Low calorie diets are typically high in carbohydrates (55 percent – 60 percent of total daily energy intake), low in fat (< 30 percent of energy intake), and produce a negative energy balance. Other strategies focus on decreasing the proportion of carbohydrates or fats. Low carbohydrate, high fat/protein diets (e.g. Atkins) induce weight loss primarily through decreased calorie intake but can have mixed effects on lipid profiles. Very-low-calorie diets (VLCDs) – typically 800 kcal per day – can be effective to induce rapid weight loss, especially when used as a short-term adjunct prior to bariatric surgery.

Exercise. Aerobic exercise can induce weight loss as well as decrease blood sugar levels for those with impaired glucose tolerance, though it is often difficult for morbidly obese patients due to comorbidities such as osteoarthritis. There is some debate regarding the optimal level of physical activity necessary to induce weight loss. The National Heart, Lung and Blood Institute (NHLBI) Obesity Education Initiative Expert and the United States (U.S.) Preventive Services Task Force guidelines suggest that at least 30 minutes of aerobic activity daily (amounting to an energy expenditure of 2,500 to 3,500 kcal per week) is necessary to promote weight loss and reduce comorbidities.[3]

Behavior Modification. Interventions focusing on education frequently include a community-based program to provide detailed strategies to assist with weight loss. Recommendations may include those regarding diet and exercise, as well as counseling regarding the deleterious effects of obesity and associated comorbidities. Cognitive behavioral modification is a form of education that targets specific psychological processes that may interfere with weight loss or maintenance.

Medications. Anti-obesity medications rely on increasing metabolism, decreasing appetite or altering food absorption. Commonly used drugs have included orlistat, which inhibits pancreatic lipases and prevents fat absorption, and sibutramine, a serotonin-norepinephrine reuptake inhibitor that decreases appetite. The latter was recently withdrawn from the U.S. and other markets due to increased risks of myocardial infarction and stroke.[4] Conventional pharmaceutical therapy for weight loss has not been very effective at producing significant and sustained weight loss in obese patients.[5-6] The combination of diet and weight loss medications like orlistat results in a mean weight loss of only 3-4 kg at one year.[5] Such medications can improve glycemic control and dyslipidemia in obese patients with type 2 diabetes, but this improvement is modest.[7]

Conventional therapy for diabetes also includes specific medications meant to lower plasma glucose levels. Pharmacotherapy for obese patients with diabetes includes insulin or oral hypoglycemic agents, which work through a variety of mechanisms (e.g. sulfonylureas, which increase insulin secretion; biguanides, which reduce hepatic glucose production; and thiazolidinediones or glitazones, which reduce insulin resistance mainly in the periphery). Medications used for obese patients with diabetes, such as insulin or sulfonylureas (e.g.

glyburide), do not produce significant weight loss and can even cause weight gain, exacerbating insulin resistance and glucose intolerance.[8] Cardiovascular risk reduction medications (statins, aspirin, angiotensin converting enzyme inhibitors, etc.) are also mainstays of diabetes management.

Bariatric Surgery

Bariatric surgery was first introduced in the 1950s and has evolved significantly since that time, leading to some procedures that were very common initially (e.g. jejunoileal bypass) being abandoned due to unacceptably high complication rates or poor long-term benefit (i.e., vertical banded gastroplasty). The most common procedures currently performed are gastric bypass, laparoscopic adjustable gastric banding, and gastric sleeve. These procedures result in weight loss via different mechanisms, and some employ a combination of mechanisms. In general, bariatric surgery employs three mechanisms to induce weight loss: 1) restricting the size of the upper portion of the stomach limits the quantity of food a patient can consume at a single meal, 2) malabsorptive procedures decrease the proportion of nutrients that are absorbed from a meal, and 3) a combination of hormonal changes are induced by creating a small gastric pouch (and outlet) along with a proximal bypass. Details of selected bariatric procedures (those performed frequently now) are provided below.

Gastric Bypass. Roux en Y gastric bypass (RYGB), which we will refer to as "gastric bypass" throughout the report, achieves weight loss through a complex mechanism. The surgery involves creating a small gastric pouch (and outlet) along with a proximal intestinal bypass. This small pouch (30 cc) is connected to a segment of the jejunum (which is downstream), thus bypassing the duodenum and very proximal small intestine. Although the procedure generates minimal malabsorption, significant changes in hormones and neural signals to the gastrointestinal tract lead to hunger control and satiety. In addition, following ingestion of high-density carbohydrates, many patients will experience the resultant "dumping" syndrome, whose unpleasant symptoms include flushing, palpitations, abdominal pain, cramping, and diarrhea. As a result, patients develop an aversion to high-carbohydrate foods. The overall result is that patients make major changes in their diet and eating habits. Gastric bypass for weight loss has been performed regularly since the early 1980s. It was first performed laparoscopically in the early 1990s and is now one of the most common types of weight loss procedures.

Laparoscopic Adjustable Gastric Band. Gastric banding achieves weight loss by creating gastric restriction. The uppermost portion of the stomach is encircled by a band to create a gastric pouch with a capacity of approximately 15 to 30 cubic centimeters (cc). The band consists of an inflatable doughnut-shaped balloon whose diameter can be adjusted in the clinic by adding or removing saline via a reservoir port positioned beneath the skin. The bands are adjustable to allow the size of the gastric outlet to be modified as needed, depending on the rate of a patient's weight loss. Weight loss is achieved mainly by restricting caloric intake. Currently, almost all of the banding procedures are performed laparoscopically (laparoscopic adjustable gastric banding, or LAGB). While this procedure is technically reversible (e.g., removal of the band for failed weight loss), doing so exposes the patient to potential risks associated with a second operation and, of course, will necessitate identifying an alternative method for weight loss.

Gastric Sleeve. Gastric sleeve (also known as vertical sleeve gastrectomy) is a relatively new restrictive type of procedure. Approximately 60 to 80 percent of the stomach is removed laparoscopically, leaving a small tube (or "sleeve") which remains connected to the original stomach outlet. The cutaway part of the stomach is removed, making this procedure irreversible, and no foreign objects are implanted in the body. The gastric sleeve can be performed on its own, or in combination with ileal interposition (known as ileal interposition associated with a sleeve gastrectomy, or II-SG). The II-SG procedure involves stapling off a segment of ileum and anastomosing it with the proximal jejunum, which remains in association with the gastric sleeve. Another variation consists of ileal interposition associated with a diverted sleeve gastrectomy (II-DSG). The II-DSG procedure consists of an ileal segment that is anastomosed to the proximal duodenum, which remains in continuity with the gastric sleeve. This diverts the duodenum, which may have independent metabolic consequences that can impact postoperative outcomes. Weight loss is caused by the smaller size of the stomach limiting food intake, as well as lowering plasma ghrelin (a natural hormone which produces hunger). Originally gastric sleeve surgery was part of a two-stage procedure which was later followed by a malabsorptive procedure such as gastric bypass (discussed below). However many patients lost sufficient weight after the gastric sleeve such that the second stage surgery was not needed, and it has been gaining popularity as a stand-alone procedure since the early 2000s.

Biliopancreatic diversion (BPD). BPD involves removing 70 percent of the stomach along with bypassing a significant proportion of small intestine. By reducing the size of the stomach, less acid is produced, but the remaining capacity is generous compared to that achieved with gastric bypass. As such, patients eat relatively normal-sized meals and do not need to restrict intake severely. Malabsorption is caused by 1) the diversion of food downstream, decreasing the opportunity for nutrient absorption and 2) reduction in the quantities of enzymes and bile in the bypassed segment, which decreases absorption. Patients develop steatorrhea from the decrease in fat absorption.

Although this procedure is not as commonly performed as either banding procedures or gastric bypass, the approach is strongly favored by some bariatric surgery specialists. The partial biliopancreatic diversion with duodenal switch is a variant of the BPD procedure that, until recently, was performed mostly in Italy and only rarely performed in the United States. Recently, a number of centers in the United States and Canada have begun to perform this procedure, which involves resection of the greater curvature of the stomach, preservation of the pyloric sphincter, and transection of the duodenum above the ampulla of Vater with a duodeno-ileal anastomosis and a lower ileo-ileal anastomosis.

Bariatric Surgery in Lower-Weight Patients

Currently the standard criteria for bariatric surgery candidates include having a BMI $\geq$ 40 kg/m² or $\geq$ 35 kg/m² with significant obesity-related comorbidities. This is based on National Institutes of Health (NIH) guidelines from 1991[9] and has been endorsed by the Center for Medicare and Medicaid Services (CMS), which covers a variety of bariatric procedures for patients with BMI $\geq$ 35 kg/m² and comorbidities.[10] Bariatric surgery has been shown to improve or resolve metabolic conditions such as diabetes in the short term, at least in part due to the associated weight loss.[11] However there may be other mechanisms involved (particularly for RYGB) as metabolic improvements are often seen rapidly after surgery, before significant weight loss has occurred. Bariatric surgery has therefore been advocated as a treatment for

metabolic conditions even for the non-morbidly obese patients. Though experts have suggested that the minimum BMI requirement for bariatric candidates with type 2 diabetes be lowered below 35 kg/m², CMS in 2006 denied coverage for lower BMI patients with diabetes, specifically for open and laparoscopic RYGB, LAGB, and open and laparoscopic BPD/DS.[12] More recently, the U.S. Food and Drug Administration (FDA) expanded the indications for a specific brand of laparoscopic adjustable gastric banding to include patients with a BMI between 30 kg/m² and 34.9 kg/m² and at least one obesity-related comorbidity.[13]

A review of the relative risks and benefits of the various surgical and conservative approaches in patients with metabolic conditions whose BMI is <35 kg/m² was suggested by the Medicaid Medical Directors Learning Network (MMDLN). MMDLN nominated the topic to AHRQ in 2008; the topic was refined by the Southern California EPC in conjunction with key informants including bariatric surgeons, researchers, consumers, and payers.

Methods

Original Proposed Key Questions

1. What does the evidence show regarding the comparative effectiveness of bariatric surgery for treating adult patients with a BMI of 30.0 to 34.9 kg/m² and metabolic conditions, including diabetes? Are certain surgical procedures more effective than others (LAGB, gastric bypass, or sleeve gastrectomy)?

2. What does the evidence show regarding the comparative effectiveness of bariatric surgery vs. conventional nonsurgical therapies for treating adult patients with a BMI of 30.0 to 34.9 kg/m² and metabolic conditions?

3. What are the potential short-term adverse effects and/or complications associated with bariatric surgery for treating adult patients with a BMI of 30.0 to 34.9 kg/m² who have metabolic conditions?

4. Does the evidence show racial and demographic disparities with regard to potential benefits and harms associated with bariatric surgery for treating adult patients with a BMI of 30.0 to 34.9 kg/m² and metabolic conditions? What other patient factors (social support, counseling, preoperative weight loss, compliance with recommended treatment) are related to successful outcomes?

5. What does the evidence show regarding long-term benefits and harms of bariatric surgery for treating adult patients with a BMI of 30.0 to 34.9 kg/m² and who have metabolic conditions? How do the long-term benefits and harms of bariatric surgery compare to short-term outcomes (within 1 year after surgery)?

Technical Expert Panel

For each AHRQ evidence report, a Technical Expert Panel (TEP) is assembled to provide clinical expertise and context. We invited a distinguished group of scientists and clinicians, including individuals with expertise in obesity, surgery, and metabolic conditions such as diabetes, to participate in the TEP for this report. A list of members will be included in the front matter of the final report. A TEP conference call was held on October 4, 2010. On the call, staff presented the key questions as well as the preliminary literature search results and asked experts to help define the scope of the review (e.g. types of metabolic conditions and bariatric procedures to include). The panel will also review this draft report and provide feedback.

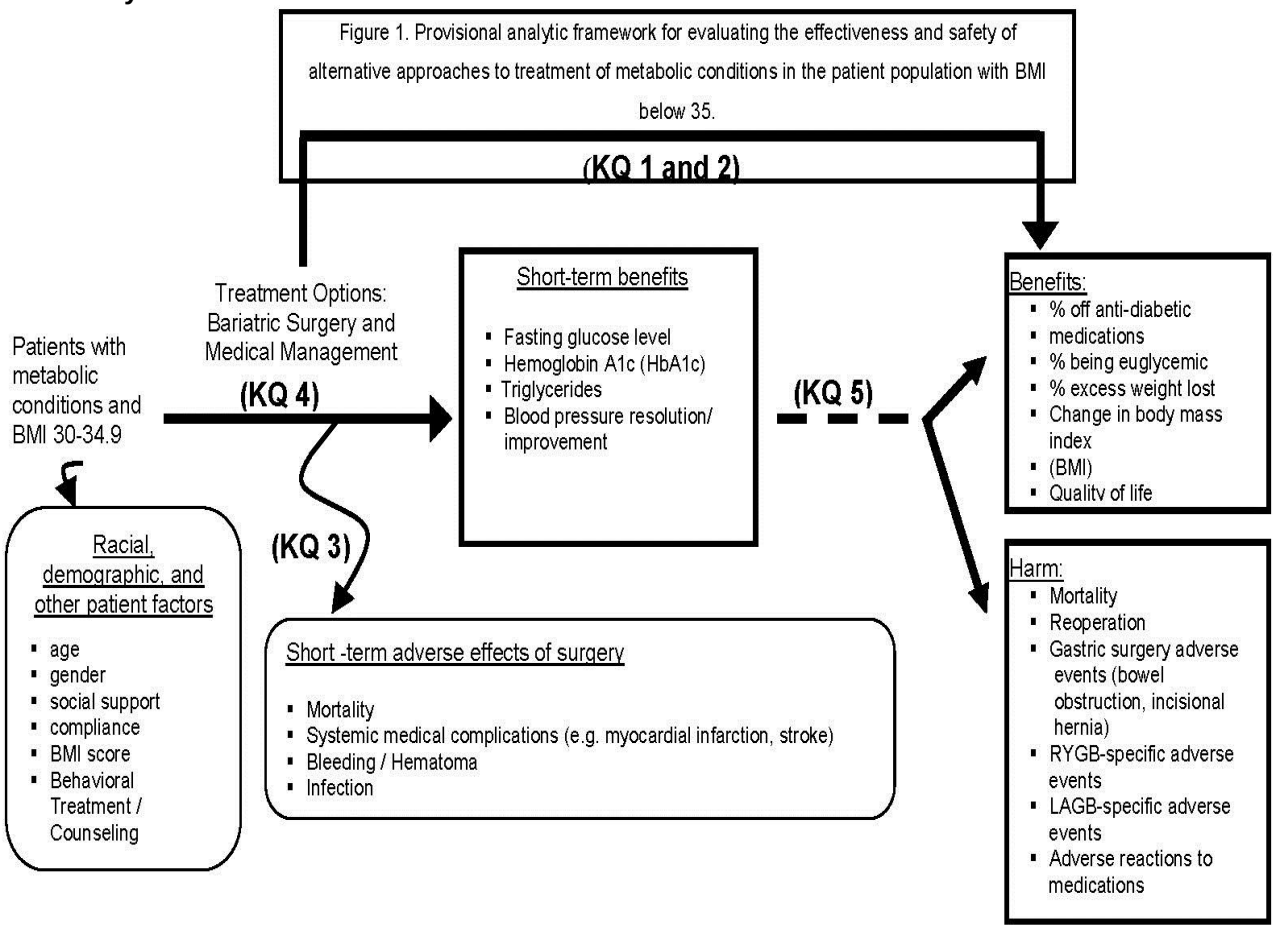
Analytic Framework

Figure 1 presents the analytic framework for this comparative effectiveness review (CER). Using data from controlled trials, cohort studies, and case series, evidence of the benefits and harms of different types of bariatric surgeries and conventional nonsurgical therapies in treating targeted patients (those with metabolic conditions and a BMI of 30 to 34.9 kg/m²) will be documented. The evidence for both short- and long-term outcomes will be assessed. Planned comparisons include: a) among different surgical procedures such as gastric bypass, LAGB,

sleeve gastrectomy, BPD to answer KQ1, and b) of surgical procedures to conventional nonsurgical therapies (diet, exercise, pharmaceuticals, etc.) to answer KQ2. Documented short- and long-term benefits and harms of surgical procedures will also be compared to answer KQ3 and KQ5.

