

## THE PRESENT AND FUTURE

### STATE-OF-THE-ART REVIEW

# Metabolic Surgery

## Weight Loss, Diabetes, and Beyond



Manan Pareek, MD, PhD,<sup>a,b</sup> Philip R. Schauer, MD,<sup>c</sup> Lee M. Kaplan, MD, PhD,<sup>d</sup> Lawrence A. Leiter, MD,<sup>e</sup> Francesco Rubino, MD,<sup>f</sup> Deepak L. Bhatt, MD, MPH<sup>a</sup>

#### 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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From the <sup>a</sup>Brigham and Women's Hospital Heart & Vascular Center, Harvard Medical School, Boston, Massachusetts; <sup>b</sup>Cardiovascular and Metabolic Preventive Clinic, Department of Endocrinology, Odense University Hospital, Odense, Denmark; <sup>c</sup>Bariatric and Metabolic Institute, Cleveland Clinic, Cleveland, Ohio; <sup>d</sup>Obesity, Metabolism and Nutrition Institute, Massachusetts General Hospital, Boston, Massachusetts; <sup>e</sup>Li Ka Shing Knowledge Institute, St. Michael's Hospital, University of Toronto, Toronto, Ontario, Canada; and the <sup>f</sup>Department of Metabolic and Bariatric Surgery, Diabetes and Nutritional Science Division, King's College Hospital, London, United Kingdom. Dr. Pareek has served on the advisory board of and received speaker's honoraria from AstraZeneca. Dr. Schauer has served on the advisory boards of The Medicines Company, GI Dynamics, Neurotronic, and Pacira; has been a consultant for Ethicon, The Medicines Company, and Novo Nordisk; and has received research support from Ethicon, the National Institutes of Health, Medtronic, and Pacira. Dr. Leiter has received research funding from, has provided continuing medical education on behalf of, and/or has acted as an adviser to Amgen, AstraZeneca, Boehringer Ingelheim, Eisai, Eli Lilly, Esperion, GlaxoSmithKline, Janssen, Merck, Novo Nordisk, Sanofi/Regeneron, Servier, and The Medicines Company. Dr. Rubino has served on the scientific advisory boards of Fractyl and GI Dynamics; has received consulting fees from Ethicon and Medtronic; has received speaker's honoraria from Ethicon and Novo Nordisk; and has received grants from the National Institute for Health Research (UK) and Ethicon. Dr. Bhatt has served on the advisory boards of Cardax, Elsevier Practice Update Cardiology, Medscape Cardiology, and Regado Biosciences; has served on the board of directors of the Boston VA Research Institute and the Society of Cardiovascular Patient Care; has been Chair of the American Heart Association Quality Oversight Committee; has served on the data monitoring committees of Cleveland Clinic, Duke Clinical Research Institute, Harvard Clinical Research Institute, Mayo Clinic, and Population Health Research Institute; has received honoraria from the American College of Cardiology (senior associate editor, *Clinical Trials and News*, ACC.org), Belvoir Publications (Editor-in-Chief, *Harvard Heart Letter*), Duke Clinical Research Institute (clinical trial steering committees), Harvard Clinical Research Institute (clinical trial steering committee), HMP Communications (Editor-in-Chief, *Journal of Invasive Cardiology*), *Journal of the American College of Cardiology* (guest editor; associate editor), Population Health Research Institute (clinical trial steering committee), Slack Publications (chief medical editor, *Cardiology Today's Intervention*), Society of Cardiovascular Patient Care (secretary/treasurer), and WebMD (continuing medical education steering committees), Clinical Cardiology (deputy editor), NCDR-ACTION Registry Steering Committee (chair), and VA CART Research and Publications Committee (chair); has received research funding from Amarin, Amgen, AstraZeneca, Bristol-Myers Squibb, Chiesi, Eisai, Ethicon, Forest Laboratories, Ironwood, Ischemix, Lilly, Medtronic, Pfizer, Roche, Sanofi, and The Medicines Company; has received royalties from Elsevier (editor, *Cardiovascular Intervention: A Companion to Braunwald's Heart Disease*); has been site co-investigator for Biotronik, Boston Scientific, and St. Jude Medical; has been a trustee of the American College of Cardiology; and has conducted unfunded research for FlowCo, Merck, PLx Pharma, and Takeda. Dr. Kaplan has reported that he has no relationships relevant to the contents of this paper to disclose.

Manuscript received September 15, 2017; revised manuscript received December 13, 2017, accepted December 15, 2017.



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The worldwide prevalence of obesity, characterized by a body mass index (BMI)  $\geq 30$  kg/m<sup>2</sup>, 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/m<sup>2</sup>), whereas 1% have morbid obesity (BMI  $\geq 40$  kg/m<sup>2</sup>). 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 ~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 ~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  $\geq 175$  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

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, naltrexone-bupropion, 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  $\geq 27$  kg/m<sup>2</sup> 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

## ABBREVIATIONS AND ACRONYMS

|                         |  |
|-------------------------|--|
| <b>AGB</b>              | = adjustable gastric banding                     |
| <b>BMI</b>              | = body mass index                                |
| <b>BPD</b>              | = biliopancreatic diversion                      |
| <b>BPDDS</b>            | = biliopancreatic diversion with duodenal switch |
| <b>CI</b>               | = confidence interval                            |
| <b>HbA<sub>1c</sub></b> | = glycated hemoglobin                            |
| <b>HR</b>               | = hazard ratio                                   |
| <b>OR</b>               | = odds ratio                                     |
| <b>RYGB</b>             | = Roux-en-Y gastric bypass                       |
| <b>SG</b>               | = sleeve gastrectomy                             |
| <b>T1DM</b>             | = type 1 diabetes mellitus                       |
| <b>T2DM</b>             | = type 2 diabetes mellitus                       |

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