Published in final edited form as:
Curr Atheroscler Rep. 2014 October ; 16(10): 445. doi:10.1007/s11883-014-0445-x.

Managing Overweight and Obesity in Adults to Reduce Cardiovascular Disease Risk

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Abstract

Obesity is a leading preventable cause of death and disability worldwide. Obesity increases the risk for clinically identifiable risk factors for cardiovascular disease (CVD) as well as a host of other metabolic, sleep, and orthopedic disorders. Coordinated and systematic interventions are needed to manage obesity and reduce these risks. The Obesity 2 Expert Panel updated previous guidelines and produced the “Guideline for the Management of Overweight and Obesity in Adults.” The Panel used data from publications from years 1999 to 2011 to address five critical questions, provide evidence statements, and recommend creation of a treatment algorithm to guide decision making about clinical care. The current review discusses the evidence statements pertaining to CVD risk in the assessment and management of patients who are overweight and obese. We summarize the FDA-approved medications for the treatment of overweight and obesity and their impact on CVD risk and risk factors, as well as ongoing clinical trials which will further inform clinical practice.

Keywords

anti-obesity agents; bariatric surgery; cardiovascular diseases; obesity; overweight; practice guidelines

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Compliance with Ethics Guidelines

Conflict of Interest

Jon O. Ebbert reports consulting fees from GlaxoSmithKline and grants from Pfizer and Orexigen, outside the submitted work. MDJ reports consulting fees from Takeda, Eiasi, Novo Nordisk, and Vivus, outside the submitted work. MYE reports no conflicts.
Muhamad Y. Elrashidi declares no conflict of interest.
Michael D. Jensen reports personal fees from Takeda, Eiasi, Novo Nordisk, and Vivus,

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Introduction

Worldwide, 35% of adults over the age of 20 years are overweight (body mass index [BMI] 25–29.9) and 11% are obese (BMI ≥ 30) [1]. The prevalence of overweight and obesity increased dramatically in the United States between 1990 and 2010 and continues to increase in developing nations [2]. Two-thirds of the world's population live in nations where mortality is more likely to be associated with overweight or obesity than due to being underweight [1]. The increasing prevalence of obesity threatens to reverse life expectancy gains achieved by developed nations [3]. Overweight and obesity accounts for 5% of global deaths [4] killing 2.8 million people each year [5]. Health care providers are often asked to provide advice to patients regarding the best approaches to reduce weight and improve health. By using stringent methodology to evaluate the literature, the Obesity 2 Expert Panel developed sound guidelines for providers to implement evidence-based management of patients who are overweight or obese.

To update the evidence base for the identification, evaluation, and treatment of overweight and obese adults, the Obesity Guidelines 2 Expert Panel was convened by the National Heart, Lung, and Blood Institute (NHLBI) in 2008 [6]. The Obesity Guidelines 2 Expert Panel was charged with updating the previous guidelines published in 1998 [7]. NHLBI collaborated with the American Heart Association, the American College of Cardiology, and The Obesity Society to disseminate the report. Guideline development followed stringent methodology [8] and included the literature from the years 1999 (following the publication of the first report) to 2011. The Panel employed a critical question (CQ) model to drive the information discovery process. They originally suggested over 20 CQs and finally selected 5 to address in depth. The 5 were chosen based upon their relevance for primary care practitioners in evaluating and treating overweight and obese patients and the likelihood that sufficient high-quality evidence would be available to address the issue. The NHLBI used the Institute of Medicine reports "Clinical Guidelines We Can Trust" and "Finding What Works in Health Care – Standards for Systematic Reviews" to develop rigorous methods to complete the work. After identifying the CQs and the criteria for evaluating the literature, two methodology groups worked with the Panel. The goal was to identify and quality rate the literature and develop evidence tables that could be graded and used to create evidence statements. Evidence statements, in turn, served as the basis for the recommendations, which were first assessed using the NHLBI grading system and subsequently rated using the approach employed by the American Heart Association and the American College of Cardiology. Both approaches are summarized in the publication [9]. The Panel also constructed a "Chronic Disease Management Model for Primary Care of Patients with Overweight and Obesity" treatment algorithm to guide decision making about clinical care.