Benefits and harms for specific subpopulations (by gender, age, and race/ethnicity) and other patient factors (social support, counseling, preoperative weight loss, compliance with recommended treatment) will be examined and summarized to answer KQ4.

Figure 1. Analytic framework



Literature Search

Our search for studies began in April, 2009, with an electronic search of PubMed® and Embase for reports on bariatric surgery and metabolic conditions. We also searched the CINAHL (Cumulative Index to Nursing and Allied Health Literature), Cochrane library of systematic reviews, Cochrane Central Register of Controlled Trials (CENTRAL) and the Cochrane Database of Abstracts of Reviews of Effects (DARE). (The Cochrane Collaboration is an international organization that helps people make well-informed decisions about health care by preparing, maintaining, and promoting the accessibility of systematic reviews on the effects of heath care interventions.) Other sources included Clinicaltrials.gov, references of included studies, and relevant reviews, and personal files from projects with related topics. Reviewers

performed additional reference mining by scanning titles listed in the reference section of each selected study to identify additional potential articles. The literature search was updated in March, 2010, October, 2010 after the TEP call, and search updates were conducted monthly through September, 2011.

Appendix A shows our specific search terms. We also searched for studies of nonsurgical treatments (diet, exercise, education, medications, and other interventions) The following bariatric procedures: laparoscopic adjustable gastric banding (LAGB), gastric sleeve, vertical-banded gastroplasty, Roux-en-Y gastric bypass (RYGB), and biliopancreatic diversion (BPD) were included in our searches. Jejunoileal bypass, one of the earliest procedures performed for weight loss, was not included, as this procedure was abandoned about 25 years ago due to a high rate of complications. We used various search terms for each type of procedure. For example, for Roux-en-Y gastric bypass, we also used: gastric bypass, RYGB, laparoscopic gastric bypass, and open gastric bypass. We ordered all articles on metabolic conditions and weight loss interventions, regardless of language or publication date.

The strongest evidence to assess the relative benefits and harms of bariatric surgery with nonsurgical therapy would come from randomized controlled trials dissecting comparing the treatment options, including only patients in the BMI range of our key questions (30 kg/m^2 – 34.9 kg/m^2) and measuring relevant outcomes such as glucose control and use of diabetic medications, but also the outcomes that treating diabetes is meant to prevent: microvascular and macrovascular complications.

Because a priori we expected there to be very few RCTs comparing surgical with nonsurgical therapy, we expected – as in our prior Evidence Report a surgical and nonsurgical weight loss therapies in more obese patients[14] – that we would need to make indirect comparisons between the best available data on the effects of surgery and the best available data on the effects of nonsurgical therapy. For the former, we expected to use case series data. For the latter, there is a voluminous literature on the management of diabetes, and we expected to use existing systematic reviews supplemented with any recent trials published after the search dates of these reviews. This use of literature is depicted in Figure 2.

Article Review

Study Inclusion

We searched the literature for systematic reviews, case series, cohort, case control and controlled trials. Editorials, historical pieces, and descriptive articles without data were excluded. The studies included in this report are of one of the following types.

Review articles identified by the search were classified as either systematic (including meta-analyses) or nonsystematic. *Systematic reviews* were identified by reading the methods section of the article to determine whether an acceptable method was employed to identify evidence (such as a description of the name of the computerized database searched and the full set of search terms used, as well as details about the method for accepting and rejecting identified articles).

Randomized controlled trials (RCTs) are studies where the participants are definitely assigned prospectively to one of two (or more) alternative forms of intervention, using a process of random allocation (e.g., random number generation, coin flips).

Controlled clinical trials (CCTs) are studies where participants (or other units) are either

(a) definitely assigned prospectively to one of two (or more) alternative forms of health care using a quasi-random allocation method (e.g., alternation, date of birth, patient identifier)
OR
(b) possibly assigned prospectively to one of two (or more) alternative forms of health care using a process of random or quasi-random allocation.

Observational studies (such as cohort and cases series) are those where the investigators do not control who gets the interventions.

To be included, studies had to report on one of the surgical procedures or conservative nonsurgical treatments described in the introduction, and had to include patients with BMI 30.0 to 34.9 kg/m² with metabolic conditions such as type 2 diabetes. Systematic reviews of interventions both surgical and non-surgical were the exception to this rule, since they often synthesized data over a number of studies with varying BMI patient population. The following studies were excluded: 1) studies that did not report any outcomes of efficacy, effectiveness, or safety/adverse events; 2) non-surgical studies with less than one year followup; 3) non-surgical studies already included in previous systematic reviews; 4) background articles; and 5) single case reports.

Screening

Using a single-page "screening form" (included in Appendix B), we reviewed the studies retrieved from the various sources against our exclusion criteria. Items included specific surgical procedure or nonsurgical treatment, study design, sample size, and type of outcomes reported (i.e. metabolic conditions, mortality, adverse events). Two reviewers, each trained in the critical analysis of scientific literature, independently reviewed each study and resolved disagreements by consensus. The lead investigator resolved any disagreements that remained after discussions between the reviewers.

Data Abstraction & Synthesis of Results

Results from controlled trials, case-control studies, cohort studies, and cases series were abstracted by researchers using Distiller® software. Because of study heterogeneity, pooling was not possible; thus, we summarize the data qualitatively. Data abstracted included metabolic outcomes (glucose, blood pressure, lipids) and weight loss, mortality, and other adverse events. Other details included trial name (if applicable), setting, population characteristics (including sex, age, ethnicity, and diagnosis), eligibility and exclusion criteria, any cointerventions, other allowed medication, comparisons, and results for each outcome. Intent-to-treat results were recorded if available.

Assessment of Methodological Quality

To arrive at a quantitative measure for controlled trials, the Jadad scale was used, which was originally developed for drug trials.[15] This method measures quality on a scale that ranges from 0–5, assigning points for randomization and blinding and accounting for withdrawals and dropouts. (Across a broad array of meta-analyses, an evaluation of the scale found that trials scoring from 0–2 report exaggerated results when compared with trials scoring from 3–5.[16] The latter scores indicate studies of "good" quality and the former indicate those of "poor" quality.)

For any disagreement that arose during the quality assessment, issues were discussed in the project meeting, and group decisions were made by the research team.

To assess the quality of included systematic reviews and meta-analyses, we used AMSTAR - a measurement tool for the 'assessment of multiple systematic reviews.[17] This tool contains eleven yes/ no items, such as whether the literature search was comprehensive, if dual abstraction was used, and if individual study characteristics are displayed. The tool has strong face and content validity, inter-rater reliability, and construct validity.[18] A copy is included in Appendix B.

Grading the Evidence for Each Key Question

The overall strength of evidence for intervention effectiveness was assessed by using guidance suggested by the U.S. Agency for Healthcare Research and Quality (AHRQ) for its Effective Health Care Program.[19-20] This method is based loosely on one developed by the Grade Working Group,[21] and classifies the grade of evidence according to the following criteria:

High = High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence on the estimate of effect.

Moderate = Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.

Low = Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of effect and is likely to change the estimate.

Insufficient = Evidence either is unavailable or does not permit a conclusion.

The evidence grade is based on four primary (required) domains and four optional domains. The required domains are risk of bias, consistency, directness, and precision; the additional domains are dose-response, plausible confounders that would decrease the observed effect, strength of association, and publication bias. Information on the required domains is presented in Table 1 below.

Table 1. Grading the strength of a body of evidence: required domains and their definitions

Domain	Definition and Elements	Score and Application
Risk of Bias	Risk of bias is the degree to which the included studies for a given outcome or comparison have a high likelihood of adequate protection against bias (i.e., good internal validity), assessed through two main elements: • Study design (e.g., RCTs or observational studies) • Aggregate quality of the studies under consideration. Information for this determination comes from the rating of quality (good/fair/poor) done for individual studies	Use one of three levels of aggregate risk of bias: • Low risk of bias • Medium risk of bias • High risk of bias
Consistency	The principal definition of consistency is the degree to which reported effect sizes from included studies appear to have the same direction of effect. This can be assessed through two main elements: • Effect sizes have the same sign (that is, are on the same side of “no effect”) • The range of effect sizes is narrow.	Use one of three levels of consistency: • Consistent (i.e., no inconsistency) • Inconsistent • Unknown or not applicable (e.g., single study) As noted in the text, single-study evidence bases (even megatrials) cannot be judged with respect to consistency. In that instance, use “Consistency unknown (single study).”

Domain	Definition and Elements	Score and Application
Directness	The rating of directness relates to whether the evidence links the interventions directly to health outcomes. For a comparison of two treatments, directness implies that head-to-head trials measure the most important health or ultimate outcomes. Two types of directness, which can coexist , may be of concern: Evidence is indirect if: • It uses intermediate or surrogate outcomes instead of health outcomes. In this case, one body of evidence links the intervention to intermediate outcomes and another body of evidence links the intermediate to most important (health or ultimate) outcomes. • It uses two or more bodies of evidence to compare interventions A and B – that is, studies of A versus placebo and B versus placebo, or studies of A versus C and B versus C but not A versus B. Indirectness always implies that more than one body of evidence is required to link interventions to the most important health outcomes. Directness may be contingent on the outcomes of interest. EPC authors are expected to make clear the outcomes involved when assessing this domain.	Score dichotomously as one of two levels directness • Direct • Indirect If indirect, specify which of the two types of indirectness account for the rating (or both, if that is the case) -- namely, use of intermediate/ surrogate outcomes rather than health outcomes, and use of indirect comparisons. Comment on the potential weaknesses caused by, or inherent in, the indirect analysis. The EPC should note if both direct and indirect evidence was available, particularly when indirect evidence supports a small body of direct evidence.

Domain	Definition and Elements	Score and Application
Precision	Precision is the degree of certainty surrounding an effect estimate with respect to a given outcome (i.e., for each outcome separately) If a meta-analysis was performed, this will be the confidence interval around the summary effect size.	Score dichotomously as one of two levels of precision: • **Precise** • **Imprecise** A precise estimate is an estimate that would allow a clinically useful conclusion. An imprecise estimate is one for which the confidence interval is wide enough to include clinically distinct conclusions. For example, results may be statistically compatible with both clinically important superiority and inferiority (i.e., the direction of effect is unknown), a circumstance that will preclude a valid conclusion.

EPC = Evidence-based Practice Center

For this systematic review, we focused on the inherent risk of bias in study design (e.g., in general, randomized controlled trials have less bias than observational studies) and within study design, certain aspects of execution and reporting (e.g. proportion lost to followup, baseline differences between the comparison groups). Regarding consistency, we judged the evidence as consistent if, *all other factors being equal*, a super majority of the studies reported results in the same direction. For directness, we judged the evidence to be direct if, *all other factors being equal*, studies reported relevant health outcomes such as weight loss, micro or macrovascular complications of diabetes, stroke myocardial infarction, etc. rather than indirect outcomes such as fasting blood sugar or HbA1c. For precision, we defined the evidence as precise if, all other factors being equal, the data were sufficiently within its 95% confidence interval to support a

decision, i.e. if the evidence is on one side of a decision threshold. The most important additional domain was publication bias, because surgeons submitting case series for publication may be unrepresentative of the community as a whole.

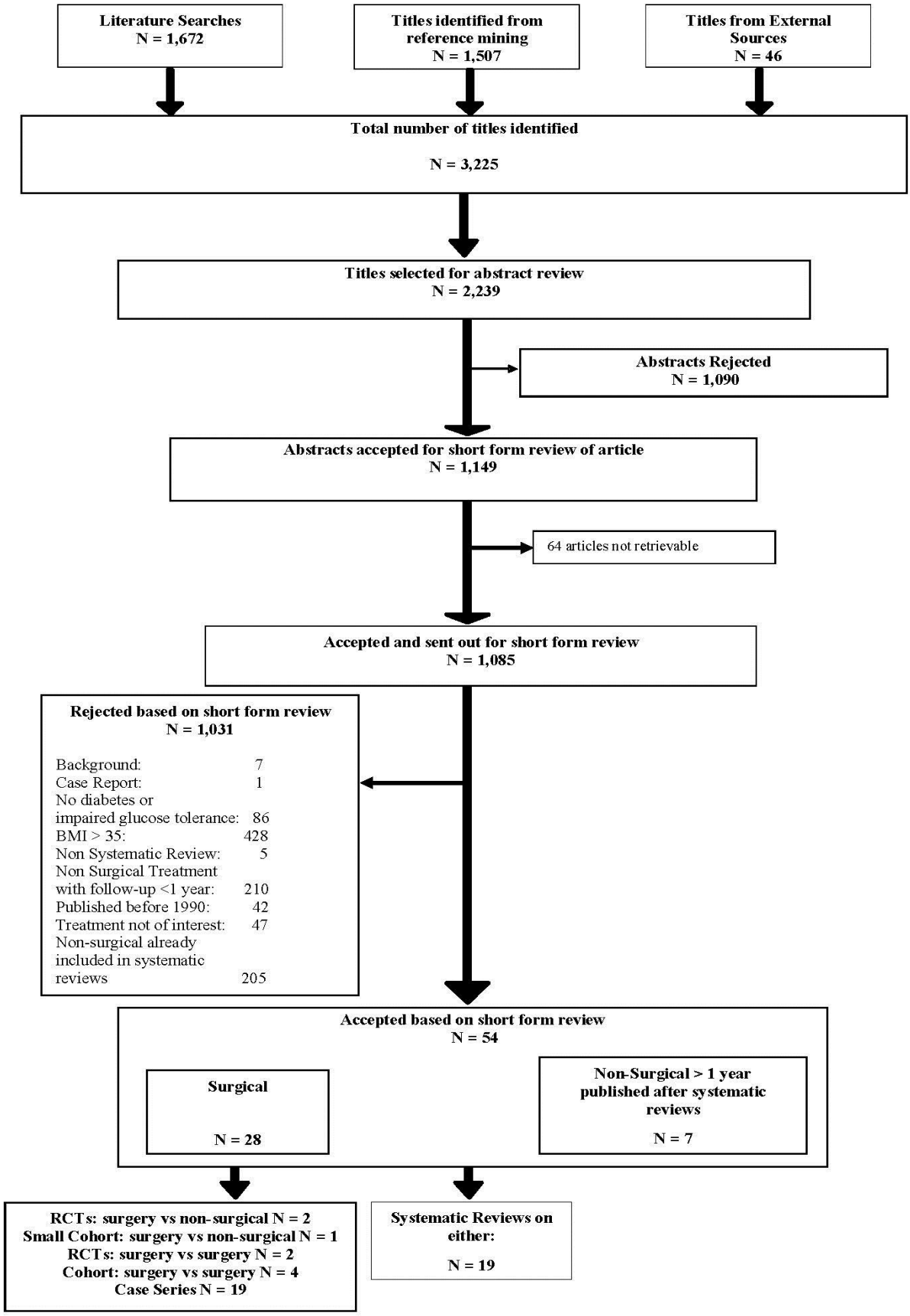
Peer Review

A draft of this report was prepared in September, 2011, and sent to the TEP members and national and international experts for review. Peer reviewer comments will be considered by the EPC in preparation of the final report. Synthesis of the scientific literature presented here does not necessarily represent the views of individual reviewers, and service as a peer reviewer or member of the TEP cannot be construed as endorsement of the report's findings.

Results

Figure 2 displays the results of our literature search. We identified 3,225 titles through our electronic database searches, reference mining, Scientific Information Packets received from manufacturers, and expert panel suggestions. Our researchers selected 2,239 for further review; almost half were rejected upon abstract review. Of the 1,085 studies that underwent full-text review, we included 28 surgical studies, 19 systematic reviews, and seven non-surgical studies published after those reviews. The most common reasons for exclusion of surgical studies were focus on patients with higher BMI (428 studies) or the study did not report on diabetes or other metabolic outcomes (86 studies). The most common reasons for excluding non-surgical studies were followup of less than one year or inclusion in the previous systematic reviews that we summarized.

