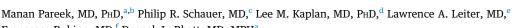
#### THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

# **Metabolic Surgery**

## Weight Loss, Diabetes, and Beyond

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#### ABSTRACT

The alarming rise in the worldwide prevalence of obesity is paralleled by an increasing burden of type 2 diabetes mellitus. Metabolic surgery is the most effective means of obtaining substantial and durable weight loss in individuals with obesity. Randomized trials have recently shown the superiority of surgery over medical treatment alone in achieving improved glycemic control, as well as a reduction in cardiovascular risk factors. The mechanisms seem to extend beyond the magnitude of weight loss alone and include improvements in incretin profiles, insulin secretion, and insulin sensitivity. Moreover, observational data suggest that the reduction in cardiovascular risk factors translates to better patient outcomes. This review describes commonly used metabolic surgical procedures and their current indications and summarizes the evidence related to weight loss and glycemic outcomes. It further examines their potential effects on cardiovascular outcomes and mortality and discusses future perspectives. (J Am Coll Cardiol 2018;71:670–87)

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approximately one-third of patients in the control group (9). Sustained, modest weight loss with lifestyle improvement versus control was also seen at 10 years in the Finnish Diabetes Prevention Study, but not at 10-year follow-up in the Diabetes Prevention Program (10,11).

Healthy lifestyle measures should be promoted in all individuals as primary, secondary, and tertiary prevention for overweight or obesity and associated complications (12,13). In patients with obesity, the major components of lifestyle therapy consist of reduced calorie intake, physical activity, and behavioral interventions. The energy deficit should generally be ~500 to 750 kcal daily (12,13). Moderate aerobic exercise of >150 min per week, distributed over 3 to 5 days, combined with resistance exercise 2 to 3 times per week, is recommended. Behavioral changes

(e.g., self-monitoring and goal setting) should be included as part of the intervention. The weight loss goal is 10% in subjects with pre-diabetes or the metabolic syndrome and at least 5% to 15% in those who have T2DM (13).

Combining weight loss drugs with lifestyle intervention can produce greater weight loss compared with lifestyle intervention alone (13,14). These medications may reinforce behavioral or lifestyle changes, increase the potential for physical activity, and have beneficial effects on related comorbidities. Many antiobesity drugs have been marketed over the years, but some were later withdrawn because of unacceptable adverse effects (15,16). The 5 antiobesity agents currently approved by the U.S. Food and Drug Administration are orlistat, lorcaserin, naltrexonebupropion, phentermine-topiramate, and liraglutide (13,17). A 2016 meta-analysis by Khera et al. (18) found significant 1-year weight loss for these drugs in comparison with placebo, ranging from 2.6 kg with orlistat to 8.8 kg with phentermine-topiramate. Contemporary guidelines suggest the addition of antiobesity medication to lifestyle measures in individuals with BMI  $\geq$ 30 kg/m<sup>2</sup> or BMI  $\geq$ 27 kg/m<sup>2</sup> with at least 1 obesity-associated comorbidity who are motivated, but have failed to lose weight or maintain weight loss by using high-intensity lifestyle intervention alone (Table 1) (13,14,17). Drug therapy may also be initiated concomitantly with lifestyle therapy in patients with BMI  $\geq 27 \text{ kg/m}^2$  who have (severe) weight-related complications (13). If  $\geq 5\%$  of body weight has not been lost after 3 months of therapy or there are issues with tolerability or safety, the drug should be discontinued. If the weight loss criterion is

he worldwide prevalence of obesity, characterized by a body mass index (BMI)  $\geq$ 30 kg/m², has more than doubled from approximately 5% in 1975 to 13% in 2014 (1,2). About 4% of persons are severely obese (BMI  $\geq$ 35 kg/m²), whereas 1% have morbid obesity (BMI  $\geq$ 40 kg/m²). Assuming unaltered trends, as much as one-fifth of the world population may have obesity by 2025 (1). In the United States, more than one-third of adults have obesity, with considerable differences in prevalence depending on race and socioeconomic status (3).

Obesity is a well-known risk factor for type 2 diabetes mellitus (T2DM) (2). Thus, there has been a parallel increase in the prevalence of T2DM, currently standing at 9% worldwide and projected to reach  $\sim$ 12% by 2025 (4). When the growing population is taken into account, the global burden of diabetes is likely to rise by more than 50% in the next decade (4,5). The metabolic abnormalities associated with obesity increase the risk of cardiovascular disease, including coronary artery disease and heart failure (6). Indeed, most of the  $\sim$ 7% of deaths for which a BMI above 25 kg/m<sup>2</sup> appears responsible can be related to cardiovascular disease or T2DM (2). The underlying mechanisms have not been fully elucidated, but they may include metabolic, hemodynamic, and inflammatory effects of having an increased adipose tissue mass (6).

Regardless of how achieved, weight loss has the potential to mitigate the adverse effects of obesity (6). The purpose of this review is to describe contemporary metabolic surgical procedures, their indications, and the effects of these procedures on weight loss, glycemic outcomes, cardiovascular outcomes, and mortality among adult individuals.

#### MEDICAL MANAGEMENT OF OBESITY

Although behaviorally based treatments can deliver statistically significant weight loss, the magnitude is generally modest, and the weight loss is often not durable (7). A 2014 meta-analysis by Dombrowski et al. (8) showed a significant, but small difference in 1-year weight loss of 1.6 kg with diet and physical activity compared with a control group. Conversely, the randomized Look AHEAD (Action for Health in Diabetes) trial (9) provided an example of a successful lifestyle intervention program. Among overweight or obese individuals with T2DM, one-half of those assigned to intensive lifestyle intervention (calorie goal of 1,200 to 1,800 kcal daily and ≥175 min of moderate intensity physical activity weekly) had a clinically meaningful weight loss of  $\geq 5\%$  (mean 4.7%) of their initial weight at 8 years as compared with

## ABBREVIATIONS AND ACRONYMS

Pareek et al.

AGB = adjustable gastric

BMI = body mass index

**BPD** = biliopancreatic diversion

BPDDS = biliopancreatic diversion with duodenal switch

CI = confidence interval

HbA<sub>1c</sub> = glycated hemoglobin

HR = hazard ratio

OR = odds ratio

RYGB = Roux-en-Y gastric bypass

SG = sleeve gastrectomy

T1DM = type 1 diabetes mellitus

T2DM = type 2 diabetes mellitus

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