We will review the Panel's CQs pertaining to cardiovascular disease (CVD) and the evidence statements highlighting relationships between BMI and risk factors for CVD as supported by a high or moderate strength of evidence data. We will next discuss recommendations for management of overweight and obese adults and the impact of reductions in BMI on CVD risk factors as supported by a moderate or high strength of evidence. Published data on medications approved by the US Food and Drug Administration

(FDA) for the treatment of overweight and obesity are reviewed as well as ongoing trials, which will inform the evidence base in this critical clinical area.

Weight Loss and CVD Risk

The Expert Panel asked: *"Among overweight and obese adults, does achievement of reduction in body weight with lifestyle and pharmacological interventions affect CVD risk factors, CVD events, morbidity, and mortality?"* Twenty-eight meta-analysis and systematic review articles informed the evidence base for this CQ [9].

Diabetes

A high strength of evidence suggests that weight loss of 2.5 to 5.5 kg sustained beyond 2 years using a lifestyle intervention (LSI) reduces the risk of developing diabetes by 30% to 60%. Risk reduction occurs irrespective of the use of orlistat, an inhibitor of pancreatic lipase that results in moderate fat maldigestion.

Weight loss improves blood glucose control among overweight and obese adults with type 2 diabetes mellitus (T2DM) and is supported by a high strength of evidence. A 2% to 5% loss of body weight with LSI over 1 to 4 years reduces hemoglobin A1c (HbA1c) by 0.2% to 0.3%, and greater weight loss is associated with even further reductions. Losses of 5% to 10% at 1 year are associated with HbA1c reductions of 0.6% to 1.0% and reduced the need for diabetes medications. Weight losses of 2% to 5% are more likely to be associated with clinical meaningful reductions in fasting glucose levels (≥ 20 mg/dL) than maintenance of a stable weight, defined as experiencing ≤ 2% weight gain or < 2% weight loss.

Compared to placebo, orlistat is effective for furthering reductions in fasting blood glucose levels among overweight and obese adults with T2DM. In combination with LSI, orlistat is associated with 2 to 3 kg greater weight loss at both 1 and 2 years, respectively. Orlistat is also associated with greater reductions in fasting glucose (averaging 11 and 4 mg/dL at 1 and 2 years, respectively) and an average reduction in HbA1c of 0.4% at 1 year.

A moderate strength of evidence suggests that over 4 years, weight regain may occur in the setting of LSI. However, reductions in HbA1c remain clinically meaningful and below preintervention levels.

Lipids

Among overweight and obese adults, a high level of evidence supports a direct association between weight loss with LSI and improvement in lipid profile measures. On average, a 3 kg weight loss is associated with triglyceride (TG) reductions of 15 mg/dL. Weight loss of 5 to 8 kg lowers low-density lipoprotein cholesterol (LDL-C) by 5 mg/dL and increases high-density lipoprotein cholesterol (HDL-C) by 2 to 3 mg/dL. Orlistat combined with LSI is associated with a 3 kg greater weight loss and reductions of 8 to 12 mg/dL in LDL-C, 1 mg/dL in HDL-C, and variable TG changes.

The Panel found a moderate strength of evidence to support the statement that, among overweight and obese patients with T2DM, an 8% weight loss at 1 year and 5% weight loss

over 4 years increases HDL-C by 2 mg/dL and reduces TGs. Attaining a 5% weight loss over 4 years with LSI is associated with fewer newly prescribed lipid-lowering medications.

Hypertension

There was a high strength of evidence that among overweight and obese adults with increased risk for CVD, a direct relationship exists between the amount of weight loss achieved at 3 years through LSI and reductions in blood pressure (BP). Weighted mean reductions in systolic (3 mm Hg) and diastolic (2 mm Hg) BP is achieved with a 5% weight loss. There was a moderate strength of evidence to suggest that overweight and obese adults with T2DM who attain a 5% weight loss over 4 years are prescribed fewer antihypertensives compared to controls without similar weight loss.