Figure 2. Study/Literature flow diagram



KQ1: What does the evidence show regarding the comparative effectiveness of bariatric surgery for treating adult patients with BMI of 30 to 34.9 and metabolic conditions, including diabetes? Are certain surgical procedures more effective than others (laparoscopic adjustable gastric banding, gastric bypass, or sleeve gastrectomy)?

KQ2: What does the evidence show regarding the comparative effectiveness of bariatric surgery versus conventional non-surgical therapies for treating adult patients with BMI of 30 to 34.9 and metabolic conditions?

Of the 28 studies reporting bariatric surgery results in patients with diabetes or impaired glucose tolerance (IGT) and BMI of less than 35 kg/m^2, two were head to head trials comparing surgical procedures, four were cohort studies comparing surgical procedures, two were controlled trials with a non-surgical comparison arm, one was a small matched trial with a non-surgical arm, and the rest were observational studies with no comparison. Four of these studies included only a portion of patients with diabetes or impaired glucose tolerance (IGT); in the rest, all patients had diabetes.

An important consideration when assessing outcomes across time points in these studies (for example, 4-6 month data and 10-12 months data) is that the patients, contributing data at 4-6 months outcome may not be the same patients contributing data at the 10-12 months outcome, either within study or across studies. Table 2 displays the follow-up times when BMI, HbA1c, and fasting glucose were measured, organized by procedure type. There were eight studies with a gastric bypass arm and five with a LAGB arm. There were at least three studies on sleeve gastrectomy. (We found seven publications on sleeve outcomes by DePaula. It was unclear how the populations overlapped; attempts to contact the authors have not been successful. One DePaula article reported one month outcomes for 420 consecutive patients; the six other articles reported on various subsets of these 420.) Six studies included a BPD arm.

At least half the studies included follow-up between 10 and 12 months post-surgery. Unfortunately, only three studies followed patients more than two years; only one of these reported HbA1c or fasting glucose.

Table 2: Bariatric Outcomes by Followup Time

STUDY	SURGERY	0-3MTHS	4-6MTHS	7-9MTHS	10-12MTHS	13-24MTHS	>24MTHS
Cohen, 2006[22]	RYGB					+	
Lee, 2008[23]	RYGB				*+#		
Ferzli, 2009[24]	RYGB				*+#		
Geloneze, 2009[25]	RYGB		*+#		#		
DeMaria, 2010[26]	RYGB	*	*		*	*	
Lee, 2011[27]	RYGB	*#	*#		*#		
Shah, 2009[28]	RYGB			*#			
Shah, 2010[29]	RYGB	+#	+#	*+#			
Angrisani, 2004[30]	LAGB		*		*	*	*
Parikh, 2006[31]	LAGB				*	*	*
Sultan, 2009[32]	LAGB		*		*	*	
Choi, 2010[a33]	LAGB						
DeMaria, 2010[26]	LAGB	*	*		*	*	
DePaula, 2008[34-40]	Sleeve	*+		*+#		*+#	*+#
Kumar, 2009[41]	Sleeve		*+#			*+#	
Lee, 2011[27]	Sleeve	*#	*#		*#		
Noya, 1998[42]	BPD			*			
Cohen, 2007[43]	BPD	*	*	*			
Scopinaro, 2007[44]	BPD				*+	*+	*+
Chiellini, 2009[45]	BPD				*#	*#	
Ramos, 2009[46]	BPD	*#	*#				
Scopinaro, 2009[47]	BPD	*+#	*+#	*+#	*+#		

* BMI
\# HbA1c
\+ Glucose
[a] only usable outcome is % diabetes remission: defined as "% improved/resolved" not otherwise specified.

Head to head trials of bariatric surgery versus non-surgical interventions

We identified three studies assessing weight loss and diabetes outcomes for bariatric surgery compared to non-surgical interventions in our target population, information is displayed in Table 3. Two studies were RCTs of laparoscopic adjustable gastric bypass from the same research group; O'Brien[48] focused on patients with BMI 30 kg/m^2 - 35 kg/m^2 and Dixon[49] assessed patients with somewhat higher BMI (range 30 kg/m^2 - 40 kg/m^2). The comparison arms included medical care and usual diabetes care. Patients were followed up to 24 months. A third study by Chiellini[45] matched five BPD patients to seven patients in a supervised low calorie diet arm, and only one month followup data were available. Pooling these data was not considered appropriate based on the heterogeneity in the baseline weight and differences in the selection of outcomes and time points; thus the results are discussed in narrative form.

O'Brien[48] performed an RCT comparing laparoscopic adjustable gastric bypass (n=40) and medical management (n=40), which included low calorie diet, pharmacotherapy, and behavioral changes. Patients had a mean baseline BMI of 33 kg/m^2 and were well-matched for baseline characteristics; the randomization process was well-described as were dropouts. No patients were excluded from the analysis. One patient randomized to the surgical arm dropped out preoperatively; 7 patients in the medical management did not follow-up out to 24 months. (Blinding was not possible for this type of study.)

Both groups lost a similar amount of weight by six months (13.8 percent of initial weight in both arms). The surgical arm continued to lose weight out to 24 months (21.6 percent of initial weight), but the medical arm regained much of the weight they initially lost. At the last followup, the surgical arm (n=39) had a mean BMI of 26.4 kg/m^2 and the medical arm (n=33) mean BMI was 31.5 kg/m^2. The surgical group experienced significantly greater weight loss (P<0.001). The majority of other outcomes were improved to a statistically significant degree in the surgical arm as compared to the medical arm, including diastolic blood pressure and lipid levels. Fasting blood glucose was lower in the surgical patients at 24 months as compared to the medical group (which did not experience a decrease). Metabolic syndrome was present in 37.5 percent of patients in both groups at baseline and decreased to 2.7 percent in the surgical patients (P<0.001) and 24 percent in the medical patients (P=0.22) at followup. Surgical group improved the metabolic syndrome in a greater proportion of patients than the medical group (P=.0006). Other laboratory values, such as HbA1c or use of diabetes medications, were not reported. Of note, quality of life (by SF-36 short form) scores improved to a statistically significant degree in 5 of the 8 domains in the surgical group (8 of 8 subscores) as compared to the medical group (3 of 8).

Dixon et al[49] performed a similar study but included patients of somewhat higher BMI (mean baseline 37 kg/m^2). Sixty patients were randomized to LAGB or diabetes care as usual. Authors described the randomization process and dropouts; patient baseline characteristics were similar following randomization.

At two years, 55 of 60 patients completed the followup. Surgical patients lost a mean of 21.1 kg initial weight compared to 1.5 kg for the conventional treatment arm (P<0.001 between groups). BMI decreased to 29.6 kg/m^2 in the surgery patients and 36.7 kg/m^2 in the conventional therapy group (P<.0001 between groups). Fasting blood glucose (105.2 versus 139.6) was significantly lower in the surgery patients at two years as compared to the medical group (mean difference -32.8 [95 percent CI -53.1, -12.3]). HbA1c was also improved to a greater degree in the surgical patients at two years as compared to the convention therapy group (6.00 versus 7.21; mean difference -1.43 [95 percent CI -2.1, -0.80]). Remission of type 2 diabetes was seen in 73 percent in the surgical group and 13 percent in the conventional therapy group. Relative risk of remission was 5.5 [95 percent CI 2.2, 14.0] in the surgical group compared to convention therapy

group. Remission of diabetes was defined as fasting plasma glucose levels less than 126 mg/dL and HbA1c less than 6.2 percent without the use of oral hypoglycemic or insulin. Eighty percent of surgery patients had HbA1c <6.2 percent at 24 months compared to 20 percent of conventional therapy group (P<0.0001). Resolution of type 2 diabetes was related to weight loss and lower baseline HbA1c levels.

One small study by Chiellini[45] compared patients undergoing BPD (n=5) to those managed by diet (n=7). The study did not specify what variables the patients were matched on and only one month followup was reported. In this very short-term followup, HbA1c and weight were significantly lower in both groups. The BPD group did see a significant change in the blood glucose (at 2 hr) during an oral glucose tolerance test, whereas the diet arm did not.

Table 3. RCTs with Comparison Non-Surgical Arms

Author/ Study type	Procedure/ # patients	Weight Change, kg (SD)	BMI at 24 mo [95% CI]	Fasting Blood Glucose change, mg/dL (SD)				Metabolic Syndrome, % at 24 mo, [change]
		Weight Outcomes at 24 months		**Diabetes and Metabolic Syndrome Outcomes at 24 months**				
O'Brien [48] RCT	LAGB (n=40)	-20.5, (6.4)	26.4 [25.6, 27.2]	-7.3 (15.2)				2.7, [-35]
	Medical Care (n=40)	-6.1, (8.5)	31.5, [30.6, 32.4]	0.35 (8.3)				24, [-12]
	Betw grp comparison[+]	95% CI [-18.9, -11.6]	P<0.001	95% CI [-13, -0.7]	---	---	---	P=.0006
		Weight Change, kg (SD)	**BMI at 24 mo [change]**	**Fasting Blood Glucose change, mg/dL (SD)**	**HbA1c, % change, (SD)**	**HbA1c <6.2% at 24 mo**	**Taking DM meds, % at 24 mo, [change]**	**Diabetes remission*, % at 24 mo [change]**
Dixon [49] RCT	LAGB (n=30)	-21.1 (10.5)	29.6, [-7.4]	-51.2, (37.2)	-1.81, (1.24)	80%	13.3, [-79.7]	73 [-73]
	Conventional (n=30)	-1.5 (5.4)	36.7, [-0.5]	-18.4, (41.2)	-0.38, (1.26)	20%	73.3, [-13.4]	13 [-13]
	Betw grp comparison[+]	-19.6 [23.8,15.2] P<0.001	P<0.001	-32.8 [-53.1, -12.3] P=0.002	-1.43 [-2.1, -0.80] P<0.001	P<0.001	P<0.001	P<0.001

[+] Between group comparisons are mean difference and 95% CI

* s n=33 in the Medical Care Group

* Diabetes remission defined as fasting blood glucose <126mg/dL, HbA1c <6.2% without the use of insulin or oral hypoglycemics

Head to head trials of surgical procedures

We identified two RCTs comparing surgical procedures in our target population (Table 4). Lee[27] randomized 60 diabetic patients to gastric bypass or sleeve gastrectomy. Baseline demographics and clinical characteristics (mean BMI=30.3 kg/m^2) were similar between the groups. At 12 months followup between group comparisons showed that the gastric bypass group lost more weight: BMI was 22.8 kg/m^2 gastric bypass, compared to 24.4 kg/m^2 for SG (P=0.009). Diabetes type 2 outcomes were also better in the gastric bypass group with 93 percent remission compared to 47 percent in sleeve gastrectomy group (P=0.001). Diabetes type 2 remission defined as fasting plasma glucose levels less than 126 mg/dL and HbA1c values less than 6.5 percent without the use of oral hypoglycemics or insulin. HbA1c decreased by 4.2 percentage points in the gastric bypass versus 3.0 percentage points in the SG patients (P<0.05). Fasting glucose was lower in the gastric bypass patients compared to sleeve gastrectomy (99.3 versus 140.1; P<0.001). Total cholesterol level, triglycerides, LDL, HDL improved in both groups but to a greater degree in the gastric bypass patients. A composite measure of diabetes improvement (HbA1c<7 percent, LDL<100 mg/dL, and triglycerides<150 mg/dL) revealed greater improvement in the gastric bypass group 57 percent versus 0 percent; P<0.001). Complication rates were similar between groups and were minor. Operative time and hospital stay were no different.

Depaula[40] randomized patients to two variations of ileal interposition: with sleeve gastrectomy (II-SG) or with a diverted sleeve gastrectomy (II-DSG). In both, the stomach is resected into a tube and a segment of ileum is repositioned in an antiperistaltic direction in a proximal location in the gastrointestinal tract. The latter procedure also diverts the stomach contents to bypass the proximal flow of pancreatic/biliary tract. They enrolled 38 diabetic patients with similar baseline characteristics (weight, gender, length of time with diabetes). At 24 months postoperative, both groups achieved weight loss: 22.7 kg/m^2 (II-DSG) versus 22.2 kg/m^2 (II-SG) (P=0.623). II-DSG had statistically significantly greater lowering of HbA1c (percent HbA1c<6: 81.3 percent versus 35.3 percent (P=0.023) and mean fasting blood glucose (99.06 +/- 20.87 versus 114.6 +/- 34.5; P=0.008). Other comorbidities were improved but not different between the surgical groups including LDL, total cholesterol, triglycerides, HDL, and hypertension. Similar results were found for mean microalbuminuria, which decreased from 61.7 ug/min to 27.45 after II-SG and from 62.75 to 23.97 after II-DSG (p=.245). The four patients with pre-operative macroalbuminuria had all resolved at followup. (The authors do not report this outcome by surgery type.) The complication rate was similar between the groups, but notable for several intraoperative complications (most notably ischemic bowel segments), which were addressed that the time of the operation and were presumably related to technical factors of a new operation that would be part of an early learning curve experience.

Cohort studies with surgical procedure comparisons

Four cohort studies compared outcomes between two surgical procedures [26,34-35,37] in our target population. One compared gastric bypass to laparoscopic gastric band and three compared two variations of ileal interposition. Demaria[26] looked at a large retrospective database of patients operated on from 2005 to 2007 (n=66,264) and identified 235 who met the lower weight criteria (BMI ≥30 and <35 kg/m^2). 109 patients underwent gastric bypass, the same number had had laparoscopic adjustable gastric band (the remaining 17 underwent other procedures). The study methods did not comment on the rationale of procedure choice for patients, but groups did not differ by baseline weight (33.7 kg/m^2 versus 33.9 kg/m^2), gender, race, or age. Followup was 61.9 percent and 69.2 percent at 6-12 months for gastric bypass and laparoscopic adjustable

Table 4. RCTs with Comparison Surgical Arms

Author/ Study type	Procedure/ # patients	Weight Change %	BMI, kg/m^2 (SD)	Fasting Blood Glucose mean, mg/dL (SD)	HbA1c %, mean, (SD)	Metabolic Syndrome No (%)	Successful treatment diabetes^, No (%)	Diabetes remission*, No (%)
		Weight Outcomes at 12 months		**Diabetes and Metabolic Syndrome Outcomes at 12 months**				
Lee[27] RCT	Gastric bypass (n=30)	-23.3	22.8 (2.2)	99.3, (19.4)	5.7 (0.5)	2 (6.6)	17 (57)	28 (93)
	Sleeve gastrectomy (n=30)	-19.9	24.4, (2.4)	140.1, (53.0)	7.2 (1.5)	18 (60.0)	0 (0)	14 (47)
	Betw grp comparison[+]	P=0.02	P=0.009	P<0.001	P<0.001	P<0.001	P<0.001	P=0.02
		Weight Outcomes at 24 months		**Diabetes and Metabolic Syndrome Outcomes at 24 months**				
						HbA1c <6%, percent	**HbA1c <7%, percent**	
DePaula[40] RCT	II-SG (n=18)	-27.9 (8.2)	22.1, (3.1)	114.6 (33.7)	6.31 (.87)	35.3	82.4	
	II- DSGl (n=20)	-33.8 (5.1)	22.7, (1.8)	99.0 (20.0)	5.39 (.71)	81.3	100	
	Betw grp comparison[+]	P=0.34	P=0.62	P=0.008	P=0.059	P=0.023	NR	

[+] Between group comparisons are mean difference and 95% CI

II-SG=sleeve gastrectomy with ileal interposition; II-DSG=sleeve gastrectomy with ileal interposition and duodenal diversion

^ Successful treatment of diabetes mellitus (HbA1c <7%, LDL-C <100 mg/dL, and triglycerides <150 mg/dL)

* Remission defined as fasting plasma glucose levels less than 126 mg/dL and HbA_{1c} values less than 6.5% without the use of oral hypoglycemics or insulin.

