

The Science of Obesity Management: An Endocrine Society Scientific Statement

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ABSTRACT The prevalence of obesity, measured by body mass index, has risen to unacceptable levels in both men and women in the United States and worldwide with resultant hazardous health implications. Genetic, environmental, and behavioral factors influence the development of obesity, and both the general public and health professionals stigmatize those who suffer from the disease. Obesity is associated with and contributes to a shortened life span, type 2 diabetes mellitus, cardiovascular disease, some cancers, kidney disease, obstructive sleep apnea, gout, osteoarthritis, and hepatobiliary disease, among others. Weight loss reduces all of these diseases in a dose-related manner—the more weight lost, the better the outcome. The phenotype of “medically healthy obesity” appears to be a transient state that progresses over time to an unhealthy phenotype, especially in children and adolescents. Weight loss is best achieved by reducing energy intake and increasing energy expenditure. Programs that are effective for weight loss include peer-reviewed and approved lifestyle modification programs, diets, commercial weight-loss programs, exercise programs, medications, and surgery. Over-the-counter herbal preparations that some patients use to treat obesity have limited, if any, data documenting their efficacy or safety, and there are few regulatory requirements. Weight regain is expected in all patients, especially when treatment is discontinued. When making treatment decisions, clinicians should consider body fat distribution and individual health risks in addition to body mass index. (*Endocrine Reviews* 39: 1 – 54, 2018)

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Introduction

What's past is prologue

Some would say that the obesity epidemic began in the 1980s, but history provides a broader view (1–3). Evidence of obesity in humans can be found in primitive art that dates back to the Paleolithic age (4). Two thousand five hundred years ago, Hippocrates cautioned that sudden death is more common in those who are naturally fat than lean (5).

In 1760, the English physician Malcolm Flemyng wrote that obesity can be called a disease, because it obstructs the free exercise of the animal functions and can shorten life (6). In 1810, William Wadd (Secretary of the Royal College of Surgeons in London) stated that the increase of wealth and the refinement of modern times may have banished plague and pestilence, but it has introduced nervous disorders and increased the frequency of corpulence (7).

Modern concepts of the pathophysiology of obesity date back to the end of the 18th century when Antoine Lavoisier established that life was synonymous with oxidation (8). More than 100 years later, Atwater and Rosa (9) applied the laws of thermodynamics to human beings, and during the 20th century, researchers discovered that hypothalamic tumors and tumors of the pituitary gland could cause obesity (10–12).

Obesity treatments date as far back as Hippocrates, who recommended lifestyle changes to obese patients (13, 14). Two thousand years later, William Banting (an undertaker living in London in the 19th century) wrote one of the first “popular” diet books (15).

“Drug” therapies can be traced back at least to the 10th century when Hisdai ibn Shaprut cured “Sancho

the Fat” of obesity using theriac—a mixture of more than 64 ingredients (16).

The first English language texts dealing with obesity treatment were published in 1727 and 1760 and recommended chamomile soap and vinegar, as well as other remedies (6, 17, 18).

By the beginning of the 20th century, doctors were using a number of medications for treating obesity (e.g., thyroid extract, dinitrophenol, and amphetamine), often with unfortunate outcomes (19).

The discovery of leptin in 1994 (20) (a peptide produced in adipose tissue) marks the beginning of the “molecular era” for obesity. People who are deficient in this peptide become massively obese. Leptin replacement therapy completely reverses obesity for these individuals. However, leptin treatment has proven ineffective in the typical obese patient who is not leptin deficient.

Rapid advances in basic science related to maintaining an appropriate amount of body fat have provided insights into potential treatments for obesity. This newer understanding of the regulation of food intake and body weight provides the basis for promising future developments (21, 22).

Headwinds in the management of obesity

Despite progress in understanding obesity, advancements in the clinical management of the disease struggle against several headwinds.

First, obesity is a stigmatized condition. The general public and health professionals often respond negatively to overweight persons, which can negatively affect treatment (23).

Second, the desire for the cosmetic effects of weight loss often far exceeds the desire for the health benefits associated with reducing weight (24–26). This may

well account for the fact that there are more women seeking help in managing obesity than men, even though the health issues related to obesity are similar between the sexes (27–29).

Although a modest 5% to 10% weight loss has proven health benefits, it often does not provide the cosmetic benefit that patients are looking for. This results in a mismatch between the patient's goals for weight loss and what diet and exercise can realistically achieve (30). The same is true with surgical approaches to weight loss; patients often value the appearance of lost weight much more than the health benefits (25, 29, 31–33).

Defining Obesity

Introduction

Historically, the medical community defined excess weight and its associated health consequences using population-based anthropometric measurements, (*i.e.*, sex-specific body weight and height using life insurance tables) (36, 37). However, these data only represented insured individuals based on normative standards without considering adiposity, and clinicians eventually abandoned these tables in favor of body mass index (BMI), which is a measure of body weight adjusted for height [weight (kg)/height (m²)].

The National Institutes of Health and the World Health Organization have both adopted BMI as a criterion for defining obesity (36, 38). This made interpretation simpler, eliminated the need for sex-specific height/weight tables, and provided a measurement that is better correlated with other estimates of adiposity. The measurement is based on the observation that body weight is proportional to the squared height in adults with normal body frames. In adults, classification systems (38) and obesity guidelines (39, 40) define healthy body weight as a BMI between 18.5 and 24.9 kg/m², overweight between 25.0 and 29.9 kg/m², and obesity ≥ 30 kg/m². In children and adolescents, the U.S. Centers for Disease Control and Prevention (CDC) BMI-for-age growth charts define overweight as a BMI at or above the 90th percentile of standard weight and obesity as a BMI above the 95th percentile of standard weight.

BMI provides the most useful population-level measurement of overweight and obesity, and numerous large population studies across multiple continents have demonstrated its utility as an estimate of risk (41–43). Additionally, current assessment and management guidelines from the United States, Canada, and Europe recommend measuring BMI as a first screening step in evaluating adult and pediatric patients for obesity (39, 44–46).

This stigma of obesity as a cosmetic issue vs a health issue also affects how the U.S. Food and Drug Administration (FDA) reviews drugs that manage weight loss. The FDA holds antiobesity drugs to a higher standard of review than other drugs, requiring that the risks from these medications be very low compared with drugs of other classes (34).

Finally, the lack of reimbursement by health insurers has resulted in poor sales of drug therapies for obesity, which only further dampens the pharmaceutical industry's interest in developing drug therapies for obesity (35).

Overweight and obesity are worldwide problems (1) that affect >100 million Americans or 68.5% of the adult population. The most recent data from the 2013 to 2014 U.S. National Health and Nutrition Examination Survey indicate that obesity (defined as BMI ≥ 30 kg/m²) affects ~35.0% of men and 40.4% of women in the United States (47). Among children and adolescents aged 2 to 19 years, the prevalence of obesity in 2011 to 2014 was 17.0% (47). Fig. 1 shows the percentage of U.S. men and women categorized as overweight, obese, or extremely obese between 1960 and 2012. The category of extreme obesity (BMI > 40 kg/m²) shows the greatest proportional change and is the most difficult group to effectively treat without surgery.

Among adult men, the prevalence of obesity is: Hispanic, 37.9%; black, 38.0%; white, 34.7%; and Asian, 12.6%. In women, the prevalence of obesity is: black, 57.2%; Hispanic, 46.9%; white, 38.2%; and Asian, 12.4%. In children and adolescents, 17.0% of 2- to 19-year-olds are obese, with males and females equally affected (47). The prevalence of obesity among children and adolescents is: Hispanic, 21.9%; black, 19.5%; white, 14.7%; and Asian, 8.6% (47).

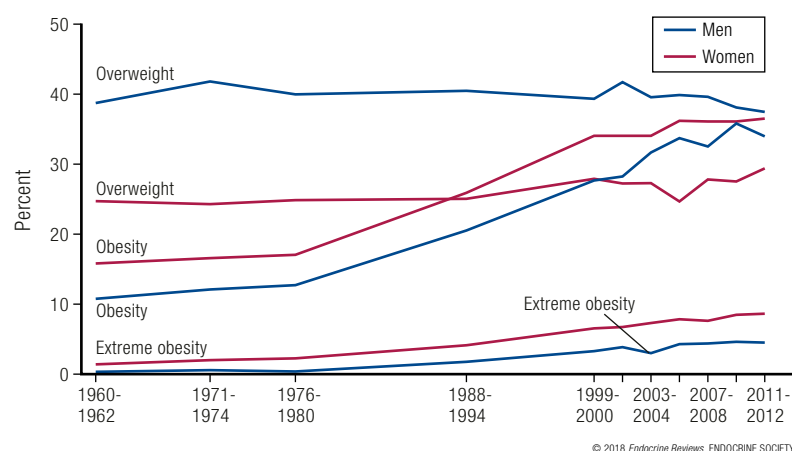


Figure 1. Trends in the United States for adults with obesity or overweight, 1960–1962 to 2011–2012 (48).

Limitations of the BMI

Adults

Although research had demonstrated the utility of BMI in assessing population-based mortality and disease-specific morbidity, there are two major limitations in using BMI alone to diagnose obesity in an individual.

The first is the inability of BMI to distinguish weight associated with muscle vs fat.

Population studies have demonstrated a high specificity of using BMI cutoff values to diagnose obesity but low sensitivity to identify adiposity, thus missing approximately half of people with excess fat (49). This is particularly concerning in the elderly population, where a reduced lean body mass (sarcopenia) might be misclassified as a healthy BMI (50). Dual-energy x-ray absorptiometry or air displacement plethysmography are both accurate methods to assess lean body mass and body fat, but they are expensive and thus impractical for routine clinical application.

Using bioelectric impedance to measure body water provides a relatively inexpensive measure of body fat mass vs fat-free mass (as body fat contains more water). However, this method has large interindividual variations, suggesting that this method may be insufficient for estimating individual body fat mass and fat-free mass (51).

BMI also does not distinguish body fat distribution, a known determinant of metabolic risk. Measuring fat distribution helps identify higher risk individuals, because increased visceral fat predicts the development of the metabolic syndrome, type 2 diabetes mellitus (T2DM), and total and cardiovascular mortality risk better than total body fat alone (52–55). Several anthropometric techniques are available to estimate the distribution of body fat, such as waist circumference alone, the ratio of waist circumference divided by hip circumference (waist-to-hip ratio ([WHR]), and the ratio of waist circumference divided by height (waist-to-height ratio). These measures have been associated with the risk of developing heart disease, T2DM, and other chronic problems associated with obesity (56, 57). Combining waist circumference with BMI provides a way to incorporate weight distribution into measures of obesity. Studies have demonstrated a strong link between waist circumference and BMI for both cardiovascular disease (CVD) and T2DM (58, 59). Waist circumference is most useful in individuals with a BMI of ≤ 35 kg/m² (39). However, despite its promise, most clinicians only use BMI and not waist circumference as a gauge of risk from obesity. Beyond recommending annual BMI and waist circumference testing, the American Association of Clinical Endocrinologists also recommends evaluating other potential associated events (60).

Genetic factors are involved in the relationship of waist circumference to risk of CVD or T2DM. A polygenic risk score for increased WHR adjusted for

BMI was significantly associated with adverse cardiometabolic traits and higher risks for both T2DM and coronary heart disease (61). A 1 standard deviation increase in WHR adjusted for BMI was associated with a 77% higher risk of T2DM (odds ratio, 1.77 [95% confidence interval (CI), 1.57 to 2.00]) and a 46% higher risk of coronary heart disease [odds ratio, 1.46 (95% CI, 1.32 to 1.62)].

Children

There has also been concern about the association between obesity and visceral or central adiposity among children and adolescents, which has led to suggestions for using waist circumference in pediatric patients as well (62). However, there are many issues with the implementation of this in routine pediatric practice, such as lack of standardized definitions of waist circumference and the inability of waist circumference to add much to the strong association between BMI and comorbidity in children (63). If clinicians are going to use waist circumference to help define obesity in children, it is likely that we will need population-based percentile values, similar to those for BMI (64–66).