Knowledge Gaps

The Expert Panel could not identify systematic reviews or meta-analyses addressing whether age, sex, race, or baseline BMI and waist circumference modified the potential benefits of weight loss on CVD risk factors. Data were not identified by the Panel to inform whether baseline comorbidities and CVD risk factors modified the beneficial effects of weight loss.

More data is needed to demonstrate the relationship between weight loss and mortality. A low strength of evidence supports the observation that overweight and obese adults with T2DM who lost 9 to 13 kg had a 25% decrease in mortality compared to stable weight individuals. This data was obtained from observational (cohort) studies. The advantage of these studies is that they provide information about real-world care of weight stable adults. The disadvantage is the inability to assure that those who lose weight and those who do not are similar, which is a clear strength of prospective, randomized clinical trials. For ethical reasons, participants in prospective, randomized clinical trials of weight loss interventions must be provided with aggressive pharmacotherapy for comorbidities. The effectiveness of these interventions in reducing CVD risk factors is equal to that of intensive LSI, as evidenced by the extremely low event rates in both arms of the Look AHEAD trial [10].

BMI and CVD Risk

The Expert Panel asked: *"Are the current cut-point values for overweight (BMI 25–29.9 kg/m^2) and obesity (BMI ≥ 30 kg/m^2) compared with BMI 18.5 to 24.9 kg/m^2 associated with elevated CVD-related risk? Are the waist circumference cut-points of > 102 cm (male) and > 88 cm (female) associated with elevated CVD-related risk? How do these cut-points compare with other cut-points in terms of elevated CVD risk?"* Fifteen meta-analysis and systematic review publications informed the evidence base for this CQ [9].

When analyzed as a continuous variable, a higher BMI confers an increased risk for several adverse health outcomes. Across the entire range, it is associated with a higher risk for T2DM, fatal coronary heart disease (CHD) and combined fatal and nonfatal CHD. A higher BMI is also associated with a higher risk for combined fatal and nonfatal stroke. In addition, it is associated with a higher risk for ischemic, hemorrhagic, and fatal stroke. Among overweight and obese men and women, analyses of BMI as a continuous variable demonstrate that higher BMIs are associated with higher all-cause mortality. Of note, the

Panel found that across the entire range of BMI, mortality was increased both at lower and higher BMIs – the so-called "j-shaped curve." In contrast, morbidity and mortality increased as a continuous function of waist circumference with no evidence of a j-shaped relationship.

The risk conferred by currently utilized cut-points for overweight and obesity compared to normal weight vary by clinical endpoint and gender. Overweight and obesity are associated with an increased risk for fatal CHD and combined fatal and nonfatal CHD compared with normal weight in both sexes. However, unlike CHD, only the obesity cut-point is associated with an elevated risk of fatal CVD in both men and women compared to normal weight. The current obesity cut-point is associated with an elevated risk for all-cause mortality compared with normal weight.

We do not believe that BMI and waist circumference measures are well-suited to be diagnostic criteria. However, they are simple, inexpensive anthropometric measures that, if routinely measured in clinical practice, can alert clinicians to the potential need to screen for obesity-related comorbidities.

Knowledge Gaps

The Expert Panel identified that additional studies are needed to inform the identification of alternative BMI and waist circumference for predicting CVD risk. In addition, consideration should be given to the incorporation of other measures, such as body fat percentage, in order to enhance risk prediction.

Bariatric Surgery and CVD Risk

The Expert Panel asked: *"What are the long-term effects of [bariatric] surgical procedures on weight loss, weight loss maintenance, cardiovascular risk factors, related comorbidities, and mortality?"* [9] To evaluate for endpoints for weight loss and change in CVD risk factors, the Panel required studies to have a minimum of 2 years postsurgical follow-up. Included studies also were required to have a nonsurgical comparator group in order to increase the strength of inference regarding outcomes. Thirty-five articles (22 studies) met inclusion criteria to inform this CQ with only five articles informing efficacy. The bariatric surgical procedures assessed were: laparoscopic adjustable gastric banding, laparoscopic Roux-en-Y gastric bypass (RYGB), open RYGB, biliopancreatic diversion, and sleeve gastrectomy.