[@] Metabolic Syndrome defined by the National Cholesterol Education Program Adult Treatment Panel III criteria

gastric band patients, respectively. At 6-12 months, gastric bypass patients lost more weight than those undergoing laparoscopic adjustable gastric band (6-12 months: BMI 27.1 kg/m^2 and 30.9 kg/m^2; P=0.0002). Gastric bypass achieved better diabetes control for all time intervals as the number of patients off diabetes medications (at 6-12 months: 55.2 percent versus 27.2 percent; P=.0199), with the exception of the latest followup at 12-24 months (but only 4 gastric bypass and 11 LAGB patients were followed up at that time interval). For patients with diabetes controlled with oral medications, 60.9 percent and 38.5 percent, for gastric bypass and laparoscopic adjustable gastric band, respectively, were able to stop their diabetes medications within 3-6 months. For patients on insulin and oral medications, 50 percent and 11.1 percent, respectively, were able to stop their medications. Complications, while minor, occurred more commonly in the gastric bypass group (18 percent versus 3 percent, P<0.05).

Three studies by the same authors[34-35,37] reported on differences between ileal interposition with sleeve gastrectomy (II-SG) and ileal interposition with diverted sleeve gastrectomy (II-DSG) for individuals with BMI <35 kg/m^2 and diabetes. These studies likely include a similar overlap of patients but with different followup and slightly different weight ranges. Two studies[34-35] included patients with BMI 24-35 kg/m^2 and the third looked at patients with BMI 20-34 kg/m^2. In a recently published study for patients with BMI 24-35 kg/m^2,[35] 60 patients were included, all with diabetes for longer than three years. Patients in each group were similar with regards to BMI, gender, age, but those in the II-DSG had a longer mean time with diabetes (11.4 +/- 4 versus 8.3 +/- 4.5 years). Patients lost similar weight between the groups. II-SG and II-DSG patients both experienced improvement in diabetes, remission rates of 70.0 percent and 68.4 percent (HgA1c<6 percent, off medications). The authors concluded II-DSG may be slightly better at improving the metabolic syndrome but additional studies and longer length of followup are warranted. Depaula[34] also reported on 39 patients that appear to be in the same cohort study above (published about six months earlier) and their overall findings were similar. Yet another Depaula study[37] looked at patients with BMI 20 kg/m^2 - 34 kg/m^2 (n=58) and found that both II-SG and II-DSG were effective at generating improvements in diabetes and other related gut hormones but did not provide direct procedure comparisons.

Patients with BMI < 30. One case series[36] looked at use of II-DSG to treat diabetes in non-obese individuals (BMI=21-29 kg/m^2). Sixty-nine patients met the inclusion criteria, which included diabetes of at least three years and a HbA1c>7.5 percent in past three months. The mean baseline BMI was 25.7 kg/ m^2 (21.8 to 29.2 kg/m^2) and the mean time with diabetes was 11 years (3-18 years). Postoperative followup was a mean of 21.7 months (7-42 months); neither number of patients followed up at any time point nor a median was provided. All patients lost weight, with mean followup BMI of 21.8 +/- 4.1 (P<0.001 from baseline). 95.7 percent were off diabetes medications and had HbA1c <7 percent. 65.2 percent had achieved HbA1c<6 percent. Fasting blood glucose (218 to 102 mg/dL) and postprandial glucose (305 to 141 mg/dL) decreased. Hypertension was controlled (≤130/≤85 mmHg, off medications, by causal blood pressure measurement) in 91.3 percent of patients (46 were diagnosed with hypertension during preoperative work-up) and there was improvement in hypercholesterolemia (95 percent) and hypertriglyceridemia (92 percent) of patients, although the followup time for “improvement” was often unclear.

Observational studies - diabetes outcomes

Table 5 displays data from the observational studies. The left side of the table presents data for the studies where all patients entering had type 2 diabetes or IGT, the right displays the remaining handful of studies.

BMI. For the diabetes studies, the baseline BMI ranged from 29.8 kg/m^2 for gastric sleeve to 33.9 kg/m^2 for LAGB, for studies with less than one year followup. The absolute change in BMI for gastric bypass was 3.1 kg/m^2, LAGB was 2.3 kg/m^{2,} for gastric sleeve 3.9 kg/m^2, and for BPD 3.5 kg/m^2, respectively, although the number of BPD patients is very small. In addition, two studies that included some non-diabetic patients who underwent LAGB reported a BMI decrease of 3.1 kg/m^2.

There were no BPD studies that reported weight loss outcomes at one year or greater. For the other surgical procedures, studies with at least one year followup had a baseline BMI that ranged from 27.4 kg/m^2 (gastric sleeve) to 33.9 kg/m^2 (LAGB). Postoperative BMI was much lower than the earlier one year followup (22.7 kg/m^2). The patients who received RYGB lost 7.6 kg/m^2 while those who received LAGB or gastric sleeve lost 4.0 and 4.7 kg/ m^2,respectively.[23-24,26-27]

Blood Glucose. Metabolic improvements after surgery were expressed in various ways including decreases in HbA1c and plasma glucose, percentage of patients that no longer required diabetes medication, and remission or resolution of diabetes by measures not specified. There were eight studies, including nine surgery arms, which reported decreases in HbA1c at time points less than one year.[25,27-29,35,41,46-47] Baseline HbA1c values were quite high ranging from 9.3 percent for both BPD and gastric sleeve to 9.9 percent for gastric bypass. Considerable decreases were reported after surgery, with postoperative values of 7.6 percent for BPD, 6.7 percent for RYGB, and 6.6 percent for gastric sleeve. Studies that measured out to one year or more reported continued improvement in HbA1c values. They decreased to postoperative values of 5.8 percent for BPD to 6.3 percent for gastric sleeve. There were no LAGB studies that reported HbA1c data. Studies that reported data on plasma glucose also demonstrated significant metabolic improvements, most patients had hyperglycemic preoperatively (ranging from 134.0 mg/dL to 227.6 mg/dL). Studies with less than one year followup reported decreases in plasma glucose of 42.0 mg/dL for BPD to 74.4 mg/dL for RYGB. Studies with longer followup of at least one year reported even greater decreases in plasma glucose, ranging from 69.1 mg/dL for RYGB to 138.0 mg/dL for BPD. When followed for at least one year after surgery, most patients were euglycemic (mean plasma glucose of 93.2 mg/dL to 101.7 mg/dL).

Medication needs. Several studies reported the percentage of patients who no longer required medication for diabetes after surgery. The best results were from the four studies reporting on 59 patients who received BPD, with 91.5 percent of patients no longer requiring medication at less than one year after surgery.[42-43,46-47] At the other end of the spectrum, one study of 90 patients receiving LAGB found that only 21.1 percent were able to discontinue their medications at 0-3 months after surgery.[26] This only improved slightly at 3-6 months (31.8 percent) and 6-12 months (27.5 percent) (not shown). Studies on RYGB and sleeve gastrectomy reported that 50.8 percent and 87.0 percent of patients were able to discontinue medications less than one year after surgery, respectively.[25-26,28-29,35] When patients were followed for one year or more, the outcomes continued to improve. One small BPD study of seven patients reported that all of them were able to discontinue their diabetes medication.[44] Two LAGB studies reported on

this outcome with a total of 19 diabetic patients, with one study reporting that 36.4 percent of patients were able to discontinue diabetes medications[32] while the other study reported that all eight diabetic patients in a larger study were able to discontinue medication.[31] Of patients who underwent RYGB and gastric sleeve, the majority (85.4 percent and 95.7 percent, respectively) were able to discontinue diabetes medications at one year or more after surgery.[22,24,26,38]

Remission / Resolution. Several studies reported that diabetes had remitted or resolved after surgery, though the measures used were not specifically stated. Three studies reported this outcome in patients at less than one year after surgery. Of these, the best outcomes were reported in one LAGB study that included both diabetic and non-diabetic patients, with 100 percent remission or resolution seen in diabetic patients. After RYGB 97 percent of patients where reported to have diabetes remission or resolution, while somewhat fewer patients (69.7 percent) had this outcome after sleeve gastrectomy. Studies that followed patients for one year or longer found slightly less successful results. In one study of LAGB, where not all patients had diabetes, 33.3 percent of patients experienced remission or resolution.[33] Better results were reported for RYGB (93.3 percent)[27] and sleeve gastrectomy (59.6 percent).[27,36]

C-peptide. C-peptide, which is the connecting peptide of proinsulin, is secreted from cells in equimolar amounts with insulin, and its concentrations have been used to determine insulin production in vivo. Normal C-peptide levels can vary based on the laboratory and whether patients are fasting (normal 0.4 to 2.2 ng/ml) or postprandial (normal 1.2 to 3.4 ng/ml), and are even higher after a glucose load test (2.0 to 4.5 ng/ml). This makes the results somewhat difficult to interpret. There were seven studies that reported on C-peptide changes after surgery (data not shown). Baseline values in the studies ranged from 1.3 ng/ml for RYGB to 4.1 ng/ml for gastric sleeve. In one BPD study, C-peptide values increased slightly from 2.0 ng/ml at baseline to 2.1 ng/ml at 3 months and 2.5 ng/ml at 6 months after surgery.[46] There was one RYGB study that did not find a significant change in C-peptide values up to 3 months. Two RYGB studies reported mean decreases in C-peptide of 0.21 ng/ml and 0.86 ng/ml respectively.[23-24] There were four studies by the same author that reported on C-peptide values in gastric sleeve patients.[34-35,38,40] They found a mean decrease in C-peptide of 0.20 ng/ml to 1.60 ng/ml at 6 to 7 months, and a greater decrease of 2.14 ng/ml at 24 months.

Nephropathy. One case series of sleeve gastrectomy[38] reported that mean microalbuminuria decreased from 57.4 ug/min to 27.6 ug/min at two years. In the same study, prevalence of macroalbuminuria decreased from 8.3 percent to 4.2 percent. In another case series of 69 patients[36] with sleeve gastrectomy by the same authors (the samples may overlap) incidence of microalbuminuria decreased from 80 percent to 10 percent, while incidence of macroalbuminuria decreased from 20 percent to zero.

Retinopathy. One case series of sleeve gastrectomy[36] reported “objective improvement” at two years in 44.4 percent of the 18 patients with retinopathy diagnosed pre-surgery.

Table 5. Bariatric Surgery Results - by Surgery Type, 100% Diabetes Patients

Outcome	F-Up	# Studies	Surg Type	BL N	BL Mean/%	BL SE	F-up N	F-up Mean/%	F-up SE	Mean Chg
			100% DIABETES STUDIES							
BMI	<=11m	5	RYGB	181	31.8	1.3	160	28.4	1.3	-3.1
BMI	<=11m	1	LAGB	109	33.9		90	31.6		-2.3
BMI	<=11m	3	Sleeve	489	29.8	0.4	489	25.9	0.2	-3.9
BMI	<=11m	4	BPD	59	30	1.3	59	26.5	0.6	-3.5
HbA1c	<=11m	4	RYGB	72	9.9	0.4	72	6.7	0.3	-3.2
HbA1c	<=11m	0	LAGB							
HbA1c	<=11m	3	Sleeve	95	9.3	0.3	95	6.6	0.8	-2.7
HbA1c	<=11m	2	BPD	47	9.3	0.4	47	7.6	0.1	-1.6
Glucose	<=11m	2	RYGB	27	134	110.7	27	59.5	45.5	-74.4
Glucose	<=11m	0	LAGB							
Glucose	<=11m	2	Sleeve	459	198.3	0.2	459	125.9	0.9	-72.4
Glucose	<=11m	1	BPD	27	221		27	179		-42
% off Diabetes Meds	<=11m	4	RYGB				130	50.8	11.1	
% off Diabetes Meds	<=11m	1	LAGB				90	21.1		
% off Diabetes Meds	<=11m	1	Sleeve				60	87		
% off Diabetes Meds	<=11m	4	BPD				59	91.5	1.2	
Diabetes Remission/Resolution	<=11m	1	RYGB				37	97.3		
Diabetes Remission/Resolution	<=11m	0	LAGB							
Diabetes Remission/Resolution	<=11m	1	Sleeve				60	69.7		
Diabetes Remission/Resolution	<=11m	0	BPD							
BMI	>=12m	4	RYGB	190	32.5	0.9	85	23.4	0.7	-7.6
BMI	>=12m	1	LAGB	109	33.9		11	29.9		-4
BMI	>=12m	3	Sleeve	104	27.4	1.7	104	22.7	0.9	-4.7
BMI	>=12m	3	BPD	39	31.4	0.7	18	25.4	0.4	-6.3
HbA1c	>=12m	0	LAGB							
HbA1c	>=12m	3	RYGB	81	8.5	0.9	81	5.9	0.6	-2.6
HbA1c	>=12m	3	Sleeve	104	9.2	0.5	104	6.3	0.4	-2.9
HbA1c	>=12m	2	BPD	32	9.4	0.4	12	5.8	0.1	-3.4
Glucose	>=12m	3	RYGB	88	162.3	12.3	88	93.2	11.7	-69.1
Glucose	>=12m	0	LAGB							
Glucose	>=12m	2	Sleeve	74	217.4	2.4	74	101.7	1.1	-115.7
Glucose	>=12m	2	BPD	34	227.6	12.9	13	97.8	10	-138
% off Diabetes Meds	>=12m	3	RYGB				48	85.4	21.4	
% off Diabetes Meds	>=12m	1	LAGB				11	36.4		
% off Diabetes Meds	>=12m	1	Sleeve				69	95.7		
% off Diabetes Meds	>=12m	1	BPD				7	100.0		
Diabetes Remission/Resolution	>=12m	1	RYGB				30	93.3		
Diabetes Remission/Resolution	>=12m	0	LAGB							
Diabetes Remission/Resolution	>=12m	2	Sleeve				99	59.6	8.5	
Diabetes Remission/Resolution	>=12m	0	BPD							

BL: Baseline; N: Sample Size; F-up: Followup; SE: Standard Error

Table 6. Bariatric Surgery Results - by Surgery Type, <100% Diabetes Patients

Outcome	F-Up	# Studies	Surg Type	BL N	BL Mean/%	BL SE	F-up N	F-up Mean/%	F-up SE	Mean Chg
			<100% DIABETES STUDIES							
BMI	<=11m	0	RYGB							
BMI	<=11m	2	LAGB	263	33.74	0.32	244	30.68	1.04	-3.11
BMI	<=11m	0	Sleeve							
BMI	<=11m	0	BPD							
HbA1c	<=11m	0	RYGB							
HbA1c	<=11m	0	LAGB							
HbA1c	<=11m	0	Sleeve							
HbA1c	<=11m	0	BPD							
Glucose	<=11m	0	RYGB							
Glucose	<=11m	0	LAGB							
Glucose	<=11m	0	Sleeve							
Glucose	<=11m	0	BPD							
% off Diabetes Meds	<=11m	0	RYGB							
% off Diabetes Meds	<=11m	0	LAGB							
% off Diabetes Meds	<=11m	0	Sleeve							
% off Diabetes Meds	<=11m	0	BPD							
Diabetes Remission/Resolution	<=11m	0	RYGB							
Diabetes Remission/Resolution	<=11m	1	LAGB				210	100		
Diabetes Remission/Resolution	<=11m	0	Sleeve							
Diabetes Remission/Resolution	<=11m	0	BPD							
BMI	>=12m	0	RYGB							
BMI	>=12m	3	LAGB	356	33.47	0.38	313	28.74	1	-4.2
BMI	>=12m	0	Sleeve							
BMI	>=12m	0	BPD							
HbA1c	>=12m	0	LAGB							
HbA1c	>=12m	0	RYGB							
HbA1c	>=12m	0	Sleeve							
HbA1c	>=12m	0	BPD							
Glucose	>=12m	0	RYGB							
Glucose	>=12m	0	LAGB							
Glucose	>=12m	0	Sleeve							
Glucose	>=12m	0	BPD							
% off Diabetes Meds	>=12m	0	RYGB							
% off Diabetes Meds	>=12m	1	LAGB				8	100.00		
% off Diabetes Meds	>=12m	0	Sleeve							
% off Diabetes Meds	>=12m	0	BPD							
Diabetes Remission/Resolution	>=12m	0	RYGB							
Diabetes Remission/Resolution	>=12m	1	LAGB				66	33.33		
Diabetes Remission/Resolution	>=12m	0	Sleeve							
Diabetes Remission/Resolution	>=12m	0	BPD							