Because of these limitations, BMI has also emerged as the most useful approach in children >2 years of age (46).

Are there metabolically healthy people with obesity?

Adults

In cross-sectional studies, many individuals with obesity do not manifest “associated” comorbidities, such as prediabetes, dyslipidemia, hypertension, or other comorbidities (67). These individuals often have a predominantly lower body fat distribution and normal insulin regulation of adipose tissue lipolysis (68, 69). The phenotype “metabolically healthy obesity” (MHO) meets the standard BMI cutoff point for obesity (≥ 30 kg/m²) but does not have other elements of the metabolic syndrome, such as insulin resistance (70, 71). They have lower levels of visceral and ectopic fat, less liver steatosis (71), and a lower degree of systemic inflammation. Among the 27 studies identified by Rey-López *et al.* (72), there were 30 definitions of metabolic health that relied on four criteria: blood pressure (BP), high-density lipoprotein (HDL) cholesterol, triglycerides, and plasma glucose. BMI ≥ 30 kg/m² was the main criterion for obesity. In this group of studies, the prevalence of MHO ranged between 6% and 75% (67, 72–74).

Whereas short-term cross-sectional studies suggest that MHO men and women are not at increased risk of CVD, longitudinal studies suggest that this phenotype may not be benign, and that this group is at higher risk for increased carotid artery intima-media thickness, coronary calcification, impaired vasoreactivity, and/or other cardiovascular events, as well as all-cause

mortality (70, 75–79). Therefore, clinicians should view MHO as a transient or intermediary state that may progress over time to an unhealthy phenotype in many people. Cardiorespiratory fitness is one factor related to MHO. Research has shown that cardiorespiratory fitness lowers the risk of all-cause mortality for metabolically unhealthy individuals with obesity and those with and without the MHO phenotype (80–82), suggesting that the inclusion of cardiorespiratory fitness along with BMI and waist circumference may improve the assessment of risk status. Several systems are available for evaluating and staging obesity when assessing risk (80–84). Increasing physical activity might thus be a valuable recommendation for individuals with MHO. Additionally, clinicians should observe these individuals for the risk of developing cardiometabolic disease (80–86).

Children

There also has been interest in whether children and adolescents can be obese but metabolically healthy. Some pediatric patients with obesity, even some with severe obesity, have few metabolic or clinical abnormalities (83). However, the presence of obesity tends to track from childhood to adolescence and on to adulthood. Thus, there is a high likelihood that a child with obesity will become an obese adult, often with the severity of obesity increasing over time with ongoing weight gain. This makes it likely that children and adolescents with obesity, even when metabolically healthy at presentation, will develop associated diseases over time.

Age and obesity

Adults

The current guidelines for assessing obesity among adults do not consider age as an independent criterion. However, there are physiological and functional changes that occur among the aging population that may confound the interpretation of BMI and risk estimates in older people. Body composition changes associated with aging include sarcopenia, reduced bone mineral density, and the accumulation of visceral fat; BMI alone will not detect these changes (84). BMI values associated with the lowest relative mortality are slightly higher in older than in younger adults, which is often misinterpreted to suggest that obesity is not as harmful in the elderly. BMI may be a less appropriate index in the elderly because of sarcopenia (87). Centrally located fat (waist circumference) and relative loss of fat-free mass may become more important than BMI in determining the health risk associated with obesity in the elderly (88). The importance of loss of muscle mass was clearly shown in the Health ABC Study where older adults with greater thigh muscle loss had a higher risk of mortality compared with those with preserved thigh

muscle, which suggests that efforts should be made to “conserve” muscle mass in old age (89).

Children

During childhood and adolescence, there are substantial changes in growth, body composition, and pubertal status. During periods of rapid growth, weight and height may be somewhat mismatched, with weight gain preceding growth in height. However, in the past three decades, children are often gaining weight at a pace much faster than what could be considered healthy or normal.

Another critical period is the time when growth in height ceases and caloric requirements decrease. If calorie intake does not adjust, weight gain is the likely result.

Furthermore, adolescence is a time of relative insulin resistance (90). Because of this insulin resistance, adolescents who are obese become more susceptible to the development of T2DM.

Prevention of Obesity

Recent trends suggest that we are making some progress in the prevention and control of the obesity epidemic using several strategies outlined below. First, the prevalence of obesity among 2- to 5-year-old children has decreased significantly since 2003 to 2004 (91). Second, it has plateaued among 6- to 11-year-olds (47). In contrast, however, obesity has continued to increase in adult women (47).

Strategies for preventing obesity in pregnancy

Three systematic reviews relating weight gain during pregnancy and pregnancy outcomes found that dietary interventions reduced gestational weight gain and the risks of preeclampsia, hypertension, and shoulder dystocia in infants. No differences occurred in the incidence of small-for-gestational-age infants as a result of these treatments (92–94).

A 2015 Cochrane review found that diet, exercise, or both reduced excessive gestational weight gain by an average of 20%. Dietary interventions—including low glycemic index diets, supervised or unsupervised exercise programs, and diet combined with exercise—all had comparable effects. Maternal hypertension was reduced, but preeclampsia was not. No differences were found between intervention and control groups in the risk of preterm births or macrosomia. However, a 15% reduction in macrosomia occurred among women who were overweight or had obesity. Newborn respiratory distress syndrome was also decreased in the intervention groups among mothers who were either overweight or obese (95). Maternal consumption of sugar-sweetened beverages, similar to maternal smoking, may also have long-term detrimental effects on their offspring. Gillman *et al.* (96) reported that at an

average age of 7.7 years children of mothers who consumed two or more servings per day during the second trimester of pregnancy were both fatter and heavier. This provides an additional important piece of information to provide to the pregnant woman.

Strategies aimed at children

The two most important settings for the prevention of obesity in children and adolescents are early care and education (ECE) and schools. Children spend a lot of time in these settings, where there are great opportunities for instilling positive behaviors regarding nutrition and physical activity.

Early care and education

Although millions of young children are enrolled in ECE, there are only a few intervention studies on preventing or mitigating obesity in these settings (97). One of these studies is the Romp and Chomp Intervention conducted in Australia. This study used multiple ECE and community interventions directed at children 0 to 5 years of age. The interventions included logical and proven targets for weight control, such as reducing sugar-sweetened drinks and energy-dense foods, increasing fruit and vegetable intake and active play, and reducing television time. The study reported significant reductions in obesity prevalence in 2- and 3.5-year-old children compared with children who did not receive the interventions (98).

Because of the immense impact that policy and environmental changes in ECE could have on childhood obesity, widespread efforts are underway to develop and incorporate standards and programs to increase physical activity and improve diets in ECE settings (99). One such program is the U.S. Department of Agriculture's Child and Adult Care Food Program, which helps child care institutions provide nutritious foods that contribute to the wellness, healthy growth, and development of young children (100).

Schools

A recent Cochrane meta-analysis of 37 studies (including 27,946 children) (101) found beneficial effects of a number of components of school-based interventions. These included: school curricula that incorporate healthy eating, physical activity, and body image; increased sessions for physical activity and the development of fundamental movement skills throughout the school week; improvements in the nutritional quality of the food that schools supply; environments and cultural practices that support children eating healthier foods and being active throughout each day; support for teachers and other staff to implement health promotion strategies and activities (e.g., professional development, capacity building activities); and parental support and home activities that encourage children to be more active, eat more nutritious foods, and spend less time in screen-based activities (101). Beneficial effects were most notable in children 6 to 12 years old.

A number of long-term studies lasting ≥ 12 months provide more specific information on the effects of school-based interventions. We summarized these in Table 1 (102–110).

Randomized controlled trials (RCTs) have shown that the reduction or elimination of sugar-sweetened drinks (often through the substitution of calorie-free beverages) has effectively reduced rates of weight gain in children and adolescents (111). These observations are consistent with the association between reductions in sugar-sweetened drinks and both the decrease in the prevalence of obesity in 2- to 5-year-old US children and the plateau in the prevalence of obesity in 2- to 19-year-old US children. The absence of a significant effect in several of these studies may indicate that a significant caloric deficit relative to the control condition was not established or sustained (112).

Compared with efforts in specific settings, clinical interventions aimed at prevention have had limited impact (113).

Strategies aimed at adults: worksites

In 2009, the Center for Disease Control's Task Force on Community Preventive Services concluded that worksite health promotion programs that improved physical activity and/or nutrition were effective in reducing body weight and BMI (114). Studies were limited to those with at least 6 months of follow-up. A pooled effect of nine RCTs found a weight decrease of 1.3 kg, and a pooled effect of six RCTs found a decrease of 0.5 BMI units (115). Most of the studies combined informational and behavioral strategies to influence diet and physical activity; fewer studies modified the work environment (e.g., cafeteria, exercise facilities) to promote healthy choices. Recent efforts to reduce sugar-sweetened drink consumption in hospitals have effectively used labeling and choice architecture as environmental strategies to reduce sugar-sweetened drink consumption (116, 117).

Strategies for preventing obesity aimed at the entire population

Population-based messages aimed at the public concerning food and exercise require individual commitment if they are to be effective (118). If individuals follow the advice in the message, this strategy would be sufficient to overcome the epidemic of obesity. However, positive nutritional messages are often dwarfed by alternative messages urging consumption of less healthful foods, and the built environment is often a barrier to healthful exercise behaviors.

One approach might be to re-engineer the built environment to displace car use with physically active transportation options (such as walking and biking) and increase the number of accessible healthful food options (106). A systematic review by Papas *et al.* (119) identified 20 studies that examined the association

Table 1. Long-Term Studies or Preventive Interventions in Children and Adolescents

Reference	Sample	Design	Results
Epstein <i>et al.</i> , 2001 (102)	26 children	12-mo RCT	1.1% decrease in overweight prevalence with increased fruits and vegetables vs 2.4% with decreased fat and sugar
	6–11 y old	Increased fruits and vegetables vs decreased fat and sugar	Differences not significant
James <i>et al.</i> , 2004 (103)	644 children	1-y intervention; classrooms randomized to reduce sugar drink consumption	No significant difference in BMI z-score
	7–11 y old		
Ebbeling <i>et al.</i> , 2012 (104)	224 overweight or obese adolescents; mean age 15 y	RCT	Significantly lower rates of weight gain in intervention group
		Sugar-free drinks and behavior modification vs untreated control	
de Ruyter <i>et al.</i> , 2012 (105)	641 children	18-mo RCT	Significantly lower rates of weight gain among group receiving sugar-free drinks
	5–12 y old	Sugar-free drinks vs drinks containing sugar at lunch	
Sallis <i>et al.</i> , 2009 (106)	995 4th and 5th grade students	PE taught by PE instructor or teacher vs control	Some fitness measures improved in girls
			No significant differences in changes in skinfolds
Caballero <i>et al.</i> , 2003 (107)	1704 Native American children 8–11 y old	3-y study randomized by schools to control or intervention (41 schools);	No significant difference in body composition or PA
		changes in dietary intake, increased PA, classroom curriculum changes, family involvement	
Gortmaker <i>et al.</i> , 1999 (108)	1295 6th–7th grade students	2-y RCT with five intervention and five control schools	Decreased prevalence of obesity in girls
		Decreased TV, decreased fat and increased fruit and vegetable intakes, and PA	
Plachta-Danielczek <i>et al.</i> , 2011 (109)	240 intervention and 952 nonintervention children	Nutrition intervention delivered within schools and daily running games vs controls	No significant difference in increases in overweight between intervention and control students in 8-y follow-up
	Mean age 6 y old		Significant decreases in BMI z-scores with upper income students
Sahota <i>et al.</i> , 2001 (110)	636 children, 7–11 y old	Randomized by school. Teacher training, changes in school meals, and development of school actions plans to promote healthy eating and PA	No significant differences in BMI in intervention compared with control schools
	314 intervention		
	322 control		

Abbreviations: PA, physical activity; PE, physical education; RCT, randomized controlled trial; TV, television.

between obesity and the numbers of outlets for physical activity and food, 18 of which were cross-sectional. Seventeen of these studies found a significant relationship between the built environment (food outlets or physical activity opportunities) and the risk of obesity. The number of recreational facilities and likelihood of overweight in adolescents were significantly related. However, few studies have examined the impact of changes in the built environment with changes in the prevalence of obesity. One exception is a study of the impact of housing

changes among people living in poverty. Moving from a high-poverty neighborhood to a neighborhood of lower poverty was associated with a reduced prevalence of severe obesity (120).