When performed in adults with a BMI ≥ 30, bariatric surgery is associated with a mean weight loss of 20% to 35% of baseline weight at 2 to 3 years. The mean difference in weight loss between bariatric surgery and nonsurgical comparators ranged from 14% to 37% depending on the procedure used. A high strength of evidence supports that bariatric surgery is associated with greater reductions in obesity comorbidities compared to usual care, medical treatment, LSI, and supervised weight loss. Among adults with a BMI ≥ 30 who achieve 20% to 35% mean weight loss at 2 to 3 years, reductions in fasting glucose occur, the incidence of T2DM decreases, and a greater likelihood of T2DM remission is observed. The Panel also documented the likelihood of mortality and major morbidity associated with laparoscopic banding, gastric bypass, and biliopancreatic diversion, as well as the

probability of long-term complications. There was insufficient evidence to establish the incidence of perioperative and longer-term complications from the gastric sleeve procedure.

Knowledge Gaps

Bariatric surgery has the potential to beneficially affect CVD risk factors and morbidity and mortality related to CVD. The Expert Panel identified that more information is needed relating to the types of patients who would benefit most from these procedures.

Pharmacotherapy for Weight Loss

The Expert Panel elected not to formulate a CQ addressing pharmacotherapy because orlistat was the only approved medication at that time of the Panel's review. Orlistat has demonstrated efficacy for modifying CVD risk and is available over the counter. However, side effects of flatulence, oily rectal discharge, increased stool frequency, steatorrhea, and fecal incontinence limit its widespread use [11].

Since completion of the Obesity 2 Guidelines, lorcaserin and topiramate/phentermine were approved by the FDA for weight loss management. These medications potentially provide new opportunities to modify CVD risk and adverse clinical outcomes through nonsurgical weight loss approaches.

Lorcaserin

The FDA approved lorcaserin hydrochloride for clinical use in 2012 as an addition to a reduced-calorie diet and exercise in adults with a BMI ≥ 30 or those with a BMI ≥ 27 and at least one weight-related condition such as hypertension, T2DM, or hyperlipidemia [12]. Lorcaserin is a novel selective serotonin ($5\text{-}HT_{2C}$) receptor agonist that lacks the cardiovascular toxicities of fenfluramine, the previously used nonselective serotonin receptor agonist [13]. $5\text{-}HT_{2C}$ receptors located in the hypothalamus are thought to modify food intake by activating the proopiomelanocortin system inducing hypophagia [14]. Lorcaserin has a 104-fold better selectivity for $5\text{-}HT_{2C}$ compared to the $5\text{-}HT_{2B}$ receptor subtype [15]. Three phase III studies (BLOOM, BLOSSOM, and BLOOM-DM) demonstrated the efficacy of lorcaserin for weight loss in overweight and obese adults.

The BLOOM trial evaluated the efficacy and safety of lorcaserin for weight loss in obese and overweight subjects [16]. BLOOM was a 2-year trial randomizing 3182 obese or overweight adults to lorcaserin 10 mg or placebo twice daily for 52 weeks. Participants were eligible for enrollment if they had a BMI of 30–45 or 27–45 with comorbid hypertension, hyperlipidemia, CVD, impaired glucose tolerance, or sleep apnea. At 52 weeks, participants in the lorcaserin group lost an average of 5.8 kg compared with 2.2 kg in the placebo group ($P<0.001$). Lorcaserin was also associated with significant improvements in CVD risk factors as well as statistically significant differences compared to placebo in systolic and diastolic BP, total cholesterol, LDL, TGs, fasting glucose, and HbA1c. Importantly, lorcaserin was not associated with an increased incidence of FDA-defined valvulopathy.