BL: Baseline; N: Sample Size; F-up: Followup; SE: Standard Error

Observational studies – other health outcomes

Blood Pressure. Nine surgery studies reported various blood pressure outcomes. One study (primarily of non-diabetics) followed patients for 12 months after undergoing LAGB and found that the percentage of patients with hypertension decreased from 4.3 percent to 0.5 percent.[30] Three other studies also examined patient populations where not all had diabetes.[31-33] Of these, one reported that hypertension improved or resolved in 29 percent of patients, 18 months after receiving LAGB.[33] Two of these studies reported the number who no longer required antihypertensive medications; one found that 75 percent were able to discontinue 24 months after surgery, while another found that 46 percent were able to, 36 months post-op.[31-32] Two studies reported changes in diastolic blood pressure. One of these found a drop from 87 to 78mm Hg, six months after RYGB, while the other found a smaller drop, from 87 to 85 mm Hg, 24 months after LAGB.[25,49] In studies that reported changes in systolic blood pressure, decreases from 134 to 123 mmHg six months after RYGB, from 136 to 116 mmHg nine months after RYGB, and from 136 to 130 mmHg 24 months after LAGB were reported.[25,29,49]

Cholesterol. Seven studies reported cholesterol outcomes. One found that the hypercholesterolemia of seven patients resolved 12 months after BPD and did not return in 216 months of followup.[44] A study of patients receiving sleeve gastrectomy found the percentage of those with hypercholesterolemia decreased from 68 percent to 8 percent, 24 months after surgery.[38] One study found that 33 percent of those who required hypercholesterolemia medications, no longer needed them 24 months after LAGB. Of note, not all of the patients in that study had diabetes.[32] Four of the sleeve gastrectomy studies examined the LDL and HDL levels, specifically. The drop in LDL ranged from 17.6 to 41.9 mg/ dL, when patients were followed from seven to 22 months.[35-37,41] HDL cholesterol increased, as expected, in two of these studies by 2.4 and 3.2 mg/dL.[36-37] One found HDL to decrease by 1.5 mg/dL, however this was in only one patient.[41]

Triglycerides. Several studies reported triglyceride levels after surgery, measured either as absolute triglyceride levels or the percentage of patients with hypertriglyceridemia. One study reported on seven patients who underwent BPD and had baseline triglyceride levels of 311.6 mg/dl (all patients were defined as having high triglyceride levels). None of the patients still had high triglyceride levels at any time from 12 to 216 months after surgery, with mean values ranging from 97.3 mg/dl to 144.1 mg/dl.[44] Four studies reported on patients who underwent RYGB. One study with short-term followup reported a decrease in triglyceride levels from 250.0 mg/dl to 236.0 mg/dl at six months after surgery.[25] Two studies had 12 month followup, with one study reporting that patients with baseline triglyceride levels of 275.7 mg/dl lost an average of 147.4 mg/dl[50] while the small study of only seven patients mentioned earlier did not find a significant change.[24] At 48 months after RYGB, one study reported a decrease from 204.0 mg/dl to 156.0 mg/dl.[22] Studies at gastric sleeve patients all reported a decrease in postoperative triglyceride levels, including one study that reported a drop from 280.3 mg/dl to 168.2 mg/dl at nine months after surgery. There were multiple studies by the same author that reported on patients with baseline triglyceride levels of 241.0 to 274.8 mg/dl, which decreased to 123.0 mg/dl by 1 month, 114.0 mg/dl by six months, 109.0 mg/dl by 12 months, and 111.0 mg/dl by 24 months.[34-38] Almost all (94.8 percent) patients had normal triglyceride levels at 19 months after

surgery.[37] A subset of patients with higher baseline triglyceride levels (354.6 mg/dl) also decreased significantly to 116.4 mg/dl at 24 months after surgery.[40]

GERD and Sleep Apnea. Finally a few studies reported on gastroesophageal reflux disease (GERD) and obstructive sleep apnea (OSA). All of these studies included a small subset of patients who had preoperative GERD or OSA who underwent LAGB. In one study that included five patients with preoperative GERD, all had complete resolution at one year after surgery.[30] However, in a slightly larger study that included 22 patients with preoperative GERD, only 31.3 percent experienced improvement or resolution at one year after LAGB.[33] Neither study detailed the exact methods of diagnosing resolution of GERD. Of the three studies that reported on OSA, one study found that half of the 19 patients had complete resolution (defined as discontinuation of continuous positive airway pressure [CPAP] mask use) at two years after LAGB and an additional 30 percent had improvement (decreased CPAP use).[32] In another study that included seven patients with preoperative OSA, six had OSA resolution (did not require CPAP use) by three years after LAGB.[31] In a third study, only three of nine patients with OSA had improvement or resolution at one year (definition of improvement or resolution not specified).[33]

Systematic reviews on behavioral interventions

The effects of interventions such as exercise, diet, and health education on weight loss and diabetes outcomes have been studied for decades. The primary literature on this is large. In such cases we attempt to find existing reviews.[51] We identified six fair to excellent quality systematic reviews on these topics; four focused on adults with pre-existing diabetes while the other two focused on diabetes prevention in adults with impaired glucose tolerance. Details on the reviews are displayed in Table 7.

Pooling 22 RCTs with a total of 4,659 participants and a followup interval of 1 to 5 years, Norris and colleagues[52] assessed the long-term effectiveness of lifestyle and behavioral interventions on weight loss or weight control among adults with type 2 diabetes (mean BMI = 33.2kg/m², mean duration of diabetes = 6.5 years). Interventions examined included physical activity, low calorie diet, and behavioral interventions such as self-monitoring blood glucose and spousal involvement in education. Comparisons of three groups of studies were conducted: any intervention versus usual care, very low-calorie diet versus low-calorie diet, and physical activity versus no or less intensive physical activity. The pooled weight loss for intervention group (any intervention) in comparison with usual care was 1.7 kg at 1 and 2 years of followup, and the pooled weight loss for very low-calorie diets in comparison with low-calorie diets was 3.0 kg at 72 and 104 weeks of followup. Among those who received identical dietary and behavioral interventions, the pooled weight loss for intensive physical activity in comparison with no or less physical activity was 3.9 kg. Of the six intervention types (including usual care and different combinations of interventions), all interventions were associated with significant weight loss, but a very low-calorie diet combined with physical activity and behavioral therapy produced the largest weight loss effect. However, changes in glycated hemoglobin level were not significant.

Kirk and colleagues (2008) evaluated 13 studies (including nine RCTs) that examined effects of carbohydrate-restricted diets in type 2 diabetes patients (mean weight = 77 to 132 kg, mean HbA1c = 6.9 – 9.8) in North America.[53] Seven outcomes were reported: weight, fasting glucose, HbA1c, total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides. At 3 to 26 weeks followup, weight loss after carbohydrate-restricted diets ranged from 0.5 to 8.7 kg, representing 0.5 percent to 7.5 percent changes from baseline; decrease in HbA1c ranged from 0.2 to 2.2, representing 2.9 percent to 22.4 percent changes from baseline; and reduction in fasting glucose ranged from 1.8 to 83.0, representing 1.3 percent to 36.6 percent changes from baseline. They also found a greater mean reduction in fasting glucose and HbA1c in the lower-carbohydrate diet phase compared to the higher-carbohydrate diet phase. While triglyceride reductions were observed in both lower- and higher-carbohydrate phases, an especially strong relationship was found in the lower-carbohydrate phase. No significant relationships were found for the three cholesterol outcomes.

Dyson, 2008[54] reviewed 6 studies (including one RCT) that examined short-term effect and associated risks of low and reduced carbohydrate diets in type 2 diabetes patients (mean BMI = 28.5 to 42.2kg/m², mean HbA1c = 7.3 to 9.7). Meta-analysis was not conducted due to heterogeneity of the studies. Most of the studies reported small samples (N=10 to 206; only two studies had sample size over 100), short-term effects (followup duration n= 14 days – 22 months but only two studies with data beyond six months), and varying carbohydrate levels (range from <20g/day to 95g/day). All studies reported reductions in body weight and glycated hemoglobin: reductions in body weight ranged from 1.2 to 11.4 kg, reductions in BMI ranged from 0.4 to 4.1 kg/m², and reductions in HbA1c ranged from 0.5 to 1.7 points. A few studies also recorded either

reduction or discontinuation of glucose-lowering medications such as metformin and thiazoladinediones.

Kodama and colleagues[55] conducted a meta-analysis to assess the influence of fat and carbohydrate proportions on glucose and lipid parameters in type 2 diabetes patients. Pooling 22 trials with a total of 306 participants (mean BMI = 22.7 to 33.1kg/m², diabetes duration = 5 to 8 years) and an intervention period of 1.4 to 12 weeks, the study compared the effects of a low-fat high-carbohydrate (LFHC) diet and a high-fat low-carbohydrate (HFLC) diet. While no significant differences in the reduction in HbA1c, total cholesterol, and LDL cholesterol were found between the LFHC and HFLC diets, LFHC diet led to significant increases in fasting insulin (8.4 percent, with marked elevations observed when the carbohydrate/fat ratio >=3) and triglycerides levels (13.4 percent), and a significant reduction in HDL cholesterol (6 percent). They also found significant positive relationships among the change in fasting plasma glucose, fasting insulin, and triglycerides. They concluded that replacing fat with carbohydrate have negative implications for diabetes patients.

Norris and colleagues[56] examined the effects of weight-loss interventions in 9 RCTs consisting a total of 5,168 overweight or obese participants (mean BMI = 25.8 to 34.0 kg/m², mean GHb = 5.7 to 5.9) with pre-diabetes (impaired fasting glucose or impaired glucose tolerance). Most of the studies reported long-term data, with followup durations ranging from 1 to 10 years. Weight-loss strategies included diet, physical activity, and behavioral interventions, while comparison group interventions consisted of usual care or general information and counseling. Compared with usual care, these weight-loss interventions led to 2.8 kg weight loss at one year (representing 3.3 percent of baseline body weight) and 2.7 kg at two years; reduction in BMI was 1.4 kg/m² at 1 year. The most notable mean weight change was observed in the lifestyle intervention of the DPP (Diabetes Prevention Program) study, which had the largest study population. It reported a mean weight loss of 5.5 kg at an average followup of 2.8 years. A few studies reported small decreases in systolic and diastolic blood pressure, minor improvements in lipids, and 0.0 to 0.2 decreases in GHb. Three large trials also demonstrated a significant lower cumulative incidence of diabetes in the intervention versus control groups, at three to six years followup.

Gillies and colleagues[57] also reviewed studies that evaluated interventions to delay or prevent type 2 diabetes among patients with impaired glucose tolerance. Behavioral interventions included diet and exercise; pharmacological/herbal interventions included acarbose, flumamine, glipizide, metformin, phenformin, orlistat, and herbal iangtang busheng. They identified 21 RCTs and conducted a meta-analysis using 17 RCTs with a total of 8,084 participants (mean BMI = 23.8 to 37.3 kg/m², baseline risk of type 2 diabetes = 2.6 to 30.0 cases per 100 person years). They found high strength of evidence in favor of interventions compared to controls, the pooled effects (in terms of hazard ratios) were 0.51 for overall behavioral interventions (corresponding to a relative 49 percent reduction in risk of developing diabetes), 0.67 for diet, 0.49 for exercise, 0.49 for diet and exercise combined, 0.70 for oral diabetes drugs, 0.44 for orlistat, and 0.32 for the herbal Jiangtang busheng recipe. All except for the herbal Jiangtang busheng recipe were statistically significant. The authors concluded that behavioral interventions were at least as effective as pharmacological interventions.

In sum, compared to surgical options, the effects of non-surgical weight loss or weight control strategies among type 2 diabetes patients have been widely investigated. Evidence has shown that exercise, diet, lifestyle, and behavioral interventions are associated with significant weight loss and better blood sugar outcomes (e.g., decreasing HbA1c or fasting glucose) among adult patients with pre-existing type 2 diabetes. Evidence is stronger for the weight loss effect,

compared to the diabetes improvement effect, and more intensive and sustained interventions seem more effective. These findings were consistent with those found in non-diabetic but high-risk population with impaired glucose tolerance or impaired fasting glucose. Among those patients, non-surgical interventions were associated with reduced risk of developing diabetes in the long run. However, studies also pointed out that the magnitude of effects of non-surgical interventions in reducing weight and improving blood sugar outcomes are often small, although significant. Most of these systematic reviews reported that studies were very heterogeneous with respect to the interventions; thus the effects should be explained cautiously.

Table 7. Systematic Reviews on Non-Surgical Interventions

Author / Year	Intervention	Patients	Search through	# of included studies	AMSTAR	Findings
Norris, 2004[52]	Exercise, diet, behavioral	Type 2 DM mean BMI = 33 range 23-38 mean HbA1C = 10 range 7-13 Mean age = 55	August 2003	22 RCTs duration 1 year - 5 years (16/22 ≤ 1.5 yr)	10	1.7kg weight loss for all interventions pooled, vs usual care, at 1-5 years Physical activity + very low cal diet lost 3.0 kg more than physical activity + low cal diet (N = 126) Identical diets + more intense physical activity lost 3.9 kg more Differences in glycated hemoglobin & fasting glucose not significant
Kirk, 2008[53]	Low carbohydrate diets	Type 2 DM Mean weight = 77 – 132 kg Mean HbA1c = 6.9 – 9.8 North America only	April 2006	13 studies (9 RCTs) duration 3 weeks - 26 weeks	6	No pooling conducted. Weight loss ranged from 0.5 to 8.7 kg from baseline at 3 to 26 weeks Decrease in HbA1c ranged from 0.3 to 2.2 points
Dyson, 2008[54]	Low carbohydrate diets	Type 2 DM Mean weight = 76 – 131 kg Mean BMI = 28 – 42 Mean age = 51 - 66	March 2007	6 trials (1 RCT) duration 14 days - 22 months	6	No pooling conducted Weight loss ranged from 1.2 to 11.4 kg from baseline Decrease in HbA1c ranged from 0.5 to 1.4 Decrease in BMI ranged from 0.4 to 4.1 points
Kodama, 2009[55]	Low carbohydrate diets vs. low fat diets	Type 2 DM Mean BMI = 23 -33 Mean age = 48 – 66 Mean % on diabetes meds = 52	2007	19 RCTs duration < 1 year	9	Low carb high cholesterol diet led to significant increases in fasting insulin and triglycerides from base, and decreases in HDL. Changes in HbA1c were not significant.
Norris, 2005[56]	Weight loss Interventions (diet, physical activity, behavioral)	Adults with IGT, BMI range 26-34 Mean BMI 28.7 Mean age 51.2 Mean GHb 5.8	August 2003	9 RCTs f/u 1 to 10 years 7 of the RCTs were diet vs usual care/ counseling	10	Pooled results 2.8 kg weight loss at 1 year compared to usual care & decrease in BMI of 1.4; at 2 years, 2.7 kg weight loss. No pooling for GHb. Decrease in GHb ranged from 0.0 to 0.2 percentage points. 3 studies reported diabetes incidence; one reported decrease of 31% at 2.8 years.