Use of public transit has also been associated with increased levels of physical activity (121). For example, the implementation of a light rail system in Charlotte, North Carolina, was associated with a higher odds of meeting the daily physical activity requirement and a lower BMI (122). Neighborhood walkability appears to have much the same effect (123).

Food

Faith *et al.* (124) concluded that manipulating the ease of food access and/or restricting access to certain foods might influence food purchases, consumption, and possibly weight change, although this requires further research. In contrast, the food industry favors the hypothesis that obesity results from reduced levels of physical activity and strongly supports providing more places for people to exercise and more healthful food alternatives as a strategy to help overcome the obesity problem (118, 125). However, the expense of healthy food items and limited access to healthful foods in many lower income communities pose significant challenges. To address access to healthful food options, the Healthy Food Financing Initiative introduced supermarkets to underserved communities. However, this did not increase the consumption of healthful foods (126). Ideally, improved access needs to be accompanied by pricing and promotion strategies to increase consumption of more healthful products.

Some of the strategies for introducing healthful food options include introducing farmer's markets, subsidizing the availability of fresh fruits and vegetables to school children, lowering the cost of fruits and vegetables while increasing the price of high-fat or high-sugar foods in school or worksite cafeterias, and/or changing marketing strategies. These strategies, for the most part, increase fruit and vegetable consumption (127–132). Importantly, however, note that addressing fruit and vegetable consumption alone might not be enough, as the impact of fruit and vegetable consumption on obesity prevention is uncertain. However, increased fruit and vegetable consumption does confer significant health benefits. Diets high in fruits and vegetables and low in fat and sugar lowered BP across the range of salt intake in individuals who were maintaining their body weight (127, 133).

Taxation provides another strategy to reduce consumption of less healthful products by increasing their price. Smed *et al.* (134) has shown that among Europeans, increasing the tax or reducing the subsidies on unhealthful items and reducing the tax on healthful items through the value-added tax system could shift consumption toward healthier foods (135). Because of their contribution to obesity, taxation of sugar-sweetened drinks has become a major focus in the United States. Although many municipalities have imposed sales taxes on sugar-sweetened drinks, this approach is less effective than an excise tax, which increases the price of the product on the shelf. In 2014, Berkeley, California, passed a sugar drink tax of \$0.01 per ounce. A study of sugar-sweetened drinks in that city reported that consumption in low-income neighborhoods (compared with two neighboring communities) declined by 21% and water consumption increased by 63% (136). In January of 2014, Mexico imposed an excise tax of 1 peso per liter on

sugar-sweetened beverages. Colchero *et al.* (137) reported that purchases of these taxed beverages decreased 5.5% in 2014 and 9.7% in 2015, yielding an average reduction of 7.6% during the study period. Whether this translates into improvements in health outcome is currently unknown.

Increasing physical activity

As indicated above, physical activity levels in both children and adults have declined substantially. Helping incorporate exercise into how people get from where they live to where they learn, work, shop, play, and pray has become a prominent strategy to reverse this trend. Table 2 lists 10 strategies that the CDC's Guide for Community Preventive Services identified for increasing physical activity (138).

The CDC has also released a convenient guide that focuses on how to implement these strategies (139).

China provides an interesting example of how urbanization and improved incomes reduces physical activity (140, 141). As recently as 20 years ago, the bicycle was a major mode of transport for Chinese. Since then, the automobile has relegated bicycles to museums.

Obesity and Disease

Obesity and risk of death

For many illnesses related to obesity, there is a curvilinear increase in risk as a function of weight (Fig. 2) (142). The Global Burden of Disease project (142) reported this relationship between BMI and all-cause mortality in 239 prospective studies that included >10 million people with a median follow-up of 13.7 years. Nearly 4 million subjects who survived 5 years were free of chronic diseases at recruitment. There was a clear J-shaped relationship between the BMI of the 385,879 who died and all-cause mortality. The lowest

Table 2. Evidence-Based Recommendations To Increase Physical Activity in Communities

Community-wide campaigns to promote physical activity
Point of decision prompts for stair use
Individually adapted health behavior change programs
Enhanced school-based physical education
Social support in community settings
Creation of or enhanced access to places for physical activity combined with informational outreach activities
Street-scale urban design and land-use policies
Community-scale urban design and land-use policies
Active transport to school
Transportation and travel policies and practices

mortality was with a BMI of 20.0 to 25.0 kg/m². Below this (BMI, 18.5 to 20.0 kg/m²), mortality significantly increased by 13% [hazard ratio (HR), 1.13]. In the individuals with a BMI of 25.0 to 27.5 kg/m², all-cause mortality increased by 7% (HR, 1.07), and with a BMI of 27.5 to 30.0 kg/m², it increased by 20% (HR, 1.20). For grade-1 obesity (BMI 30.0 to <35.0 kg/m²), all-cause mortality increased by 45% (HR, 1.45), and for grade-2 obesity (BMI, 35.0 to <40.0 kg/m²), it increased by 94% (HR, 1.94). For those with grade-3 obesity (BMI, 40.0 to <60.0 kg/m²), all-cause mortality rose by 176% (HR, 2.76). For each 5 BMI unit increase, total mortality rose by 30%, mortality from chronic kidney disease rose by 60%, and mortality from T2DM rose by 120% (41).

Just as weight gain can increase the risk of mortality, weight loss can reduce the risk of mortality in obese individuals. The results from the Swedish Obese Subjects Study (which compared long-term follow-up of obese patients after surgical intervention for obesity with a matched but unoperated control group) showed a 29% reduction in overall mortality after 10.9 years (143). Individuals in the Look AHEAD trial had a similar outcome after a median follow-up of 10.2 years. Those who lost at least 10% of their body weight in the first year of the study had a 21% lower risk of the primary CVD outcome [HR, 0.79 (95% CI, 0.64 to 0.98); *P* = 0.034] and a 24% reduced risk of the secondary outcome [HR, 0.76 (95% CI, 0.63 to 0.91); *P* = 0.003] compared with individuals who were weight stable or gained weight. Participants in the intensive lifestyle intervention group who lost at least 10% of their body weight had a 20% lower risk of the primary CVD outcome [HR, 0.80 (95% CI, 0.65 to 0.99); *P* = 0.039] and a 21% lower risk of the secondary CVD outcome [HR, 0.79 (95% CI, 0.66 to 0.95); *P* = 0.011] compared with the control group (144).

The mechanism of obesity-associated morbidity

The effects of obesity on the body appear to be mediated by several major pathways. Fig. 3 shows how obesity as a disease process might lead to a variety of other diseases (145).

A variety of types of adipose tissue dysfunction clearly play a role in the genesis of many obesity-related diseases. These include impairments in adipocyte storage and release of fatty acids, overproduction or underproduction of “adipokines” and cytokines (146), hormonal conversion, and the adverse mechanical effects of greater tissue mass.

The pathology of obesity is closely linked with body fat distribution. Upper body/visceral or ectopic fat accumulation is a much better predictor of insulin resistance, dyslipidemia, and such than total fat. Visceral fat is considered one of the “ectopic” fat depots, along with hepatic, intramyocellular, intramuscular, and pericardial fat. Humans with the ability to respond to excess energy intake by recruiting

new, healthy subcutaneous adipocytes are relatively protected from many of the metabolic consequences of obesity. Those without this ability will store excess fat in ectopic depots, including liver, visceral fat, and muscle (147). This is supported by the finding that larger subcutaneous fat cells are associated with more accumulation of visceral fat during overfeeding, because they cannot expand to store more fat (148).

One study reported that the predisposition for T2DM was associated with impaired recruitment of new adipose cells to store excess lipids in subcutaneous adipose tissue (149). Another study reported that adults who develop more leg adipocytes in response to overfeeding have a lesser increase in abdominal subcutaneous adipose size (150). Fabbrini *et al.* (151) showed that those with MHO are resistant to the adverse metabolic effects of moderate weight gain, whereas metabolically unhealthy people are predisposed to such adverse effects. These authors concluded that increased adipose tissue capacity for lipogenesis might help protect people with MHO from weight gain-induced metabolic dysfunction, at least with modest weight gain during shorter periods of time.

In addition to the known toxic effects of excess fatty acids, abnormalities in the hormonal function of adipose tissue may contribute to metabolic disease. Adiponectin is the most abundant peptide produced by adipose tissue (152). It improves insulin sensitivity and vascular function. Adiponectin concentrations are inversely related to adipocyte size and visceral fat mass. In contrast, most adipokines are secreted in larger quantities as fat cells increase in size.

Researchers have discovered a large number of adipokines, but their exact role in disease is often unknown. The angiotensinogen produced by adipose tissue is a precursor for angiotensin, which can contribute to the risk for hypertension. Additionally, the aromatase enzymes in adipose tissue can convert sterols (androstenedione) to estrogen, which may explain the greater risk of breast and endometrial cancer in women with obesity, particularly postmenopausal women with obesity where estrogens derived from fat are their principal source of estrogens (153).

Type 2 diabetes mellitus

There is overwhelming evidence that BMI, central adiposity, and the increase in body weight predict future T2DM (154). A meta-analysis of prospective studies provided evidence that as upper body adiposity increases, both the risk of the metabolic syndrome and of developing T2DM also increase (155). The duration of obesity in younger compared with older individuals is also associated with a greater risk for T2DM (156). Weight gain in adult life increases the risk of developing T2DM, particularly in the age range 25 to 40 years (157).

The duration of increased body weight is also a risk factor for T2DM. For a given level of excess BMI-years

in the National Longitudinal Survey, younger individuals compared with older ones (and Hispanic and black compared with white individuals) had a higher risk of developing T2DM (153).

Weight loss is clearly beneficial in reducing the risk of converting to diabetes. In the Diabetes Prevention Program, a median weight loss of 5.5% during 2.8 years reduced the risk of converting from prediabetes to diabetes by 58% (158). Similarly, bariatric surgery has repeatedly reversed diabetes to normal glucose tolerance (159–161).

Cancer

Certain forms of cancer are significantly increased in individuals who are overweight (162, 163). Males face increased risk for neoplasms of the colon, rectum, and prostate. In women, cancers of the reproductive system, including breast (164), endometrium (165), and gallbladder, are more common. Women who gained 25 kg or more after age 18 were at increased risk of breast cancer (RR 1.45 $P < 0.001$). Women who gained 10 kg or more after menopause were also at increased risk for breast cancer compared with women whose weight remained stable. Women who lost and maintained ≥ 10 kg and who did not use postmenopausal hormones were at lower risk than those who maintained weight (RR, 0.43) (166).