The BLOSSOM trial randomized participants by BMI similar to BLOOM (30–45 and 27–29.9 with an obesity-related comorbid condition). Mean weight loss with lorcaserin 10 mg

twice per day was 5.8%, 4.7% with lorcaserin once per day, and 2.8% with placebo (P<0.001 vs. lorcaserin twice a day) [17]. Compared to placebo, lorcaserin was associated with significant reductions of total cholesterol and TGs and increases in HDL-C. Lorcaserin effects on other lipid parameters were not dose dependent.

The BLOOM-DM study evaluated efficacy and safety of lorcaserin for weight loss in overweight and obese subjects with T2DM [18]. BLOOM-DM enrolled 604 participants with T2DM on metformin or sulfonylurea therapy with a HbA1c of 7% to 10% and a BMI of 27 to 45. Participants were randomized to lorcaserin 10 mg twice daily, lorcaserin 10 mg once daily, or placebo for 52 weeks. Lorcaserin twice daily was associated with a mean weight change of −4.5%, −5.0% with lorcaserin once daily, and −1.5% with placebo (P<0.001 for each). Reductions in HbA1c were 0.9% (lorcaserin twice daily), 1.0% (lorcaserin once daily), and 0.4% (placebo) and were statistically significant (P<0.001) for each; fasting glucose decreased 27.4 mg/dL, 28.4 mg/dL, and 11.9 mg/dL, respectively (P<0.001 for each). No evidence of valvular disease attributable to lorcaserin was evident.

Topiramate/Phentermine

Phentermine/topiramate controlled release (PHEN/TPM CR) was FDA approved in 2012 for use in addition to a reduced-calorie diet and exercise for chronic weight management in obese (BMI ≥ 30) or overweight (BMI > 27) adults with one obesity-related associated comorbidity [19]. Phentermine is a sympathomimetic drug with activity similar to amphetamine. It induces weight loss through appetite reduction caused by norepinephrine release in neurons that regulate hypothalamic appetite signals [20]. Topiramate (TPM) is FDA approved for seizure disorders and the prevention of migraine headaches. It has an effect on energy balance by reducing appetite [21–23]. Both drugs have been shown to be effective for weight loss [24]. The CONQUER, EQUIP, and SEQUEL trials have evaluated the evidence for the use of PHEN/TPM CR for the treatment of overweight and obesity.

The CONQUER trial randomized 2487 overweight or obese adults with a BMI of 27 to 45 with ≥ 2 comorbidities (i.e., HTN, hyperlipidemia, DM, prediabetes, or abdominal obesity) to placebo, PHEN/TPM CR 7.5/46 mg once daily, or PHEN/TPM CR 15/92 mg once daily for 56 weeks [25]. Change in body weight at 56 weeks was –1.4 kg, –8.1 kg (P<0.0001), and –10.2 kg (P<0.0001) in participants assigned to placebo, PHEN/TPM CR 7.5/46 mg, and PHEN/TPM CR 15/92 mg, respectively. Improvements in CVD risk factors were greater with the higher dose of PHEN/TPM CR and were significant for PHEN/TPM CR 15/92 mg compared to placebo for systolic BP, diastolic BP, total cholesterol, LDL, HDL, TGs, fasting glucose, and HbA1c.

The EQUIP trial randomized 1267 participants with a BMI ≥ 35 to placebo, PHEN/TPM CR 3.75/23 mg, and PHEN/TPM CR 15/92 mg for 56 weeks [26]. The PHEN/TPM CR 15/92 mg group lost a mean percentage of 10.9% of baseline body weight (P<0.0001 vs. placebo and 3.75/23 mg), PHEN/TPM CR 3.75/23 mg group lost 5.1% (P<0.0001 vs. placebo), and placebo lost 1.6%. The PHEN/TPM CR 15/92 mg group had statistically significant mean reductions compared to placebo in systolic BP, diastolic BP, fasting glucose, total cholesterol, LDL, HDL, and TGs. Mean percent reductions of the PHEN/TPM CR 15/92 mg

group compared to PHEN/TPM CR 3.75/23 mg were statistically significant for diastolic BP, TGs, and HDL-C.