Author / Year	Intervention	Patients	Search through	# of included studies	AMSTAR	Findings
Gillies, 2007[57]	Treatment to delay or prevent DM (pharma, diet, exercise)	Adults with IGT Mean age ranged 38.7 to 56.7 Mean BMI ranged 23.8 to 37.3	July 2006	12 RCTs of behavioral interventions 12 RCTs of herbal / pharmacological 4 other studies	9	Hazard ratios for progression to diabetes: 0.51 for lifestyle vs standard advice 0.70 for oral diabetes meds vs control 0.44 for orlistat vs control 0.32 for herbal jiang tang bushen vs advice

AMSTAR: Measurement tool created to assess the methodological quality of systematic reviews; BMI: Body Mass Index; DM: Diabetes Mellitus; GHb: Glycohemoglobin, HbA1C: Hemoglobin; IGT: Impaired Glucose Tolerance; RCTs: Randomized Controlled Trials

Systematic reviews on diabetes medications

Three high quality systematic reviews focused on the efficacy and safety of diabetes medications in patients with type 2 diabetes. One of the reviews[58] examined incretin-based agents (exenatide, liraglutide, vildagliptin, and sitagliptin), another[59] examined oral agents (second-generation sulfonylureas, biguanides, thiazolidinediones, meglitinides, and α-glucosidase inhibitors), and the third[60] examined newer agents available for blood glucose control (exenatide, sitagliptin and vildagliptin, glargine and detemir, and thiazolidinediones). These three reviews provide evidence that most blood glucose control medications were effective in glycemic control; some of them also led to weight loss. However, clinical data such as effects on all-cause mortality and cardiovascular mortality is limited. Results are summarized in Table 8.

Fakhoury and colleagues[58] conducted a systematic review and a meta-analysis to compare incretin-based agents with placebo. They identified 38 RCTs directly comparing exenatide, liraglutide, vildagliptin, and sitagliptin with placebo. Mean baseline HbA1c of participants included in the study ranged from 6.7 to 9.4, mean duration of diabetes from 1.7 to 9.0 years, and mean baseline weight from 61.5 to 104.0 kg. Duration of trials ranged from 4 to 52 weeks. While all incretin-based agents significantly reduced HbA1c level in comparison with placebo (WMD= -0.79, -0.75, and -0.67 for sitagliptin, exenatide, and vildagliptin, respectively), liraglutide was found to produce the greatest reduction (WMD= - 1.03). A statistically significant weight gain was found in vildagliptin and sitagliptin groups, while a statistically significant weight reduction was found in exenatide and liraglutide groups, especially in the exenatide group. Participants in sitagliptin and exenatide groups were more likely to experience some hypoglycemia compared to participants in the placebo group. The authors concluded that incretin-based agents produced beneficial effect on glycemic control, and some agents also led to weight loss.

Bolen and colleagues[59] reviewed the benefits and harms of oral agents in treating type 2 diabetes patients in the U.S. Two hundred and sixteen controlled trials and cohort studies and two systematic reviews were included in this study. They found very limited data on clinical end points such as cardiovascular mortality. No evidence was found to support the effectiveness of oral agents on major clinical end points such as all-cause mortality, cardiovascular mortality or morbidity, peripheral arterial disease, neuropathy, retinopathy, or nephropathy. However, most oral agents showed a beneficial effect on intermediate outcomes such as glycemic control: thiazolidinediones, metformin, and repaglinide decreased HbA1c level by about one absolute percentage point; nateglinide and α-glucosidase inhibitors produced weaker reductions in HbA1c by about 0.5 absolute percentage point. Most oral agents other than metformin were associated with one to five kg of weight gain. Different agents were associated with different adverse events: sulfonylureas and repaglinide were associated with greater risk for hypoglycemia,

thiazolidinediones with greater risk for heart failure, and metformin with greater risk for gastrointestinal problems. The authors concluded that older agents such as second-generation sulfonylurea and metformin were at least as effective as other oral agents on intermediate outcomes such as glycemic control.

A group of UK researchers reviewed newer pharmacological agents for blood glucose control in type 2 diabetes patients from four classes:[60] the glucagon-like peptide-1 (GLP-1) analogue exenatide; dipeptidyl peptidase-4 (DPP-4) inhibitors sitagliptin and vildagliptin; the long-acting insulin analogues, glargine and detemir; and thiazolidinediones. While focused on cost-effectiveness and comparing newer agents with Neutral Protamine Hagedorn (NPH), the study found that exenatide and DPP-4 inhibitors were all clinically effective in glycemic control: in patients with inadequate control on dual oral combination therapy, adding exenatide produced a one percent reduction in HbA1c level; when combined with metformin, the DPP-4 inhibitors reduced HbA1c level by about 0.8 percent. Exenatide was found to be associated with an added benefit of weight loss. Hypoglycaemia, weight gain, heart failures, fractures, and cardiovascular events were among the side effects associated with the agents.

Table 8. Systematic Reviews on Diabetes Medications

Author / Year	Intervention	Patients	Search through	# of included studies	AMSTAR	Findings
Fakhoury, 2010[58]	Incretin-based medications: exenatide, liraglutide, vildagliptin, and sitagliptin	Type 2 DM mean weight = 61.5 - 104.0 kg mean HbA1C = 6.7 - 9.4 Mean age = 50.9 - 62.9	July 2009	38 RCTs Duration 4 - 52 weeks	7	All agents significantly reduced HbA1c level in comparison with placebo (pooled results of weighted mean differences: -1.03, -0.79, -0.75, -0.67 for liraglutide, sitagliptin, exenatide, and vildaglitin, respectively); weight loss associated with exenatide (WMD= -1.10).
Waugh, 2010 [60]	Medications: exenatide, sitagliptin and vildagliptin, glargine and detemir, and thiazolidinedion es	Type 2 DM mean weight/BMI/HbA1c separately reported for each arm	April 2008	Hard to count # of included studies since reported separately for individual arms; but > 24 RCTs and 10 Systematic reviews Duration >=12 weeks	9	Exenatide and DPP-4 inhibitors were effective in glycemic control: adding exenatide produced a 1 point reduction in HbA1c in patients with inadequate control on dual oral combination therapy; DPP-4 inhibitors + metformin reduced HbA1c by 0.8 points; pioglitazone + insulin reduced HbA1c by 0.54 points.
Bolen, 2007[59]	Oral medications: second-generation sulfonylureas, biguanides, thiazolidinedion es, meglitinides, and α-glucosidase inhibitors	Type 2 DM	January 2006	216 Controlled trials and cohort studies 2 Systematic reviews Duration >= 3 mon	10	Pooled result: thiazolidinediones, metformin, and repaglinide decreased HbA1c by one absolute percentage point; No pooling for nateglinide and α-glucosidase inhibitors: reduced HbA1c by 0.5 absolute percentage point; No effectiveness evidence on all-cause mortality, cardiovascular mortality or morbidity, peripheral arterial disease, neuropathy, retinopathy, or nephropathy.

AMSTAR: Measurement tool created to assess the methodological quality of systematic reviews; DM: Diabetes Mellitus; HbA1C: Hemoglobin; RCTs: Randomized Controlled Trials, WMD: Weight Mean Difference

Major trials published after the systematic reviews

Since the systematic reviews discussed above were published, long-term followups of several of the included studies have been conducted. These studies assessed the long-term (10 – 20 years followup) effects of non-surgical interventions in China[61] (behavioral intervention), U.S.[62] (behavioral and medications), and the United Kingdom[63] (medications). Overall, weight loss effects that were often observed during active intervention period did not persist in the long run, while the reductions in diabetes incidence and diabetes-related end points persisted. This effect seemed consistent across cultures. However, behavioral interventions did not lead to any significant reduction in some major clinical end points such as mortality. Pharmacological interventions seemed to reduce mortality in the long run, but this effect was only observed in the U.K. study[63]. More studies are needed to investigate long-term effects of non-surgical interventions.

In China, Li and colleagues[61] conducted a 20-year followup study of the China Da Qing Diabetes Prevention Study (CDQDPS), which compared behavioral interventions (diet, exercise, and diet plus exercise) with a control group among adults with impaired glucose tolerance. Long-term effect on the risk of diabetes, diabetes-related macrovascular and microvascular complications, and mortality were reported. Although changes in body weight during the entire 20-year followup period did not differ significantly by intervention and control groups, participants in the intervention group had a 43 percent lower incidence of diabetes over the 20-year period, compared to those in control group. The average annual incidence of diabetes and 20-year cumulative incidence of diabetes were lower in the intervention group (7 percent annual incidence and 80 percent cumulative incidence) than those in the control group (11 percent annual incidence and 93 percent cumulative incidence). Diabetes onset was delayed an average of 3.6 years in the intervention group. However, no significant difference was observed in the rate of first CVD event, CVD mortality, and all-cause mortality between intervention group and control group. The authors concluded that behavioral interventions produced a long-lasting reduction in the incidence of type 2 diabetes.

In U.S., Knowler and colleagues[62] conducted a 10-year followup study of the Diabetes Prevention Program (DPP) and investigated the persistence of the diabetes incidence and weight loss effects of behavioral and medication interventions that were observed during the intervention period. The effect of an intensive behavioral intervention and metformin on diabetes incidence, weight loss, and cardiovascular disease risk were compared with that of placebo. During the 10-year followup period, the original behavioral group lost the most weight initially, and then gradually regained weight (but still weighted less than they did at baseline), while the original metformin group maintained a modest weight loss. Cumulative incidence of diabetes in the 10 years was reduced by 34 percent in the behavioral group and 18 percent in the metformin group. It remained lower in the behavioral and metformin groups than in the placebo group, although diabetes incidence during the 10-year followup did not differ significantly between groups. Diabetes onset was delayed in behavioral group and metformin group by four years and two years, respectively, compared to placebo group. The authors concluded that both behavioral and metformin interventions reduced cumulative incidence of diabetes; this effect persisted for at least 10 years.

In UK, Holman and colleagues[63] performed a 10-year followup study of the United Kingdom Prospective Diabetes Study (UKPDS), which compared effects of an intensive glucose therapy (sulfonylurea or insulin or, in overweight patients, metformin) with conventional dietary therapy.

No significant difference in mean body weight had been found between groups. After one year, between-group differences in mean glycated hemoglobin levels were lost: participants in both groups had similar glycated hemoglobin improvements. However, the sulfonylurea/insulin group maintained significant reductions in relative risk for any diabetes-related end point (risk reduction 9 percent) and microvascular disease (risk reduction 24 percent) observed during the active intervention period. Overtime, the sulfonylurea/insulin intervention reduced risks for diabetes-related mortality, myocardial infarction, and all-cause mortality by 17 percent, 15 percent, and 13 percent, respectively, compared to the conventional dietary therapy. Among overweight patients, over 10 years, metformin reduced risks for any diabetes-related end point, diabetes-related mortality, myocardial infarction, and all-cause mortality by 21 percent, 30 percent, 33 percent, and 27 percent, respectively.

Four very large new RCTs recently published initial findings that were not included in the systematic reviews; findings that differ from those of the reviews are described here. The studies assessed behavioral interventions in four countries: the Finnish Diabetes Prevention Study in Finland[64], the Indian Diabetes Prevention Programme (IDPP) in India[65], the PREDIMED trial in Spain,[66] and another large trial in the UK. Findings from these four studies suggested that behavioral interventions were effective across different ethnic populations, despite their different BMI and other clinical and diabetes related characteristics.

In Finland, Ilanne-Parikka and colleagues[64] reported on the Finnish Diabetes Prevention Study and assessed effects of behavioral intervention on metabolic syndrome and its components. Mean BMI at baseline was 31.2, with a standard deviation of 4.6 kg/m^2. With a mean followup of 3.9 years, they found that the intensive behavioral intervention produced a significant reduction in the prevalence of metabolic syndrome (from 74.0 percent to 58.0 percent), compared to the standard care provided to the control group (from 74.0 percent to 67.7 percent). A reduction in the prevalence of abdominal obesity in the long term was also observed in intervention group (odds ratio = 0.48).

In India, Ramachandran and colleagues[65] conducted a RCT in urban Asian Indians (mean BMI 25.8, SD 3.5 kg/m^2) with persistent IGT that evaluated the effects of behavioral modifications and metformin on the development of type 2 diabetes. With a median followup duration of 30 months, they found that compared to the control group, both behavioral modification and metformin significantly reduced the cumulative incidence of diabetes at year 3 (39.3 percent, 40.5 percent, and 55.0 percent in behavioral modification, metformin, and control group, respectively), while no added benefit was observed to combine lifestyle modification and metformin (39.5 percent). This represented a relative risk reduction of 28.5 percent, 26.4 percent, and 28.2 percent with behavioral modification, metformin, and the combination, in comparison with control, respectively.

In Spain, Salas-Salvado and colleagues[66] reported one year data from the PREDIMED trial, which evaluated the effect of two diet interventions (Mediterranean diet plus virgin olive oil and Mediterranean diet plus nuts) on metabolic syndrome status compared with a control (low-fat diet advice) among older participants at high risk for CVD. Mean BMI at baseline was 29.3 kg/m^2. They found a significant reduction of overall prevalence of metabolic syndrome in the Mediterranean diet plus nuts group (prevalence reduced by 13.7 percent), compared to that in control group (prevalence reduced by 2.0 percent). Although no significant difference in the incidence rates of metabolic syndrome was observed among groups, the effect of Mediterranean diet plus nuts seemed more a consequence of higher rates of reversion among those who had the metabolic syndrome at the baseline. Mediterranean diet plus virgin olive oil showed a non-

significant reduction in metabolic syndrome prevalence. The authors concluded that a beneficial effect on metabolic syndrome could be achieved by diet alone.

Finally, a 12-month RCT[67] was carried out in 13 sites in primary care in UK to evaluate the effectiveness of a structured group education program focused on behavior change among newly diagnosed type 2 diabetes patients (mean BMI= 32.3 kg/m²; mean HbA1c=8.1). In addition to weight loss and blood glucose outcomes, this study also reported behavioral outcomes (smoking status and physical activity), psychosocial outcomes (illness belief and depression), and quality of life at 4, 8, and 12 months. Compared to usual care, the education intervention was found to be associated with significant weight loss (2.98 kg in education intervention group vs. 1.86 kg in usual care group), a significant reduction in triglyceride levels at eight months, a significant reduction in smoking status at all time points, and a significantly greater increase in physical activity at 4 months. The education intervention group also showed significantly greater understanding of their illness and its seriousness, and had a lower depression score. However, changes in HbA1c level and quality of life scores were not significantly different between groups at any time point.

Summary

Table 9 displays a summary of data on interventions and outcomes in patients with diabetes or impaired glucose tolerance. While direct comparisons of these interventions have in many cases not been assessed in randomized trials, it is nonetheless useful to present the data in a side-by-side format. We discuss the limitations of such comparisons in detail in the discussion section; readers should keep in mind that patients enrolled in the nonsurgical trials of medication and behavioral interventions may differ in important ways from those participating in the surgical studies.

Short term outcomes. In sum, there is moderate strength evidence that bariatric surgery is an effective way to treat diabetes in patients with BMI of at least 30 but less than 35 in the short term. At one year, surgery patients have shown significantly greater weight loss than usually seen in studies of diet, exercise, or other behavioral interventions. And with the exception of exenatide, diabetes medications do not cause significant weight loss. While both behavioral interventions and various medications have been shown to lower HbA1c levels significantly, the decreases reported in bariatric surgery patients at one year are greater. In addition, improvements in diabetes outcomes have been reported as early as one month post-surgery.[39] Improvements in hypertension, LDL cholesterol, and triglycerides have also been reported at one year in surgery patients. We judged this evidence as moderate due to sparseness of data - only two RCTs directly comparing surgery with other interventions, and both came from the same group of researchers. Observational data, which start as “low” strength evidence, were upgrade due to consistency of results. Thus, the total body of evidence is considered moderate strength.

Long term outcomes. There are few long-term data on patients in this weight class with diabetes who have undergone bariatric surgery. We found only four studies with follow-up of more than two year; none of these were RCTs. One of these studies, a case series of LAGB patients in Italy, reported follow-up at five years;. Five-year data were reported for only 29 of the 210 initial patients in this study, for a follow-up rate of only 13.8 percent. Another case series followed up on BPD patients for over 10 years; there were only seven patients total. Thus, the evidence that bariatric surgery is an effective way to treat diabetes in patients with BMI of at least 30 kg/m^2 but less than 35 kg/m^2 in the long term is insufficient. In contrast, behavior and

medication interventions have been studied extensively in recent decades; several large long-term RCTs have found improved HbA1c levels continue for ten years. Long-term trials and meta-analyses have reported clinically significant improvements in microvascular and macrovascular outcomes.