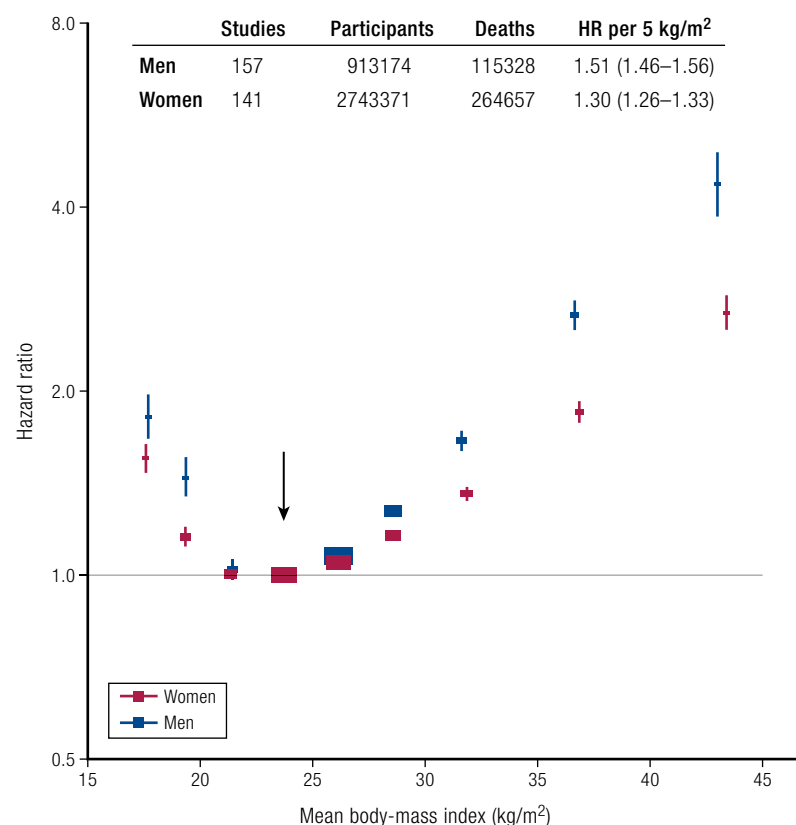


Figure 2. BMI and all-cause mortality. Vertical bars are 95% CI. The Global Mortality Collaboration, 2016 (142).

Breast cancer is not only related to total body fat but also may have a more important relationship to central body fat (167). This relationship to body fat may also help explain why breast cancer risk is increased at age 75 in women in the highest vs the lowest quartile of BMI (168). Circulating, unconjugated estradiol may mediate the relationship between increased body fat and breast cancer (169), as well as the relationship between increased body fat and the risk of endometrial cancer (169).

Myocardial infarction

Many studies show that as BMI increases, there is an increased risk for heart disease (170, 171) and heart failure (172). Data from the Nurses' Health Study indicate that the risk for U.S. women developing coronary artery disease is increased 3.3-fold with a BMI > 29 kg/m² compared with women with a BMI < 21 kg/m² (173). A BMI of 27 to < 29 kg/m² increases the relative risk to 1.8. Weight gain also strongly affects this risk at any initial BMI. That is, at all levels of initial BMI (and within BMI categories) there was a graded increase in risk of heart disease with increasing waist circumference. Similarly, within waist circumference categories there was an increased risk of heart disease with increasing BMI (171). Major risk of CVD was increased 6% for each 1.1 kg/m² increase in BMI among 6452 British men (174).

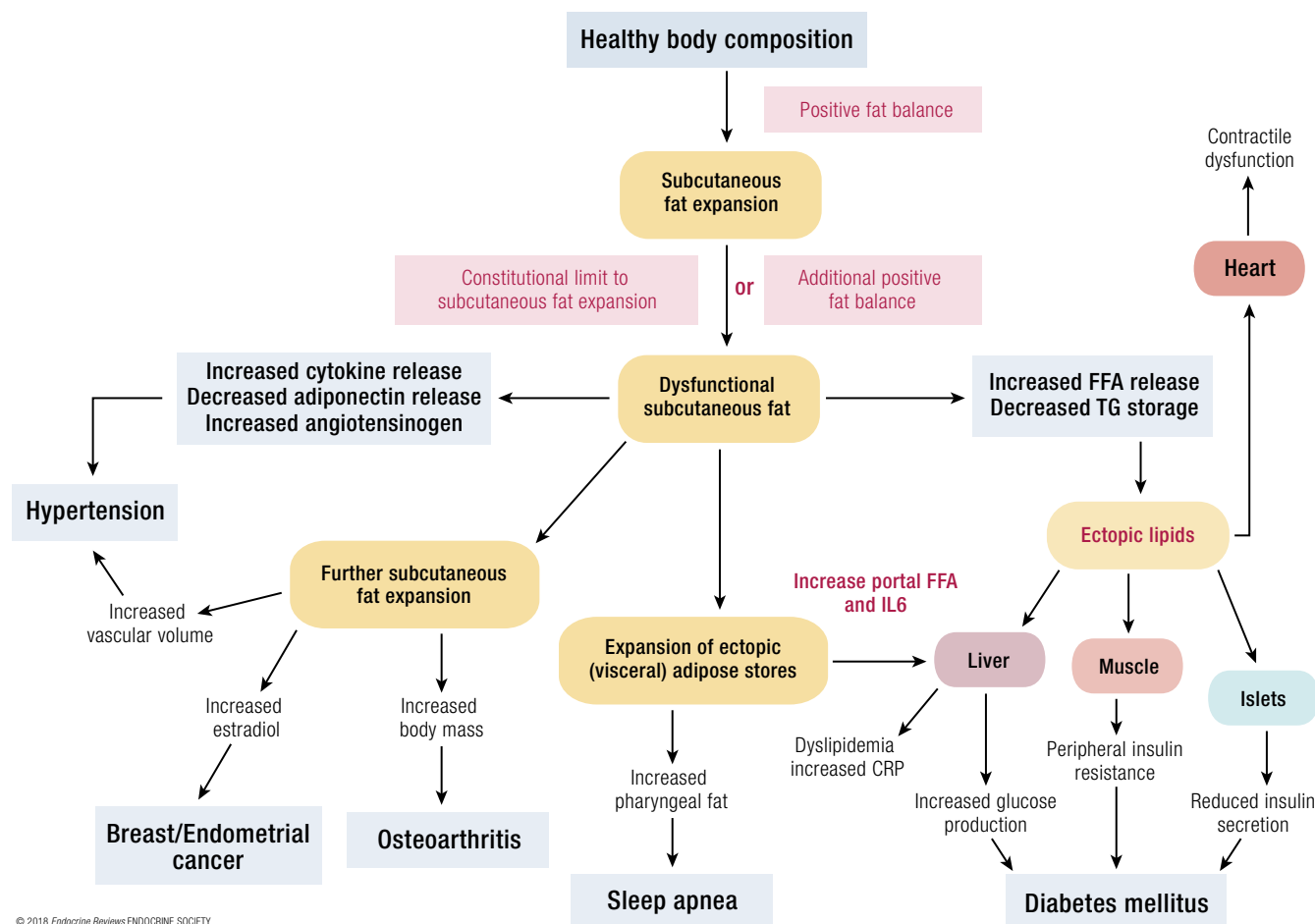
Central adiposity, as reflected in waist circumference, is also a strong predictor of the risk for CVD (173). When increased central adiposity is added to other components of the metabolic syndrome, the prediction is even higher. Using the National Health and Examination Survey data, Janssen *et al.* (175) showed that BMI predicted the risk of the metabolic syndrome in men. However, when BMI is adjusted for waist circumference as a continuous variable, waist circumference accounted for essentially all of the risk for the metabolic syndrome. In a meta-analysis including 10 studies, indices of abdominal obesity (including WHR and waist circumference) were better discriminators than BMI of cardiovascular risk factors, including T2DM, hypertension, and dyslipidemia (176).

Both atrial fibrillation (177, 178) and congestive heart failure (170, 179) have a higher risk in subjects who are overweight. In the Multi-Ethnic Study of Atherosclerosis, the risk of congestive heart failure in obesity was associated with elevated levels of inflammatory markers (interleukin-6 and C-reactive protein) and albuminuria (180).

Heart failure and the obesity paradox

Obesity increases the risk of heart failure, yet some studies have found that elevated BMI may improve survival in individuals who already have congestive heart failure, a phenomenon called "the obesity paradox" (181–183). This appears to contradict the

Figure 3. A schematic model of the intermediary mechanisms for dyslipidemia, insulin resistance, T2DM, heart disease, hypertension, some forms of cancer, OSA, NAFLD, and osteoarthritis.



curvilinear relationship of BMI to body weight (41, 88–91, 93).

One possible explanation is “selection bias.” This occurs when studies select individuals as higher risk because they are identified after the disease develops rather than before. A simple way to eliminate this bias is to match the start of exposure to the start of follow-up. The same is true regarding the effect of obesity on the risk of mortality (43, 184–187). Alternatively, the obesity paradox may reflect some capacity of the individual with obesity to overcome cardiovascular risk. Still another explanation for this paradox may be the difference between what BMI tells us and what the underlying fat distribution is doing. In a recent study, Padwal *et al.* (187) found that BMI and body fat have different predictive values for cardiovascular risk. If fat is the culprit, then measuring BMI may lead to an erroneous conclusion (187).

Hypertension and stroke

Hypertension is a global public health problem. Roughly 1 billion people worldwide are estimated to have clinically significant elevations in BP (188), with

~50 million of them in the United States (189). Hypertension is the most important of 67 risk factors for worldwide risk of coronary heart disease, stroke, renal disease, and all-cause mortality (29). Furthermore, antihypertensive therapy results in reductions of incidence of stroke, myocardial infarction, and heart failure (190).

Among hypertensive individuals who reduced their BP levels following a successful weight-loss intervention, those who maintained weight loss also maintained lower BP levels, and those who regained weight returned to their baseline BP levels (191). In a meta-analysis of 25 studies, Neter *et al.* (192) found that weight loss averaging 5.1 kg after diet and/or exercise programs reduced BP by 4.4/3.5 mm Hg (systolic BP/diastolic BP). The studies with weight losses >5 kg showed larger decreases in BP than those with less weight loss.

Obstructive sleep apnea

In contrast to the relatively benign effects of excess weight on most components of respiratory function, overweight predisposes to obstructive sleep apnea

(OSA), which can be severe and life-threatening (193). OSA is more common in men than women. An increased snoring index and increased maximal nocturnal sound intensity are characteristic. Nocturnal oxygen saturation is significantly reduced (194). A study of obese patients with diabetes using polysomnography showed that 30.5% of the participants had moderate OSA, and 22.6% had the severe form. Waist circumference was significantly related to the presence of OSA, and severe OSA was most likely in individuals with a higher BMI (195). Independently of obesity, OSA is associated with features of the metabolic syndrome, including hypertension, T2DM, and increased cardiovascular risk, possibly mediated by stress responses and hypoxia. Excess daytime sleepiness is an important consequence and can be a risk for driving and other tasks that require alertness (195).

Hepatobiliary disease

Gallbladder disease

Obesity is associated with an increased risk of gallbladder disease. In a meta-analysis of gallbladder disease and obesity, Aune *et al.* (165) reported that the risk of gallbladder disease increased even within normal BMI ranges. For each 5-unit increase in BMI, the relative risk of gallbladder disease increased 63%. For a 10 cm increase in waist circumference, the increase in relative risk was 46%.

Nonalcoholic fatty liver disease

Fatty liver disease is often associated with obesity (196). Excess liver fat without inflammation/hepatocellular injury is called nonalcoholic fatty liver disease (NAFLD), which may progress to nonalcoholic steatohepatitis (NASH) and eventually cirrhosis. The diagnosis of NAFLD requires evidence of excess liver fat in the absence of secondary causes. NASH is diagnosed when there is evidence of hepatocellular injury (most often in the context of fatty liver) and is of greater concern because it poses a genuine risk of progression to fibrosis, cirrhosis, greater risk for hepatocellular carcinoma, and cirrhosis-related liver failure.

The prevalence of NAFLD ranges from 6% to 30%, depending on the diagnostic approaches and populations studied. The estimated prevalence of NASH is 3% to 5%. Both liver fat and fibrosis were increased as a function of time in nonhuman primates fed a high-fructose diet vs nonhuman primates without the added fructose (197).

NAFLD is considered by some to be the hepatic manifestation of the metabolic syndrome (198). Fatty liver is extremely common in patients undergoing bariatric surgery (prevalence 84% to 96%). The prevalence of fatty liver in the United States has been increasing steadily from 1988 to 2008 with obesity as an independent predictor (199). In a meta-analysis of 21 studies (13 of which were prospective), Li *et al.* (200)

found that obesity produced a 3.5-fold increased risk of developing NAFLD. Moreover, there was a dose response to rising BMI, with the relative risk increasing 1.20 for each 1 unit increase in BMI. Another meta-analysis (201) found that for each 1 unit increase in waist circumference, the odds ratio of NAFLD increased 1.07, and for each 1 unit increase in BMI, the odds ratio increased 1.25. The prevalence is greater in Hispanic than white populations and less in blacks than whites. NAFLD and NASH are also more common in persons with T2DM.