The SEQUEL trial was a CONQUER 52-week extension study [27]. At week 108, PHEN/TPM CR was associated with significant weight loss compared to placebo with a mean change from baseline of –1.8%, –9.3%, and –10.5% for placebo, 7.5/46 mg, and 15/92 mg, respectively. PHEN/TPM CR 15/92 mg was associated with statistically significant mean changes compared to placebo in fasting glucose and HbA1c. Treatment with PHEN/TPM CR 15/92 mg and 7.5/46 mg led to greater reductions in TGs and greater increases in HDL than placebo.

Ongoing Investigations

Since completion of the Obesity 2 Guidelines, data has emerged exploring the role of bariatric surgery in controlling and alleviating T2DM. The Diabetes Surgery Study compared RYGB surgery with a lifestyle/medical management program in patients with HbA1c level ≥ 8.0% and a BMI between 30.0 and 39.9 [28]. The STAMPEDE trial compared gastric bypass and sleeve gastrectomy to intensive medical therapy alone in adults with uncontrolled T2DM and class I and II obesity [29]. Findings from both these studies suggest that bariatric surgery is more effective than intensive medical therapy at controlling or alleviating T2DM. However, a significant proportion of patients undergoing bariatric surgery will not have long-term remissions and the risk benefit balances have not been rigorously assessed.

The STAMPEDE investigators subsequently reported on outcomes 3 years after randomization [10]. The proportion of patients with glycemic relapse (defined as attaining a HbA1c < 6.0% at 1 year but not maintained at 3 years) was 80% in the medical therapy group, 50% in the sleeve gastrectomy group (P=0.34), and 24% in the gastric bypass group (P=0.03). For patients undergoing bariatric surgery, attainment of the primary endpoint was predicted by a reduction in BMI (OR 1.33; 95% CI 1.15–1.56) and presence of diabetes < 8 years (OR 3.3; 95% CI 1.2–9.1). Patients receiving medical therapy alone maintained a 4 kg weight loss at 3 years. In contrast, gastric bypass patients maintained greater mean weight loss (−26.2 kg; P<0.001 vs. medical therapy) as did those who received sleeve gastrectomy (−21.3 kg; P<0.001 vs. medical therapy). Patients in the gastric bypass group required significantly fewer T2DM medications compared to those in the sleeve gastrectomy group. A greater improvement in 5 of 8 physical and mental health measures of quality of life were reported among gastric bypass patients compared to medical therapy group. No subsequent adverse events were reported in either group after the initial 1-year follow-up results.

Conclusions

The Obesity Guidelines 2 Expert Panel identified strong evidence that a direct relationship exists between BMI and CVD risk and that weight loss is associated with beneficial changes in risk factors for CVD. To effectively capitalize on this updated evidence summary, health care providers now need to frame the approach for incorporating this knowledge into existing systems designed to enhance the identification and treatment of chronic disease.

The Panel's chronic disease management model provides a powerful framework and foundation for this evolution of care delivery.

Successful implementation of this model will require clinical champions and an alignment of health care resources. Strategies for reducing real and perceived barriers to the patient engagement with clinicians in addressing overweight and obesity need to be deployed. Developing resources for clinicians and self-help guides for patients to facilitate health behavior will be critical for moving patients through the algorithm. Creating access to coaching and instruction on comprehensive lifestyle interventions will be required to help patients achieve and maintain weight loss goals. Clinicians will also need training on the indications for and safe use of newly available pharmacotherapies. Tools facilitating shared decision making around complex components of the Panel's model, such as bariatric surgery, need to be developed to guide clinical encounters and fully engage patients. The use of information technology to support patient efforts and goal tracking outside the clinical encounter will be successful if clinicians can become familiar with existing technologies.

Conceptualizing obesity as a chronic disease can evolve both clinical practice and reimbursement models to encourage routine assessment and management of weight concerns, as has occurred for tobacco dependence. Successful incorporation and widespread utilization of the Panel's chronic disease management model offers our greatest hope for reducing the morbidity and mortality associated with overweight and obesity.

Acknowledgments

This work was supported by National Institutes of Health grants DK40484 and DK45343.

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