Table 9. Summary of data on interventions and outcomes in patients with diabetes or impaired glucose tolerance

Outcome	Behavioral changes (data almost entirely from RCTs)	Intervention Medications (data almost entirely from RCTs)	Bariatric Surgery (data almost entirely from observational studies)
Weight loss at one year:	2.8 kg for diet, exercise, behavioral vs usual care	Weight gain from 1 to 5 kg with some drugs. 2 kg weight loss with exenatide. No weight change with metformin.	BMI loss of 2 to 4 kg/m^2 (about 10 kg for someone 5 foot 6 inches tall)
Weight loss at two years:	2.7 kg for diet, exercise, behavioral vs usual care	Data unavailable	BMI loss of 4 to 8 kg/m^2 ((about 18 kg for someone 5 foot 6 inches tall)
Long term weight loss (five years and more):	1.7 kg for diet, exercise, behavioral vs usual care at 5 years	Little data; the US Diabetes Prevention Program Outcomes Study (DPPOS) found no significant change with metformin at 10 years	BMI loss of 5.7 kg/m^2 at 5 years one study of LAGB
HbA1C at one year:	Decrease of 0.3 to 2.2 points	Decrease of 0.5 to 1.0 points	Decrease of 1.6 to 4.0 points
HbA1C at two years:	No significant change	Data unavailable	Decrease of 2.6 to 3.4 points
HbA1C at five years and more:	Little data; the US Diabetes Prevention Program Outcomes Study (DPPOS) found HbA1C concentrations lower in behavioral group at 10 years (vs. placebo)	Little data; the US Diabetes Prevention Program Outcomes Study (DPPOS) found HbA1C concentrations lower in metformin group at 10 years (vs. placebo)	Data unavailable
Other metabolic outcomes at one year:	Diet improved fasting glucose (1.3%-36.6% reduction) and triglycerides (11.3% - 58.9% reduction); the Spain PREDIMED study found Mediterranean diet reduced metabolic syndrome prevalence by 13.7% at 1 year; the Finnish Diabetes Prevention Study (DPS) found behavioral change reduced metabolic syndrome prevalence at 3.9 years (odds ratio: 0.62)	Most medications had minimal effects on systolic & diastolic blood pressure (< 5 mmHg change) Metformin and second generation sulfonylureas generally decreased LDL cholesterol levels	Decrease in triglycerides of 20 to 120 mg/dl
Other metabolic outcomes at five years and more:	Data unavailable	Data unavailable	Of 7 BPD patients followed, all had normal serum cholesterol and triglycerides

Outcome	Behavioral changes (data almost entirely from RCTs)	Intervention Medications (data almost entirely from RCTs)	Bariatric Surgery (data almost entirely from observational studies)
Microvascular outcomes: (Renal disease, neuropathy, retinopathy, etc)	Data unavailable	UK Prospective Diabetes Study (UKPDS) found patients taking sulfonylurea, insulin, or metformin had 24% risk reduction for microvascular disease at 10 years Decision analysis models suggests that glucose control has a strong effect on microvascular outcomes.	In a two-year gastric sleeve study, macroalbuminuria resolved in all 4 patients who had it at baseline. Of 14 patients with microalbuminuria, it had resolved in all but 3. In another gastric sleeve study by the same research group (N=69), retinopathy was diagnosed in 26.1% of patients preoperatively. Objective improvement of the retinopathy was seen in 44.4% of these patients at 7 to 42 months.
Macrovascular outcomes: (Cardiovascular disease, stroke, heart attack)	Little data; the China Da Qing Diabetes Prevention Study (CDQDPS) found no significant difference in first CVD event, CVD mortality and all-cause mortality between intervention and control group	Meta-analysis of 5 trials with 33,040 participants found that on an average A1C reduction of 0.9% there was a 19% reduction in non fatal myocardial infarction and a 15% reduction on coronary heart disease, and no statistically significant effect on stroke or all cause mortality.	Data unavailable
Prevention of diabetes:	Hazard ratio 0.51 for behavioral interventions vs standard advice at 1 to 5 years; the US Diabetes Prevention Program (DPP) found diabetes incidence in 10 years reduced by 34% by behavioral change vs. placebo, and the China Da Qing Diabetes Prevention Study (CDQDPS) found it was 43% lower in behavioral group over 20 years	Hazard ratio 0.70 for oral medications vs control at 1 to 5 years; the US Diabetes Prevention Program (DPP) found diabetes incidence in 10 years reduced by 18% in the metformin group vs. placebo	Data unavailable

KQ3: What are the potential short term adverse effects (AEs) and/or complications involved with bariatric surgery for treating adult patients with BMI of 30 to 34.9 who have metabolic conditions?

The incidence of adverse events following bariatric surgery is displayed in Table 10 for all studies, including case series and RCTs. Follow-up times varied significantly from the day of surgery to five years, though few studies reported long-term complications (past one year), few studies were clear exactly when adverse events took place, and patients who were lost to follow-up had missing adverse events data. Adverse events were identified and self-reported by the surgical team, with definitions of most complications varying from study to study. No administrative data was available to diminish these biases. In addition there were few studies that reported adverse events between different surgical procedures, making direct comparisons difficult.

Less than 1 percent of the 1,131 patients who underwent any surgical procedure died, with a mortality of 0.2 percent reported for LAGB, 0.4 percent for gastric sleeve, and no deaths reported for RYGB or BPD. Medical complications (cardiovascular, respiratory, and renal) ranged from 1-10 percent for these surgical procedures. Nearly 4 percent of patients undergoing either gastric sleeve or RYGB experienced a cardiovascular or respiratory complication. The majority of these were either an arrhythmia or pneumonia, while one BPD patient in a single study with only 10 patients suffered a pulmonary embolus. Renal complications (acute renal failure and urinary tract infections) were reported at an incidence of 0.4 percent and 1.1 percent, respectively, for gastric sleeve.

A significant minority (31.9 percent) of all surgical patients experienced gastrointestinal (GI) complications such as diarrhea and feeding difficulties. This ranged from 3.1 percent for LAGB to 47.8 percent for gastric sleeve (mostly anorexia / excessive weight loss and feeding difficulties). Eleven percent of gastric sleeve patients experienced GERD (gastroesophageal reflux disease). Less than one percent of patients undergoing RYGB experienced acute cholecystitis or common bile duct obstruction. Metabolic complications such as hyperuricemia or gout were uncommon in gastric sleeve patients (0.9 percent), while hypoglycemia was somewhat common in patients undergoing RYGB (12.5 percent) and BPD (7.4 percent). One out of 30 patients was readmitted following both gastric sleeve and RYGB, respectively.

The incidence of reported major surgical complications was 6.5 percent across all procedures, and ranged from 1.8 percent for BPD (three studies with a total of 57 patients) to 7.4 percent for gastric sleeve. Bleeding complications were reported at 3.2 percent across all surgical procedures, and pouch/anastomosis problems at 2.6 percent (ranging from 0 percent for BPD to 5.2 percent for LAGB). VBG was associated with a 3.7 percent rate of bleeding and 2.9 percent rate of other major surgical complications including reoperation. Wound complications were uncommon (2.0 percent for all surgical procedures). LAGB-specific complications such as band slippage and port or tube leaks were relatively low at only 4.7 percent, including 3.3 percent of patients who required band removal.

We judged the strength of evidence for short term harms as moderate, for the same reasons we judged the short term effectiveness data as moderate. There are only two RCTs comparing adverse events by procedure, and additionally, there may be publications bias in the cases series data. However, the AEs reported for the particular procedures were consistent and the range

among the studies was fairly precise.

Table 10. Incidence of Adverse Events - Surgical Weight Loss Treatments

Adverse Event[a]	Overall	LAGB	Gastric Sleeve	RYGB	BPD
Mortality	0.3% (3/1131)	0.2% (1/531)	0.4% (2/484)	0% (0/235)	0% (0/20)
	n=11 studies	n=5 studies	n=2 studies	n=5 studies	n=1 study
MEDICAL COMPLICATIONS					
CV/Respiratory					
Arrhythmia	0.9% (5/563)	---	0.9% (4/454)	0.9% (1/109)	---
Pneumonia	2.0% (11/563)	---	2.0% (9/454)	1.8% (2/109)	---
Pulmonary embolus	10.0% (1/10)	---	---	---	10.0% (1/10)
Any CV/Respiratory complication	3.8% (22/573)	---	3.7% (17/454)	3.7% (4/109)	10.0% (1/10)
	n=3 studies	---	n=1 study	n=1 study	n=1 study
Renal					
Acute Renal Failure	0.4% (2/454)	---	0.4% (2/454)	---	---
Urinary Tract Infection	1.1% (5/454)	---	1.1% (5/454)	---	---
Any Renal Complication	1.5% (7/454)	---	1.5% (7/454)	---	---
	n=1 study	---	n=1 study	---	---
GI					
Anorexia/Excessive wt loss	20.5% (96/469)	---	21.2% (96/454)	0% (0/15)	---
Diarrhea	2.0% (9/454)	---	2.0% (9/454)	---	---
Feeding difficulties	8.7% (17/196)	3.8% (2/53)	20.0% (2/10)	9.8% (13/133)	---
GERD	10.2% (50/491)	---	11.0% (50/454)	0% (0/37)	---
Nausea/Vomiting	7.5% (44/587)	0.9% (1/109)	7.3% (33/454)	7.5% (10/133)	---
Acute cholecystitis	0.9% (1/109)	---	---	0.9% (1/109)	---
Any GI complication	31.9% (254/795)	3.1% (8/255)	47.8% (222/464)	13.0% (24/185)	---
	n=8 studies	n=3 studies	n=2 studies	n=4 studies	---
Metabolic					
Hyperuricemia/ Gout	0.9% (4/454)	---	0.9% (4/454)	---	---
Hypoglycemia	9.8% (5/51)	---	---	12.5% (3/24)	7.4% (2/27)
Any metabolic complication	1.6% (10/614)	---	0.9% (4/454)	3.0% (4/133)	7.4% (2/27)
	n=4 studies	---	n=1 study	n=2 studies	n=1 study
Constitutional / Other[b]	0.6% (4/622)	---	0.2% (1/454)	1.8% (3/168)	---
	n=4 studies	---	n=1 study	n=3 studies	---
Readmission	3.3% (2/60)	---	3.3% (1/30)	3.3% (1/30)	---
	n=1 study	---	n=1 study	n=1 study	---
SURGICAL COMPLICATIONS					
Major Surgical Complications					
Bleeding/Hematoma	3.2% (19/590)	3.7% (1/27)	3.7% (17/454)	0.9% (1/109)	---
Pouch/Anastomosis	2.6% (21/793)	5.2% (11/210)	1.1% (5/454)	4.6% (5/109)	0% (0/20)
Other[c]	2.5% (17/672)	---	2.9% (14/484)	1.2% (2/161)	1.8% (1/57)
Any major surgical complication	6.5% (57/882)	5.1% (12/237)	7.4% (36/484)	5.0% (8/161)	1.8% (1/57)
	n=9 studies	n=2 studies	n=2 studies	n=4 studies	n=3 studies
Minor Surgical Complications NOS	10.0% (6/60)	---	10.0% (3/30)	10.0% (3/30)	---
	n=1 study	---	n=1 study	n=1 study	---
Wound	2.0% (12/587)	---	2.0% (9/454)	2.3% (3/133)	---
	n=3 studies	---	n=1 study	n=2 studies	---
Band-Related					
Slippage	---	1.7% (9/531)	---	---	---
Port/Tube Leak	---	2.0% (7/356)	---	---	---
Removal	---	3.3% (7/210)	---	---	---
Any band-related complication	---	4.7% (25/531)	---	---	---
	---	n=5 studies	---	---	---

Percentage (Number of patients with adverse event / Total number of patients)

[a] Studies may have reported on >1 adverse event category and the majority reported on >1 surgical weight loss treatment. Some patients had >1 adverse event. The total number of adverse events was counted for each category.

[b] Other includes rhabdomyolisis, major morbidity, and not otherwise specified.

[c] Other surgical complications include abscess, bladder or stomach perforation, internal hernia, ischemia, intraabdominal complications, reoperation, and not otherwise specified.

KQ4: Does the evidence show racial and demographic disparities with regard to potential benefits and harms associated with bariatric surgery for treating adult patients with BMI of 30 to 34.9 and metabolic conditions? What other patient factors (social support, counseling, pre-operative weight loss, compliance) are related to successful outcomes?

There was insufficient data in the surgery studies included in this report to assess whether racial and demographic disparities exist in terms of weight loss and metabolic outcomes. However, previous research shows that some patient-level factors are associated with successful weight loss after bariatric surgery. Regardless of procedure type, patients who lose more weight tend to be younger, have a lower preoperative BMI, and be non-diabetic.[68-70]

One recent systematic literature review identified a number of psychosocial patient factors that may be associated with weight loss after bariatric surgery.[71-72] This review was based on observational studies that included all bariatric patients, including those with baseline BMI> 35 kg/m^2 and those without diabetes. Data specific to patients with a BMI less than 35 kg/m^2 and diabetes are not available. Preoperative factors include baseline BMI, with heavier patients losing less weight than their lighter counterparts in 37 out of 62 studies. Meta-analysis revealed a decrease of 10.1 percent EWL (excess weight loss) for super obese versus non-super obese patients (95 percent CI 3.7 percent – 16.5 percent). Some programs request that bariatric candidates lose a modest degree of weight (generally 10-20 pounds) in the weeks immediately prior to surgery. This mandatory preoperative weight loss was associated with successful outcomes after bariatric surgery in seven out of 14 studies. In a meta-analysis on the association between preoperative weight loss versus no weight loss and postoperative weight loss, the preoperative weight loss group lost a mean of 5.0 percent greater EWL (95 percent CI 2.7 to 7.3 percent).[73]

Social support is believed to be an important component of successful weight loss, and support group attendance in particularly is associated with improved weight loss outcomes after surgery. For example, one study of RYGB patients found that when controlling for time elapsed since surgery, the number of support group meetings attended explained some variance in weight loss ($R2 = .09$, $P<0.05$).[74] Another study of patients who underwent LAGB reported that patients who attended support groups had greater weight loss starting at 6 months after surgery, and continuing at 12 months (9.7 vs. 8.1 BMI points decrease at 12 months, $P<0.05$).[75-76]

Support groups can help to provide continuing postoperative education regarding exercise and dietary recommendations, as well as identify any problems early on. Increased postoperative activity was also associated with greater postoperative weight loss in the majority of studies (11 out of 13 studies). A meta-analysis assessing the association of exercise versus no exercise and postoperative weight loss at 12 months showed that the exercise group lost a mean of 4.2 percent greater total BMI (95 percent CI 0.3 to 8.1 percent).[71] Other factors that may be predictive of postoperative weight loss include specific eating habits or disorders, such as hunger (two out of two studies) and emotional eating (three out of six studies). The emotional and physical stresses of such dramatic weight loss can trigger maladaptive responses in patients with preexisting eating disorders. The impact of other eating disorders and psychiatric disorders such as depression is not clear. This is in part due to variability in how eating and psychiatric disorders are defined from study to study, which survey instruments are used, and the follow-up time.

KQ5: What does the evidence show regarding long-term benefits and harms of bariatric surgery for treating adult patients with BMI of 30 to 34.9 and who have metabolic conditions? How do they compare to short-term outcomes (within 1 year from surgery)?