Gout and osteoarthritis

Gout

Aune *et al.* (202) reported on the relationship of BMI to the risk of gout in 10 prospective studies that included 27,944 cases of gout among a population of 215,739 (median follow-up of 10.5 years). The summary relative risk for a 5-unit increment in BMI was 1.55 for all studies combined (95% CI, 1.44 to 1.66). The summary relative risk per 5-unit increase in BMI was 1.62 for men (95% CI, 1.33 to 1.98) and 1.49 for women (95% CI, 1.32 to 1.68). The relative risks were 1.78, 2.67, 3.62, and 4.64 for persons with a BMI of 25, 30, 35, and 40 kg/m², respectively, compared with persons with a BMI of 20 kg/m². The study also associated increased risk with BMI in young adulthood, WHR, and weight gain from age 21 to 25 to midlife, but the analyses included few studies.

Osteoarthritis

Osteoarthritis is likewise significantly increased in individuals who are overweight or obese. The osteoarthritis that develops in the knees and ankles may be directly related to the trauma associated with the degree of excess body weight (203). However, the increased osteoarthritis in non-weight-bearing joints suggests that some components of the excess weight may alter cartilage and bone metabolism independent of weight bearing. Increased rates of osteoarthritis account for a significant component of the cost of overweight and for the associated disability (204). Okoro *et al.* (204) found that class-3 obesity (BMI > 40 kg/m²) was associated with survey-reported disability among individuals >45 years of age who reported arthritis, as well as those who did not report arthritis.

Effects of obesity during pregnancy

A narrative analysis of 22 reviews on pregnancy in women with obesity (205) showed that gestational diabetes, preeclampsia, gestational hypertension, depression, instrumental and cesarean birth, and surgical-site infection are more likely to occur in pregnant women with obesity compared with women with a healthy weight. Obesity in pregnancy is also linked to greater risk of preterm birth, large-for-

gestational-age babies, fetal defects, congenital anomalies, and perinatal death. Additionally, breastfeeding initiation rates are lower, and there is greater risk of early breastfeeding cessation in women with obesity compared with healthy-weight women.

Diet, Exercise, and Lifestyle in Managing Obesity

Diet in managing obesity—food is more than calories

Introduction

The idea that single food items or diets are able to promote and maintain weight loss has stimulated numerous studies to investigate different proportions of dietary fat, protein, or carbohydrates as weight-loss diets (206) (Table 3). Underlying all of these dietary approaches, however, is the fact that to lose weight, energy balance must be negative. Although calories are the essential component of energy balance, and reducing them is important for weight loss, food consists of more than calories. When choosing a diet, it is important to select foods that you enjoy and substitute lower calorie healthy foods that can improve the quality of your diet. Macronutrient composition aside, a reduction of energy intake is still an essential component of the effectiveness of any diet. In the Diabetes Prevention Program, calorie reduction was the major predictor of weight loss (207). Reduced intake in fat was the second predictor, and physical activity was only an important predictor when the calorie intake was unchanged (207).

A calorie deficit of 500 kcal/d produces a weekly deficit of ~3500 kcal, which is roughly equivalent to the energy in 1 pound (0.45 kg) of fat tissue (208). Although this calculation would predict linear weight loss, weight loss is not linear; it is curvilinear. At the initial stage, weight loss tends to be more rapid, and then slows until it reaches a plateau (208–211). The initial reduction of calorie intake initiates a number of compensatory mechanisms, which tend to drive food intake up and reduce weight loss (212–214).

Several factors contribute to the different patterns of response during weight loss. The first is the initial rate of weight loss (215). In the Look AHEAD trial, a multicenter clinical trial in individuals with diabetes, those in the highest tertile of initial weight loss in the first 2 months had nearly twice as much weight loss at 4 and 8 years compared with those in the lowest tertile of weight loss in the first 2 months. This could be explained by the fact that adherence to any dietary program is critical to successful weight loss (211, 216–218).

Genetic variation can also influence weight loss, as can the biological response to different diets (219, 220). In both the Diabetes Prevention Program (219, 220) and the Preventing Overweight Using Novel Dietary

Strategies (POUNDS Lost) Study (220–227), individuals with the A genotype of the fat mass and obesity-associated (*FTO*) gene had greater weight loss when assigned the high-protein diets but not when eating the low-protein diets (222). Another analysis, which examined eight clinical trials in overweight or adults with obesity, reported that the *FTO* genotype did not modify the response to diet (228). Using genetic profiles may thus be of value in the future for developing personalized dietary regimens for managing obesity, but more evidence is needed for any clinical applications.

Very low-calorie diets

We define very low-calorie diets (VLCDs) as those having an energy level between 200 and 800 kcal/d. In a review comparing low-calorie diets with VLCDs, Tsai and Wadden (229) reported that VLCDs produced significantly greater short-term weight loss (16.1%) than did low-calorie diets (9.7%) but similar longer-term weight loss.

Carbohydrate subtypes, low-carbohydrate diets, and sugar-sweetened beverages

Carbohydrates, such as sugar or high-fructose corn syrup, create additional challenges to a weight-loss diet, because added sugar in beverages provides extra energy with reduced satiety, thus increasing the total energy intake (230).

In a meta-analysis, Nordmann *et al.* (231) found that weight loss was greater at 6 months with low-carbohydrate diets (defined as carbohydrate intake of <60 g/d) but not at 12 months (compared with other diets). In a meta-analysis of longer trials by Tobias *et al.* (232), interventions with similar intensity led to a significantly greater weight loss of 1.15 kg on the low-carbohydrate diets. This is in line with a meta-analysis by Bueno *et al.* (233), which showed a greater weight loss of 0.91 kg with very low-carbohydrate ketogenic diets. Although both are statistically significant, the absolute difference in weight loss was quite small (~1 kg weight reduction in a 100-kg individual). These studies over the long term are hindered by the participants' lack of adherence to the prescribed dietary regimens.

To circumvent the problem of variable effects of dietary protein in evaluating low-carbohydrate and low-fat diets (234), Hall and Guo (235) performed a meta-analysis of isocaloric low-carbohydrate/high-fat diets vs high-carbohydrate/low-fat diets where protein consumption was held constant. This analysis included 32 studies (563 subjects total), which provided all food to the subjects. Dietary carbohydrate ranged from 1% to 83% and dietary fat from 4% to 84% of total energy intake. There was a small but significant 26 kcal/d weighted mean energy expenditure difference favoring the low-fat/high-carbohydrate diets (not shown) and a small but significant 16 g/d weighted mean body fat difference favoring the low-fat/high-carbohydrate diets (Fig. 4)

Table 3. A Comparison of Various Diet Programs and Eating Plans to a Typical American Diet

Type of Diet	Example	General Dietary Characteristics	Comments	AHA/ACC/TOS Evaluation and Others
Typical American diet		Carb: 50% Protein: 15% Fat: 35% Average of 2200 kcal/d	Low in fruits and vegetables, dairy, and whole grains High in saturated fat and unrefined carbohydrates	
Balanced-nutrient, moderate-calorie approach	DASH Diet or diet based on MyPyramid food guide. Commercial diet plans such as: Diet Center, Jenny Craig, Nutrisystem, Physician's Weight Loss, Shapedown Pediatric Program, Weight Watchers, Setpoint, Sonoma, Volumetrics	Carb: 55%–60% Protein: 15%–20% Fat: 20%–30% Usually 1200–1800 kcal/d	Based on set pattern of selections from food lists using regular grocery store foods or prepackaged foods supplemented by fresh food items Low in saturated fat and ample in fruits, vegetables, and fiber Recommended reasonable weight-loss goal of 0.5–2.0 pounds/wk Prepackaged plans may limit food choices Most recommend exercise plan Many encourage dietary record keeping Some offer weight-maintenance plans/support	Meta-analysis showing DASH approach better than control or healthy diets (weight mean difference 0.87–1.5 kg).
Low- and very low-fat, high-carbohydrate approach	Ornish Diet (Eat More, Weigh Less), Pritikin Diet, T-factor Diet, Choose to Lose Diet, Fit or Fat Diet	Carb: 65% Protein: 10%–20% Fat: ≤10%–19% Limited intake of animal protein, nuts, seeds, other fats	Long-term compliance with some plans may be difficult because of low level of fat Diet can be low in calcium Some plans restrict healthful foods (seafood, low-fat dairy, poultry) Some encourage exercise and stress management techniques	Same weight loss at 6 mo comparing 30% fat to > 40% fat; strength of evidence: moderate
Low energy density	Volumetrics Diet	Carb: 55% Protein: 10%–25% Fat: 20%–35% Focus on fruits, vegetables, and soups	Four food categories: (1) Very low density—nonstarchy fruits and vegetables, nonfat milk, broth-based soups (2) Low density—starchy fruits/vegetables, grains, breakfast cereal, low-fat meats, and mixed dishes (3) Medium density—meat, cheese, pizza, fries, dressings, bread, and such (4) High density—desserts, nuts, butter, oils Focus on categories 1 and 2, some from 3, minimum from 4	More weight loss at 6 mo with low energy-dense diet; strength of evidence: RCT

(Continued)

Table 3. Continued

Type of Diet	Example	General Dietary Characteristics	Comments	AHA/ACC/TOS Evaluation and Others
Portion controlled	Use of meal replacements both liquid and solid meals			Weight loss at 1 year in Look AHEAD trial related to frequency of consuming portion-control meals
Mediterranean-style diets		Carb: 35%–40%	Eat primarily plant-based foods (fruits, vegetables, whole grains, legumes, and nuts)	
		Protein: 12%–20%	Healthy oils instead of saturated fats	
		Fat: 40%–50%	Limit red meat to a few times a month	
		Approximately 25%–30% of energy from monounsaturated fat	Eat fish and poultry at least twice a week	
			Red wine in moderation, for individuals who choose to drink alcohol	
Low-carbohydrate, high-protein, high-fat approach	Atkins New Diet Revolution, Protein Power Diet, Stillman Diet (The Doctor's Quick Weight Loss Diet), Carbohydrate Addict's Diet, Scarsdale Diet	Carb: ≤20%	Promote quick weight loss (much is water loss rather than fat loss)	Same weight loss at 6 mo comparing <30 g/d vs 55% Carb–15% protein or 40% Carb and 30% protein
		Protein: 25%–40%	Ketosis causes loss of appetite	Strength of evidence: low
		Fat: ≥55%–65%	Can be too high in saturated fat	
		Strictly limits carbohydrates to <100–125 g/d	Low in carbohydrates, vitamins, minerals, and fiber	
			Not practical for long term because of rigid diet or restricted food choices	
Higher protein, moderate-carbohydrate, moderate-fat approach	The Zone Diet, Sugar Busters Diet, South Beach Diet	Carb: 40%–50%	Diet rigid and difficult to maintain	Same weight loss at 6 mo comparing 25%–30% vs 15% protein; strength of evidence: high
		Protein: 25%–40%	Enough carbohydrates to avoid ketosis	
		Fat: 30%–40%	Low in carbohydrates; can be low in vitamins and minerals	
Glycemic load	The Glycemic-Load Diet—Rob Thompson	Carb: 40% to >55%	Focus on low-glycemic-load foods	Same weight loss at 6 mo comparing high vs low glycemic load; strength of evidence: low
		Protein: 15%–30%		
		Fat: 30%		
Low-sugar or non-sugar-sweetened beverages	Not really a diet but just a call to reduce sugar-sweetened beverages intake as a preventive strategy	No recommendation other than to reduce/remove sugar-sweetened beverages from your overall diet plan	Meta-analyses show that consumption of sugar-sweetened beverages is related to risk of obesity, T2DM, and heart disease	Weight loss less in adolescents comparing artificial vs sugar-sweetened drinks; strength of evidence: RCT comparing artificial sweetener vs sugar-sweetened beverages
Novelty diets	Immune Power Diet, Rotation Diet, Cabbage Soup Diet, Beverly Hills Diet, Dr. Phil Diet	Most promote certain foods, or combinations of foods, or nutrients as having allegedly magical qualities	No scientific basis for recommendations	

(Continued)

Table 3. Continued

Type of Diet	Example	General Dietary Characteristics	Comments	AHA/ACC/TOS Evaluation and Others
Very low-calorie diets	Health Management Resources Program, Medifast Diet, Optifast Diet	<800 kcal/d	Requires medical supervision For clients with BMI ≥ 30 or BMI ≥ 27 with other risk factors May be difficult to transition to regular meals	
Weight-loss online diets	Cyberdiet, Dietwatch, eDiets, Nutrio.com	Meal plans and other tools available online	Recommend reasonable weight loss of 0.5–2.0 pounds/wk Most encourage exercise Some offer weight-maintenance plans/support	

Abbreviations: AHA, American Heart Association; ACC, American College of Cardiology; Carb, carbohydrate; RCT, randomized controlled trial; TOS, The Obesity Society.

(235). This analysis does not support the concept of a metabolic advantage for lower carbohydrate, higher fat diets, suggesting that any benefits of such diets probably involve differences in energy intake.

Dietary fat, energy density, and low-fat diets

For decades, dietary recommendations for weight loss have emphasized a reduction in fat intake because of its high-energy content (9 kcal/g) compared with carbohydrates (4 kcal/g) (236). A meta-analysis of six trials reported no significant differences between low-fat diets (20 to 30 g/d or 20% of total energy) vs other weight-loss diets in terms of sustained weight loss (237).

A recent systematic review and meta-analysis compared the effects of low-fat interventions (<30% total fat) vs other dietary interventions on long-term (≥ 1 year) weight changes. It found that when the groups differed by >5% fat content, the higher fat interventions led to slightly greater weight loss and better adherence, although the magnitude of the differences in weight loss was small (232). The important message is that “adherence” rather than a specific diet is the important ingredient in success.

Another strategy for reducing energy density (besides reducing dietary fat intake) is to substitute foods with higher water content. One trial has compared a reduced-fat diet to a diet with extra fruits and vegetables with lower energy density. In this trial, the addition of fruits and vegetables led to greater weight loss compared with lowering fat only (238). Diets with a higher intake of fruits and vegetables evolved into the Volumetrics diet (239). The efficacy of the Volumetrics diet warrants further investigation.

Low-glycemic index diets

The glycemic index is based on the rise in blood glucose in response to test foods (240, 241). A meta-analysis by Thomas *et al.* (242) reported a significant but small

difference in weight loss of 1.1 kg that favored low-glycemic index diets. Additionally, both total and low-density lipoprotein (LDL) cholesterol fell more with low-glycemic index diets. The long-term effects of low-glycemic index diets warrant further evaluation.

Fasting glucose may provide a clue to dietary selection. Hjorth *et al.* (243) have reported that individuals with higher fasting glucose who are prediabetic may respond better to a lower glycemic index diet with more fiber and whole grain.

High-protein diets

A 2-year study comparing 12% and 25% protein diets as part of a 30% fat diet (244, 245) reported that weight loss during 24 weeks was substantially greater with the higher protein diet, and that this result was maintained up to 56 weeks but not at 104 weeks.

A meta-analysis of energy-restricted, high-protein/low-fat diets compared with standard-protein/low-fat diets showed that the high-protein diet was better at reducing body weight (−0.79 kg; 95% CI, −1.50 to −0.08 kg), fat mass (−0.87 kg; 95% CI, −1.26 to −0.48 kg), and triglycerides (−0.23 mmol/L; 95% CI, −0.33 to −0.12 mmol/L) and resulted in less of a decrease in fat-free mass (0.43 kg; 95% CI, 0.09 to 0.78 kg) and resting energy expenditure (595.5 kJ/d; 95% CI, 67.0 to 1124.1 kJ/d) (246). In the intent-to-treat analysis of the POUNDS Lost Study (218), which compared 15% and 25% protein diets, there was no difference in weight loss between these diets. However, those who adhered to a higher protein diet lost more weight. When this study used urinary nitrogen loss as a measure of protein intake, those with the greater increase in protein intake lost significantly more weight (247).

Mediterranean-style diets

Mediterranean-style diets are characterized by enhanced consumption of olive oil, nuts, whole

grain, fruits, and vegetables. In diabetic individuals, the Mediterranean diet produced a greater weight loss during 4 years than did a low-fat diet (248). Another meta-analysis (249) reported that Mediterranean diets reduced body weight 2.2 kg compared with low-fat diets. The Prevención con Dieta Mediterránea (PREDIMED) study from Spain showed that consumption of a high-fat Mediterranean diet (41.8% calorie from fat) resulted in a 0.43 kg weight loss ($P = 0.043$) and a 0.55 cm waist circumference reduction ($P = 0.48$) vs a comparison diet (37.4% calorie from fat) during 4.8 years of follow-up (250).

Balanced-deficit diets

Diets with a reduced content of carbohydrates, proteins, and fat (so-called “balanced-deficit diets”) have been widely used in managing obesity. In a meta-analysis, Avenell *et al.* (251) reported that intervention diets with an average deficit of 600 kcal/d led to

a weight loss of 5.31 kg compared with controls, and the weight-loss effect lasted up to 3 years.

In a 6-month intervention, the daily use of a commercially available portion-control plate was effective in promoting weight loss among patients with obesity and T2DM when compared with a usual-care dietary group. A meta-analysis of six studies using meal replacements showed more weight loss than low-calorie diets at 3 months (252). Data from another trial showed that portion control can increase diet quality while maintaining significant weight loss during 18 months (253).

Comparison of diets with different macronutrient composition

Several RCTs have compared diets head-to-head (216, 218, 231, 254, 255). We summarize these in Table 4 (216, 218, 254–262). These studies show improvements in hemoglobin A1c (HbA1c) in patients with T2DM and improvements in triglycerides and HDL cholesterol in

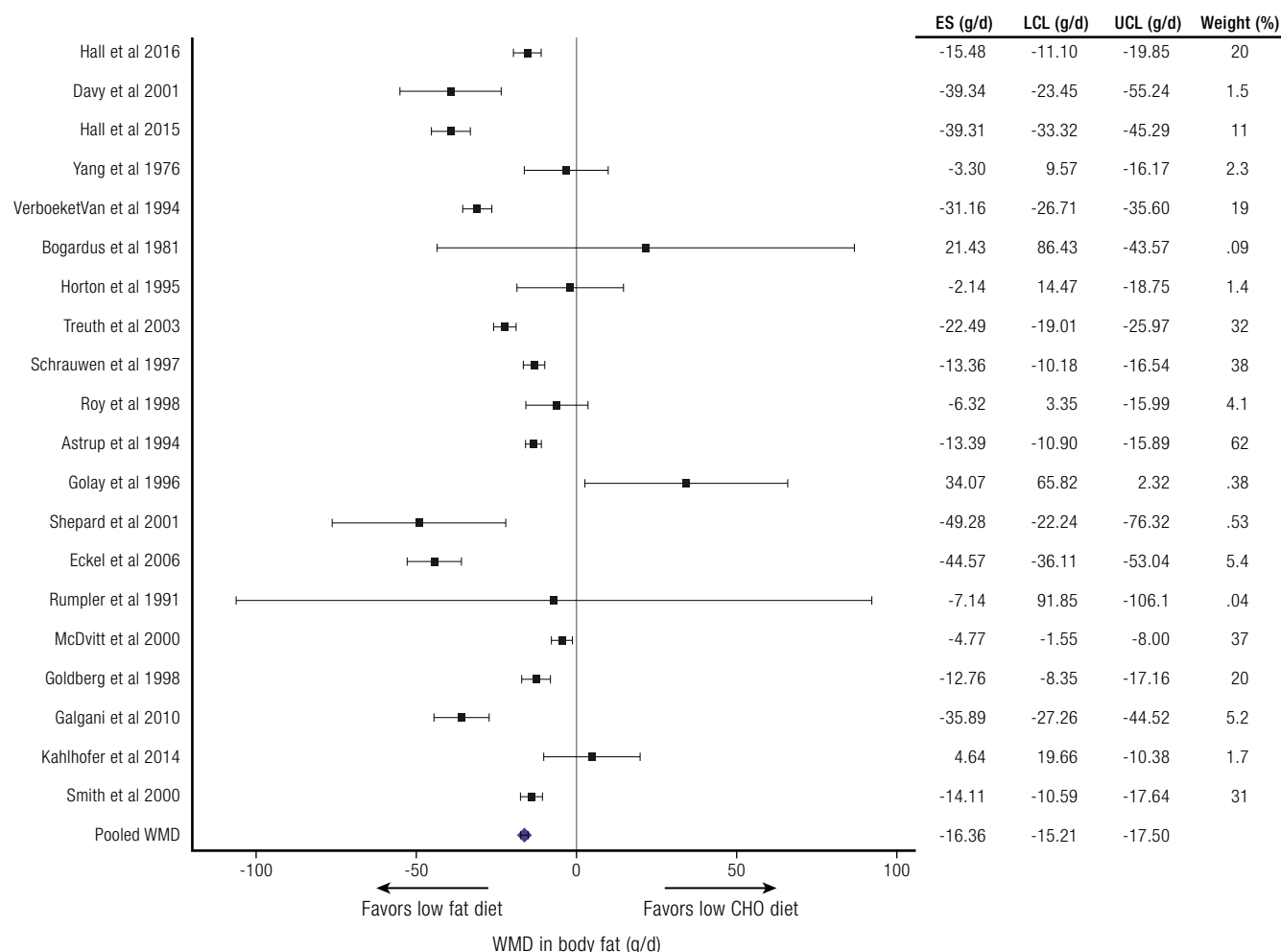


Figure 4. Weight loss comparing isocaloric low-carbohydrate/high-fat and high-carbohydrate/low-fat diets where meals were provided and protein consumption was the same. 95% horizontal CI. CHO, carbohydrate; ES, effect size; LCL, lower confidence limit; UCL, upper confidence limit; WMD, weighted mean difference. See Hall and Guo, 2017 (235).

Table 4. Weight Losses from Randomized Controlled Trials That Compared Diets With Varying Macronutrient Compositions

Study	No., Sex, and Completers	No. of Lifestyle Sessions Provided	Dietary Intervention	Weight Change	Month	Comments/Other Results
Bazzano <i>et al.</i> , 2014 (256)	148, 88% F, 80% completed	10	Low Carb (<40 g/d)	−6.5 kg ^a	12	Participants without CVD or diabetes; low carbohydrate diet group had greater decrease in body fat and triglycerides and greater increase in HDL cholesterol than did the low-fat group. C-reactive protein and 10-Year Framingham Risk Score improved more in low-carbohydrate group. No difference in BP response. Low-fat group had lower protein intake than in the low-carbohydrate group.
			Low fat (<30% fat)	−2.6 kg ^b		
Dansinger <i>et al.</i> , 2005 (216)	160, 51% F, 58% completed	4	Atkins (Low Carb)	−2.1 kg ^a	12	All patients had hypertension, dyslipidemia, and/or fasting hyperglycemia.
			Zone (30% fat)	−3.2 kg ^a		Weight loss was associated with level of adherence.
			Weight Watchers (Low calorie)	−3.0 kg ^a		Each diet decreased LDL/HDL ratio.
			Ornish (10% fat)	−3.3 kg ^a		There were no significant effects on BP or blood glucose at 12 mo.
Das <i>et al.</i> , 2007 (257)	34, % F unknown, 85% completed	52	Low glycemic load	−7.8% ^a	12	Triglycerides and total, HDL, and LDL cholesterol decreased in both groups.
			High glycemic load	−8.0% ^a		
Fabricatore <i>et al.</i> , 2011 (258)	79, 80% F, 63% completed	30	Low glycemic load	−4.5% ^a	9	All patients had T2DM.
			Low fat	−6.4% ^a		There were larger reductions in HbA1c in the low-glycemic load group.
Foster <i>et al.</i> , 2003 (259)	63, 68% F, 59% completed	3	Low carbohydrate (high protein, high fat)	−4.4% ^a	12	HDL cholesterol increased more in the low-carbohydrate group, and triglycerides were lower only in the low-carbohydrate group.
			Conventional (high carbohydrate, low fat)	−2.5% ^a		Diastolic BP decreased in both groups.
						Area under the insulin curve decreased in both groups.
Foster <i>et al.</i> , 2010 (260)	307, 68% F, 63% completed	38	Low carbohydrate	−6.3 kg ^a	24	HDL cholesterol increased more in the low-carbohydrate group.
			Low fat	−7.4 kg ^a		
Gardner <i>et al.</i> , 2007 A to Z Study (254)	311, 100% F, 80% completed	8	Atkins (low carb)	−4.7 kg ^a	12	Increase in HDL cholesterol was larger in the Atkins than in the Ornish group. Triglyceride levels decreased more in the Atkins than in the Zone group.
			Zone (30% fat)	−1.6 kg ^b		There were no differences in insulin or blood glucose between groups.
			LEARN (calorie restricted)	−2.2 kg ^{a,b}		Systolic BP decreased more in Atkins than in all other groups.
			Ornish (<10% fat)	−2.6 kg ^{a,b}		Diastolic BP decreased more in Atkins group than in Ornish group.