There were 14 surgical studies that reported outcomes at 12 months or more. Diabetes remission or resolution was seen in 94 percent of 307 patients followed for 1 year or longer, compared to 54 percent of 239 patients followed less than one year. The percentage of patients who no longer required medications for their diabetes was highest in the 128 patients followed between one and two years, with 87 percent of patients no longer requiring medications. This dropped slightly to 83 percent when looking at the 102 patients followed for two years or more. However, these longer-term outcomes were better than the 45 percent of those off of medications in the 218 patients followed up to 6 months and the 70 percent of 218 patients off of medications that were followed from 6 months to one year.

In studies which measure glucose, the mean glucose levels continued to drop with longer time of followup, from a mean decrease of 72 mg/dl in the 510 patients followed for less than six months to a decrease of 90mg/dl in the 104 patients followed from six months to one year, 94mg/dl in the 175 patients followed between one and two years and 97mg/dl in the 79 patients followed for two years or more. The hemoglobin A1c (HbA1c), however, showed the highest amount of change in the 139 patients followed from 6-11 months with a decrease of 3.12 percentage points, while studies following 197 patients from one to two years reported a mean decrease of 2.79 and one study following 72 patients for longer than two years reported a decrease of 2.4. BMI continued to decrease with time, with a mean decrease of 3.53 kg/m^2 in 786 patients followed less than six months, 4.11 in 702 patients followed up to one year, 5.26 in the 798 patients followed between one and two years and 5.53 in the 435 patients followed for two years or more.

In regards to harms, most reported morbidity and mortality at less than one year or were not specific when complications occurred. Mortality was reported in one patient at 20 months after LAGB due to sepsis following gastric perforation of a dilated pouch. This represented a 0.4 percent mortality rate in the 210 patients of that study.[30] Of the four remaining "long-term studies", there were no deaths out of 227 patients receiving LAGB and RYGB.[22,31-33] Taken together, the one death out of 437 gives a mortality rate of 0.23 percent, compared to the 0.2 percent (3/1724) mortality rate seen with the shorter-term outcomes.

Cardiovascular and respiratory complications were not reported in outcomes over one year. Gastrointestinal (GI) complications included esophagitis, feeding difficulties and hiatal hernia occurred in 4 percent (6/93) patients receiving LAGB.[31-32] This is consistent with the rate of GI complications in short-term LAGB studies and less than the 31.9 percent with GI complications overall in short-term surgical studies. Hepatobiliary complications included one patient out of 40 in the longer-term studies who developed acute cholecystitis 23 months after lap band[48] compared to one patient out of 109 patients after RYGB in the shorter term studies.[26]

LAGB-specific complications included band slippage in 1.9 percent (9/462),[30-33,48] and erosion in 1.5 percent (1/66).[33] One study reported the need for removal of the band in 3.3 percent (7/210) of patients.[30] Port related complications included port leaks, port tube leaks, and a port site seroma in 1.9 percent (9/462).[30-33] This is compared to the rate of 3.4 percent (5/149) of LAGB-specific complications reported in shorter-term outcomes.[26,48]

Though not within the parameters of this systematic review, it is interesting to note a recent European study reported long-term outcomes following laparoscopic adjustable gastric band. Consecutive patients from a single institution operated on from 1994-1997 and meeting the NIH criteria were included.[77] Of 151 patients, the mean preoperative BMI was 41.57 kg/m^2 (range, 35-57). Of these patients, only 82 (54.3 percent) were available for long-term follow-up at 13 years. The number of patients varied somewhat for each outcome depending on preoperative data availability. For example, complete weight loss data was available for 70 of 151 patients. Overall, 43 percent maintained a loss of excess weight, nearly 60 percent required reoperation, and obesity-related comorbidities such diabetes, hypertension, and sleep apnea persisted. Of 78 patients, 20 (25.6 percent) were treated for hypertension before band insertion and 23 (29.5 percent) were treated for hypertension 12 years after their laparoscopic adjustable gastric band (P=.72). Of 78 patients, 5 (6.4 percent) had type 2 diabetes before band insertion and 11 had diabetes 12 years after surgery. Of the 78 patients, two (2.6 percent) needed continuous positive pressure for sleep apnea before surgery and 6 (7.7 percent) after surgery. Nearly one-third of patients experienced band erosion, while 17 percent were converted to a gastric bypass. Intent to treat excess weight loss was 33.92 percent (range 24 percent – 143 percent). 36 patients (51.4 percent) still had the band in place and their mean excess weight loss was 48 percent (range 38 percent – 58 percent).

This study on long-term outcomes reported on patients with preoperative weight higher than that of our target population. As such, it is not clear how these results translate to a lower weight group. Additionally, the study was limited in its ability to draw conclusions as almost 50 percent of patients were not available for follow-up, which may contribute to significant bias. Thus, at this time, strength of evidence is insufficient on the long term effectiveness and harms of bariatric surgery in the population with metabolic conditions and BMI less than 35. Still, the study described above draws attention to the importance of having long-term outcomes following bariatric surgery as some obesity-related comorbidities were not resolved at 12 years and there was a high rate of significant band-related complications

Summary and Discussion

We conducted an extensive literature search, data abstraction, and quantitative analysis where possible, to assess the comparative effectiveness of bariatric surgery in patients with metabolic conditions and BMI of at least 30 but less than 35. In this chapter, we describe the limitations of our systematic review then present our conclusions. We also discuss the implications of our findings for future research.

Limitations

The literature on bariatric surgery in patients with BMI of at least 30 kg/m^2 and less than 35 kg/m^2, with diabetes, has many limitations. Most importantly, very few studies have long term followup. There are only four studies that follow patients for more than two years. Two of these report data at five years or more; one has a followup rate of only 13.8 percent, while the other includes only seven patients. Thus, we have almost no data on long-term efficacy and safety. No evidence was found on major clinical end points such as all-cause mortality, cardiovascular mortality or morbidity, or peripheral arterial disease,. Importantly, the available evidence from the diabetes literature indicates it may be premature to assume that controlling glucose to normal or near normal levels completely mitigates the risk of microvascular and macrovascular events. While it is more likely than not that this is true, conclusive proof is lacking, and the point is still debated in the diabetes literature.

Randomized controlled trials (RCTs) are considered the highest level of medical evidence. We found only two RCTs of surgery versus non-surgical treatment and only two RCTs comparing surgical procedures in this population. We acknowledge the difficulty in conducting randomized trials of surgery; however, we also identified only four cohort studies comparing procedures. The rest of our data comes from cases series reports primarily submitted by practicing surgeons. The sample sizes in most studies, regardless of methodological design, are far smaller than those of most trials of diet, exercise, and medications.

Applicability of research to the larger treatment population is important in interpreting the results of the included studies. The participation rate, the intended target population, representativeness of the setting, and representativeness of the individuals are used to assess applicability. The two RCTs of LAGB versus non-surgical interventions were conducted in Australia. The RCT comparing LAGB to sleeve gastrectomy was conducted in Taiwan, while the RCT comparing two types of sleeve gastrectomy was conducted in Brazil. This Brazilian team was also responsible for three of the four cohort studies comparing procedures. The other cohort study was conducted in the U.S. Of the remaining observational studies (case series) only three were conducted in the U.S. The other studies were conducted in Western Europe, South America, and India. Diet, behavior and culture may differ dramatically from country to country. The results seen in these populations may not be directly applicable to American patients.

Data reported on adverse events has several limitations. Most studies were not primarily designed to assess these outcomes and all studies reflect surgeon or surgery-team reported events. Additionally, follow-up times and rates were variable, and many studies did not state exactly when adverse events occurred, other than "within a year post surgery." As such, the rates of adverse events may be biased and lower than actual. Comparisons between procedure types are limited for the same reasons. We found no studies reporting adverse events in the long term.

Finally, although our literature search procedures were extensive and included canvassing experts regarding studies we may have missed, the possibility of publication bias still exists. For example the Los Angeles Times has run a series of news articles reporting on five deaths following LAGB surgery. Whether there is any causal relationship between the surgery and the deaths has not been assessed in a peer-reviewed publication yet, so no conclusions can be drawn. Still, it illustrates the potential for there to exist adverse events and/or beneficial outcomes in as-yet-undescribed populations.

Conclusions

Short term outcomes. There is moderate strength evidence that bariatric surgery is an effective way to treat diabetes in patients with BMI of at least 30 kg/m² but less than 35 kg/m² in the short term. At one year, surgery patients have shown significantly greater weight loss than can be expected from diet, exercise, or other behavioral interventions. And with the exception of exenatide, diabetes medications do not cause significant weight loss. While both behavioral interventions and various medications have been shown to lower HbA1c levels significantly, the decreases reported in bariatric surgery patients at one year are greater. In addition, improvements in diabetes outcomes have been reported as early as one month post-surgery.[39] Improvements in hypertension, LDL cholesterol, and triglycerides have also been reported at one year in surgery patients.

Long-term outcomes. There are few long-term data on patients in this weight class with diabetes who have undergone bariatric surgery. We found only four studies with follow-up of more than two years. One of these studies reported follow-up at five years; a case series of LAGB patients in Italy. Five-year data were reported for only 29 of the 210 initial patients in this study, a follow-up rate of only 13.8 percent. The other study that reported data at 5 years was a case series of only seven BPD patients. Thus, the evidence that bariatric surgery is an effective way to treat diabetes in patients with BMI of at least 30 kg/m^2 but less than 35 kg/m^2 in the long term is insufficient. In contrast, behavior and medication interventions have been studied extensively in recent decades; several large long-term RCTs have found improved HbA1c continues for ten years. Whether these interventions improve micro- and macrovascular outcomes from diabetes is still being debated; we found mixed results in the literature. Long-term trials and meta-analyses have reported clinically significant improvements in microvascular and macrovascular outcomes.

Specific bariatric procedures. We found two head to head trials comparing bariatric procedures. One average size trial (N=60) conducted in Taiwan compared RYGB to

sleeve gastrectomy; the RYGB group had better weight and diabetes outcomes at one year post surgery. The other trial (N=38) compared two variations of sleeve gastrectomy: diverted versus non-diverted. At two years, this Brazilian study found similar weight loss among groups, but greater diabetes improvements using the diverted procedure.

We also found four cohort studies that compared procedures. Three were by the same Brazilian surgical group mentioned above; they compared the two types of sleeve gastrectomy. (It is unclear whether the three studies have overlapping populations; we received no response to several queries to the authors.) They found that both procedures led to significant weight loss and improved diabetes outcomes; they concluded that the diverted sleeve gastrectomy may be slightly more effective at improving metabolic outcomes. The other cohort study, conducted in Australia, compared RYGB to LABG. This study was larger (N = 235) than the others, and had an adequate followup rate (61.9 percent for RYGB, 69.2 percent for LABG) at 6 to 12 months. Some patients were followed for two years. Weight loss was similar among groups; diabetes outcomes were generally better for RYGB patients.

We also examined observational studies of surgical procedures. Results at less than a year show clinically meaningful decreases in BMI for all types of bariatric surgery, with sleeve patients having the largest weight loss. Clinically meaningful diabetes outcomes were also reported at less than a year for all surgery types. At a year or more, decreases in BMI continued in all groups; RYGB patients had the greatest decrease. Clinically meaningful improvements in metabolic outcomes were present in all surgery groups.

Taking into consideration the entire body of evidence, we rate the strength of evidence as moderate for RYGB, LABG, and sleeve gastrectomy for treatment of diabetes and metabolic conditions in patients with a BMI of between 30 kg/m^2 and 35 kg/m^2, in the short term (up to two years). For BPD, both the number of studies and their sample sizes are much lower in this population; thus the strength of evidence for this procedure is rated low. There is insufficient evidence to determine comparative effectiveness of RYGB, LABG, and sleeve gastrectomy.

Adverse Events. Unfortunately, we found no long-term studies of adverse events. In the short term (one-year post surgery), rates of adverse events for patients with BMI of at least 30 kg/m^2 but less than 35 kg/m^2, are relatively low. Mortality rates, usually short-term in-hospital deaths, are relatively low (range: 0.3 percent to 0 percent).

The more commonly reported complications, such as gastrointestinal related (overall: 31.9 percent), were minor and tended to not require major interventions. Medical complications (overall: 3.8 percent) and metabolic disorders (1.6 percent) were also reported infrequently. Rates of major surgical complications were uncommon (range: 1.8 percent to 7.4 percent), but these often required a significant intervention or reoperation. LAGB related complications were reportedly low at 4.7 percent for all events, 1.7 percent band slippage, 2.0 percent port or tubing leak, and 3.3 percent removal rate, although these are surgeon-reported data that mostly come from studies not specifically designed to assess complication rates.

Future Research

Future research should focus on long-term outcomes of bariatric surgery in U.S. patients with diabetes and BMI of 30 kg/m^2 to 34.9 kg/m^2. There is insufficient evidence that bariatric surgery is effective in preventing the clinical consequences of diabetes – microvascular and macrovascular endpoints such as diabetic retinopathy, kidney failure, and myocardial infarction. Studies with followup of five or eight, or even 10 years will be needed.

We found only one U.S. cohort study comparing procedures; this study used the BOLD (Bariatric Outcomes Longitudinal Database), a resource created by the Surgical Review Corporation to monitor outcomes from the Bariatric Surgery Center of Excellence (BSCOE) program. As of June 2009, there were 235 patients with diabetes within our BMI range in the BOLD database. The study we identified reported outcomes at 6 to 12 months. Outcomes at 12 to 24 months were reported for only a small number of patients (6.8 percent) presumably because that followup time had not expired for most of the patients. Continued followup of these patients will be needed to assess the degree to which bariatric surgery mitigates long-term sequelae of diabetes.

Due to the lack of long-term studies, we found no evidence regarding major clinical end points such as all-cause mortality, cardiovascular mortality and morbidity, and peripheral arterial disease,. These outcomes should be tracked in any long-term study of bariatric surgery in patients with diabetes, as they are in long term studies of diet, exercise, and medication.

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Abbreviations / Acronyms

AHRQ	Agency for Healthcare Research and Quality
AMSTAR	Measurement tool created to assess the methodological quality of systematic reviews
BL	Baseline
BMI	Body Mass Index
BPD	Biliopancreatic Diversion
cc	Cubic Centimeters
CCTs	Controlled Clinical Trials
CDQDPS	China Da Qing Diabetes Prevention Study
CENTRAL	Cochrane Central Register of Controlled Trials
CER	Comparative Effectiveness Review
CHIP	Children's Health Insurance Program
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CMS	Center for Medicare and Medicaid Services
CPAP	Continuous Positive Airway Pressure
CV	Cardiovascular
CVD	Cardiovascular Disease
DARE	Cochrane Database of Abstracts of Reviews of Effects
DM	Diabetes Mellitus
DPP	Diabetes Prevention Program
EPC	Evidence-based Practice Center
EWL	Excess Weight Loss
FDA	Food and Drug Administration
F-up	Follow up
GB	Gastric Bypass
GERD	Gastroesophageal Reflux Disease
GHb	Glycated Hemoglobin
GI	Gastrointestinal
HbA1c	Glycosylated Hemoglobin
HDL	High-Density Lipoprotein
HFLC	High-Fat Low-Carbohydrate Diet
IDPP	Indian Diabetes Prevention Programme
IGT	Impaired Glucose Tolerance
II-DSG	Ileal Interposition Associated With Diverted Sleeve Gastrectomy
II-SG	Ileal Interposition Associated With a Sleeve Gastrectomy
LAGB	Laparoscopic Adjustable Gastric Banding
LDL	Low-Density Lipoprotein

LFHC	Low-Fat High-Carbohydrate Diet
MMDLN	Medicaid Medical Directors Learning Network
N	Sample Size
NHLBI	National Heart, Lung and Blood Institute
NIH	National Institute of Health
OSA	Obstructive Sleep Apnea
RCTs	Randomized Controlled Trials
RYGB	Roux en Y gastric Bypass
SE	Standard Error
SG	Sleeve Gastrectomy
TEP	Technical Expert Panel
UKPDS	United Kingdom Prospective Diabetes Study
VBG	Vertical Banded Gastroplasty
VLCDs	Very-low-calorie diets
WMD	Weight Mean Difference