(Continued)

Table 4. Continued

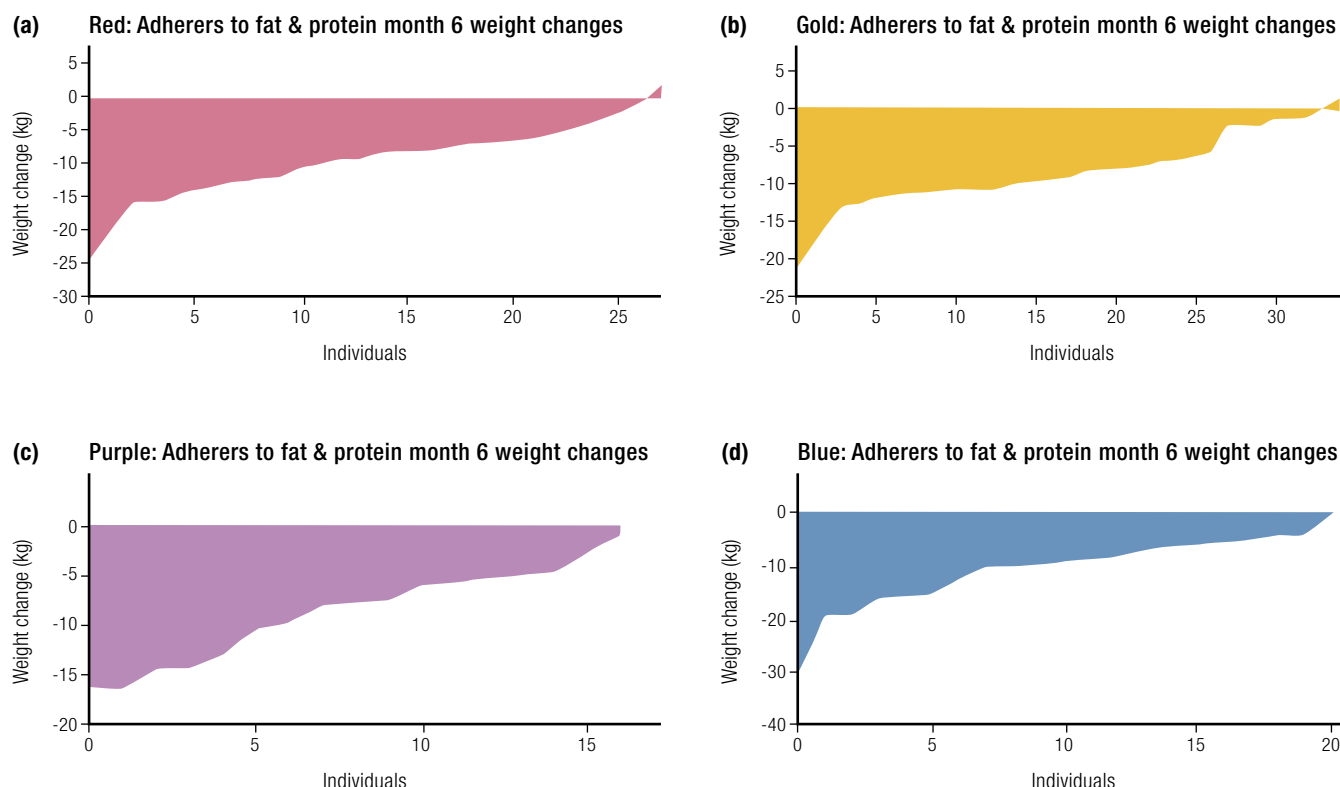
Study	No., Sex, and Completers	No. of Lifestyle Sessions Provided	Dietary Intervention	Weight Change	Month	Comments/Other Results
Sacks <i>et al.</i> , 2009 POUNDS Lost Study (218)	811, 64% F, 80% completed	66	Low fat, average protein (highest carbohydrate)	−2.9 kg ^a	24	LDL cholesterol decreased significantly more in lowest fat/highest carbohydrate group than in highest fat/lowest carbohydrate groups.
			Low fat, high protein	−3.8 kg ^a		HDL cholesterol increased more with lowest carbohydrate than with the highest carbohydrate diet.
			High fat, average protein	−3.1 kg ^a		All diets decreased triglyceride levels similarly.
			High fat, high protein (lowest carbohydrate)	−3.5 kg ^a		All diets, except the highest carbohydrate diet, decreased fasting insulin (greater decrease in the high-protein vs average-protein diets).
Shai <i>et al.</i> , 2008 DIRECT Study (255)	322, 14% F, 85% completed	24	Low fat	−2.9 kg ^a	24	No significant change in LDL cholesterol in any group.
			Mediterranean	−4.4 kg ^b		HDL cholesterol increased in all groups, significantly more in the low-carbohydrate than low-fat group.
			Low carbohydrate	−4.7 kg ^b		Triglyceride levels decreased more in the low-carbohydrate than in the low-fat group.
						In diabetic patients, only the Mediterranean diet group had a decrease in fasting glucose.
Stern <i>et al.</i> , 2004 (261)	132, 17% F, 66% completed	15	Low carbohydrate	−5.1 kg ^a	12	Triglyceride levels decreased more in the low-carbohydrate group than in the low-fat group.
			Conventional (low fat)	−3.1 kg ^a		HDL cholesterol decreased less in the low-carbohydrate group than in the low-fat group.
						Changes in total and LDL cholesterol were not significant between groups.
Yancy <i>et al.</i> , 2004 (262)	120, 76% F, 66% completed	9	Low-fat diet	−6.5% ^a	6	All patients were hyperlipidemic.
			Low-carbohydrate, ketogenic diet with nutritional supplements	−12.9% ^b		Triglycerides decreased more and HDL cholesterol increased more in the low-carbohydrate group.

Different letters (in superscript) indicate statistically significant differences ($P \leq 0.05$) in weight loss between groups.
Abbreviations: MR, meal replacements; VLDL, very low-density lipoprotein.

the groups assigned to the low-carbohydrate diet arms. One trial randomized 169 individuals with obesity to one of four popular diets, including the Atkins diet (263), The Ornish diet (264), the Weight Watchers diet (265), and the Zone diet (266). At the end of 12 months, each diet produced similar weight losses (~5 kg). Adherence to the diets was the single most important criterion of success in these trials. In one study, a low-fat diet was compared with a low-carbohydrate diet (Atkins diet) and a Mediterranean-style diet (255). Compared with the low-fat diet, individuals assigned to the Mediterranean diet and low-carbohydrate diet had significantly greater weight loss and maintenance by 24 months (255). In a meta-analysis of numerous popular diets that included 48 unique trials, low-carbohydrate diets performed equally with low-fat diets after 12 months, with the low-carbohydrate diets resulting in 7.25 kg of weight loss (95% CI, 5.33 to 9.25 kg) compared with 7.27 kg of weight loss in the low-fat diet groups (95% CI, 5.26 to 9.34 kg) (267).

The POUNDS Lost Study (the largest trial examining macronutrient composition and weight

loss) randomized participants to one of four diets, with 80% of patients providing data on body weight at the end of 2 years. The diets were: (1) 20% fat/15% protein; (2) 20% fat/25% protein; (3) 40% fat/15% protein; or (4) 40% fat/25% protein. The foods in all four diets were the same, although they differed in quantity. At the end of 6 months, 12 months, and 2 years, the weight loss was similar for all four diets (268); however, those who achieved the largest increase in protein intake lost more weight (247). The similarity of the mean weight loss in all four diet groups obscures the wide range of individual weight losses shown in Fig. 5 (243). The data from the POUNDS Lost Study are consistent with the recommendations of the American College of Cardiology/American Heart Association/Obesity Society Guideline for the Management of Overweight and Obesity in Adults, which states that “a variety of dietary approaches can produce weight loss in overweight and obese adults, and that the choice should be based on the patient’s preferences and health status” (39).



Panel (a) ($n = 38$) is the adequate-protein/low-fat group (15% protein, 20% fat, diet, 65% carbohydrate); Panel (b) ($n = 43$) is the high-protein/low-fat group (25% protein, 20% fat, 55% carbohydrate); Panel (c) ($n = 28$) is the high-protein/low-fat group (15% protein, 40% fat, 45% carbohydrate), and Panel (d) ($n = 30$) is the high-protein/high-fat group (25% protein, 40% fat, 35% carbohydrate).

Figure 5. Weight change from baseline to 6 months for each individual participant in the four dietary assignment groups ranked from the largest loser on the left to the most weight gain on the right. (a) ($n = 38$) Adequate-protein/low-fat group (15% protein, 20% fat, 65% carbohydrate); (b) ($n = 43$) high-protein/low-fat group (25% protein, 20% fat, 55% carbohydrate); (c) ($n = 28$) high-protein/low-fat group (15% protein, 40% fat, 45% carbohydrate); (d) ($n = 30$) high-protein/high-fat group (25% protein, 40% fat, 35% carbohydrate).

Commercial programs for weight loss

In a meta-analysis, Gudzone *et al.* (269) reported that the Weight Watchers diet resulted in at least a 2.6% greater weight loss than those assigned to control/education after 12 months. The Jenny Craig diet resulted in a 4.9% greater weight loss during a 12-month period vs groups receiving control/education and counseling. The Nutrisystem diet resulted in a 3.8% greater weight loss at 3 months vs control/education and counseling. VLCDs (Health Management Resources, Medifast, and Optifast) resulted in a 4.0% greater short-term weight loss than counseling, and the weight-loss effect lasted up to 6 months. The Atkins diet (not technically a commercial program, but one with affiliated diet products) resulted in 0.1% to 2.9% greater weight loss at 12 months compared with counseling (269). The differences in the amount of weight loss among various commercial diets were relatively small, and the long-term effects of these diets on weight control and chronic disease risk are still unclear.

Maintenance of long-term weight loss

As previously discussed and illustrated in the Diabetes Prevention Program (158, 270) and the Look AHEAD trial (271), maintaining weight loss is a challenge.

One study (272, 273) assigned participants to weight loss with a VLCD for 4 weeks before randomizing them to either a control diet or study diet supplemented with 48.2 g/d of protein. At the end of 3 months, the group receiving the protein supplement (to bring protein to 18% of total energy) had a 50% reduction in body-weight regain.

Data from the Women's Health Initiative indicate that reducing dietary fat intake may be of value for long-term weight maintenance (274, 275). The study reported that body weight in the low-fat diet group and the control-diet group was similar after an average of 7.5 years of follow-up (274). However, those who maintained the lowest quintile of fat intake were 1.5 kg lighter compared with those in the top quintile of fat intake, who were 0.8 kg heavier after 7 years. A recent comprehensive meta-analysis indicated that long-term effects of low-fat diets on body weight depended on the intensity of intervention in the comparison group. When compared with other dietary interventions of similar intensity, evidence from RCTs does not support low-fat diets over other dietary interventions (232).

The National Weight Control Registry identifies additional strategies for maintaining weight loss (276), which include engaging in higher levels of physical activity (e.g., 225 to 300 min/wk), eating a low-fat, low-calorie diet (1200 to 1300 kcal/d for women), and weighing themselves frequently (once a week or more) (277, 278).

Prediction of weight gain may also be related to the ability to metabolize carbohydrates. Subjects who had

a higher positive carbohydrate balance on day 15, were inactive, and ate an isocaloric high-carbohydrate diet gained less fat mass during a 4-year follow-up period (279).

Future considerations/summary

Diets with many different macronutrient compositions can result in short-term weight loss. However, weight loss reaches a plateau within the first 3 to 6 months. After that, weight is regained and often returns to baseline by 1 to 2 years.

Maintenance of long-term weight loss is strongly influenced by the ability to adhere to the dietary program. Behavioral support can significantly improve outcomes. There are variations among individuals in the response to each diet, which are larger than the difference in mean weight loss between comparison diets. Clinicians should consider genetic differences regarding dietary response to weight loss, as personalized dietary regimens might improve the efficacy of long-term weight-loss regimens.

Current data indicate that some (but not all) individuals can achieve modest long-term weight loss with any one of the diets evaluated herein. Additional research is needed to identify optimal diets for weight control and long-term health, which should extend beyond macronutrient composition and examine food quality and overall dietary patterns, as well as factors that can improve long-term compliance. The Nurses Health Study and Health Professionals Follow-up Study reported that improving diet quality was associated with less weight gain, especially in younger women or individuals who are overweight (280).

Exercise in managing obesity

Introduction

There is a significant body of evidence supporting the effect of physical activity in both short-term and long-term weight loss in adults (216, 218, 254–262).

The main components of energy expenditure (by order of magnitude) are resting energy expenditure, physical activity, and the thermic effect of food. Resting energy expenditure is the amount of energy required for a 24-hour period by the body during resting conditions. Physical activity is composed of both nonexercise activity thermogenesis and thermogenesis due to volitional activity of muscle groups. The thermic effect of food is the amount of energy (above the resting rate) used for processing and storing food.

Energy expenditure from physical activity is directly related to body weight. However, it is unclear to what extent reductions in energy expenditure from physical activity relate to the epidemic of obesity that has developed during the last 30 years. Most measurements of energy expenditure are not precise or

easy to use. Therefore, reliable longitudinal data are lacking.

Two recent studies have concluded that the current epidemic of obesity is more the result of an increase of energy intake than a decrease in energy expenditure (281–283), but this is not the universal opinion (280).

Genetic factors of physical activity

There is an important genetic component associated with the extent to which individuals engage in physical activity (284). In a study examining regular exercise among identical and fraternal twins that included both same and opposite sex pairs, environmental factors shared by children at age 13 accounted for 78% to 84% of sports participation, whereas genetic differences provided almost no contribution. By age 17 to 18 the genetic influences represented 36% of the variance in the level of participation in sports, and by age 18 to 20, genetic factors accounted for almost all (85%) of the differences in participation in sports (284, 285).

Resistance vs aerobic exercise

Although most research on the effects of physical activity on body weight has focused on aerobic types of physical activity, there is also evidence suggesting that resistance exercise may have some effect on weight loss. Resistance exercise may influence body weight by increasing lean body mass, which will result in an increase in resting metabolic rate. Resistance exercise also improves one's strength, which may result in more free-living physical activity and thus increased total daily energy expenditure (286). However, the vast majority of data indicate that resistance exercise only results in minimal reductions in body weight or body fatness (286–288).

Vigorous vs moderate exercise

A study of >4500 adults from the U.S. National Health and Nutrition Examination Survey showed that greater physical activity was associated with a lower BMI (289). This relationship only existed with moderate- to vigorous-intensity physical activity and not with low-intensity physical activity. These data imply that there is an intensity threshold of physical activity that is necessary to affect body weight and prevent excessive weight gain.

Physical activity declines with age

Despite the benefit of physical activity in weight loss, physical activity appears to decline during adolescence and remains low in most adults (290, 291). In a longitudinal study of adolescent girls, the level of activity declined in both black and white girls each year during adolescence. By age 17, black girls engaged in almost no spontaneous physical activity and white girls only engaged in very modest amounts of spontaneous physical activity (292). We do not have a comparable study in adolescent males.

Sedentary behavior

There is keen interest in the influence of sedentary behavior on a variety of health-related outcomes, including overweight and obesity. Energy expenditure in occupational activities has declined by ~140 kcal/d since 1960 in the United States, and this reduction in energy expenditure accounts for a significant portion of the increase in mean U.S. body weights for women and men since 1960 (293).

Much of the early literature in this area focused on the association between television viewing as an indicator of sedentary behavior and the risk of obesity. Television viewing is positively associated with the risk of gaining weight and the development of obesity (294, 295).

Treatment of patients who are overweight or obese using exercise with and without diet

Studies on obesity have evaluated exercise as a sole treatment, in combination with diets, and as a way to maintain weight loss. Östman *et al.* (296) performed a Medline search for studies related to physical exercise and overweight and identified six relevant RCTs. Five had a treatment interval of 12 months, and all had a dropout rate of <40%. Table 5 (296–304) has been adapted from this study with the addition of two newer trials, one 16 months long and one 8 months long. The effects from diet are significantly greater than those from exercise, but increasing physical activity may have important benefits on improving BP and cardiometabolic risk factors.

Behavioral Therapy in Managing Obesity

Behavioral modifications and/or lifestyle interventions have been an important part of weight-loss programs for more than half a century (305–307). Data from two large RCTs, the Look AHEAD trial and the Diabetes Prevention Program, support the efficacy of these approaches. These studies are the gold standard and are notable for the frequency of contact, the emphasis on individualizing therapy, and the long-term emphasis on maintaining weight loss. Fig. 6 shows data from the Look AHEAD trial. The best outcomes are with frequent, face-to-face interventions. However, incorporating this in primary care is challenging.

In a meta-analysis of behavioral weight-loss programs, LeBlanc *et al.* (308) reported a mean weight loss of –3.01 kg (95% CI, –4.02 to –2.01 kg) favoring the behavioral strategy, but the range of mean values was quite large (–0.71 to –8.30 kg).

Lifestyle interventions may also be effective for preventing weight regain (269, 309). Patients who participated in group sessions every other week for 1 year after weight reduction maintained 13 kg of their 13.2 kg end-of-treatment weight loss (309). The most successful patients monitor their weight frequently

and respond quickly to small increases in weight (276). This can be daily or several times a week, but some daily variation (-0.5 to 1.0 kg) is to be expected from fluctuations in body water.

Lifestyle methods

Self-monitoring

Self-monitoring involves recording the type and amount of foods and beverages consumed, along with their calorie content and weight gain. Self-monitoring helps patients identify their eating patterns (including times and places associated with consumption) and also helps patients select targets for reducing calorie intake (310) (Table 6).

Stimulus control

Techniques of stimulus control teach patients to manage external cues, such as the sight or smell of food, as well as times, places, and events associated with eating (278, 310). By decreasing exposure to problem foods, patients are less likely to overeat.

Goal setting

Goal setting helps patients make objective, measurable changes in eating, activity, and related behaviors (278, 310). They are guided in setting specific targets for calorie intake, minutes of physical activity, and frequency of self-monitoring.

Problem solving

Problem solving teaches patients to analyze challenges they have in adhering to their diet and activity prescriptions (278, 310, 311). Patients learn to identify a number of possible solutions to the problem, pick the most promising one, and then implement it. They learn to identify cognitive distortions (e.g., “I will never be able to lose weight because I ate that dessert”) and to replace them with rational responses (e.g., “One hundred fifty calories of cake is not going to hinder my weight loss, particularly if I walk after dinner”) (312). It is important for patients to remember that the 150 calories needs to be “subtracted” in the future either with exercise or by reducing intake of some other carbohydrate/fat-containing foods.

Short-term efficacy

The structured behavioral programs, as described above, produce an average loss of 7 to 10 kg in the first 6 months but with great variability. Some lose no weight; others lose $>10\%$. Seven to 10 kg weight loss is generally equivalent to a reduction of 7% to 10% of initial weight, because 100 kg is the average weight for patients in many studies (38, 307). Patients require a high-intensity intervention to achieve these losses; lower intensity treatment is not as effective (38). Approximately 50% to 70% of patients achieve a $\geq 5\%$

reduction in initial weight, a criterion for clinically meaningful weight loss (38). Individuals with the best attendance and greatest consistency in keeping self-monitoring records achieve the largest weight losses (277).

New developments in the delivery of behavioral treatment

Telephone-delivered programs

Sherwood *et al.* (313) demonstrated that during a 6-month period, patients who received 20 intervention session phone calls lost an average of 4.9 kg; those who received 10 intervention calls lost 3.2 kg, and those who were self-directed lost 2.3 kg. Appel *et al.* (133) reported that a group that received weekly telephone coaching for 3 months, an Internet program for recording food intake and physical activity, and monthly coaching for an additional 18 months lost a mean of 6.1 kg at 6 months. The weight loss was generally well maintained at 24 months (4.6 kg) and was not significantly different than what another group achieved using an intensive in-person intervention (5.1 kg at 24 months) (133).

Perri *et al.* (314) demonstrated that women who were enrolled in extended-care programs that included problem-solving counseling delivered in 26 biweekly sessions via telephone or face-to-face regained only 1.2 kg in 1 year of treatment, vs 3.7 kg for those in a newsletter-only group.

Several studies that used structured dietary interventions (*i.e.*, meal replacements and/or portion-controlled entrees) reported roughly equivalent weight losses when the same behavioral intervention was delivered in person or by telephone (315–317).

Digitally-delivered programs

Tate *et al.* (318) demonstrated that patients who were provided with a directory of Internet resources for weight management and also received 24 weekly lessons over 6 months via e-mail (where patients submitted their food and activity records online and received online feedback from an interventionist) lost 4.1 kg vs patients who only received the directory. In a 1-year follow-up study, Tate *et al.* (318) demonstrated that patients assigned to a low-intensity Internet intervention with the addition of weekly behavioral counseling lost 4.4 kg, whereas those receiving only the low-intensity Internet intervention lost 2.0 kg.

Harvey-Berino *et al.* (319) compared the same 24-session intervention provided either via Internet or on site. In 6 months, the on-site program resulted in 8.0 kg weight loss vs 5.5 kg for the Internet-only group.

These studies underscore the importance of patients keeping records of their food intake and physical activity and receiving feedback from a trained interventionist.

Table 5. Clinical Trials of Exercise in Individuals Who Are Overweight or Obese

Authors	Inclusion Criteria	Intervention Groups	Duration	No. Patients/ No. Follow-up	Results	Comments
Wood <i>et al.</i> , 1988 (297)	Men 120%–160% overweight	(1) Diet (–1 kg/wk); fat reduced by 30%	1 year	(1) 51/42	(1) BW –7.2 kg	TG and HDL cholesterol improved
		(2) Individual instruction (–1 kg/wk); exercise (60%–80% of maximal physical capacity, 40–50 min, three to four times per week)		(2) 52/47	Fat –5.9 kg	Diet and physical activity yield the same reduction in weight and fat at the same negative calorie balance
		(3) Control		(3) 52/42	(2) BW –4.0 kg Fat –4.2 kg (3) BW +0.6 kg Fat –0.3 kg	
Wing <i>et al.</i> , 1988 (298)	Women: 30–60 y with T2DM; >20% above ideal weight	(1) Diet (–1000 kcal/d) + walking (3 miles, three times per week)	12 mo	(1) 12	(1) BW –7.9 kg	HbA1C was reduced and medications were reduced in groups 1 and 2
		(2) Free diet + walking (3 miles, four times per week)		(2) 15	(2) BW –7.9 kg	
		(3) Diet + stretching		(3) 13	(3) BW –3.8 kg	
Wood <i>et al.</i> , 1991 (299)	Men and women: 25–49 y; overweight 120%–160%	(1) Diet (moderate reduction of energy, fat, cholesterol)	Bottom of form	(1) 87/71	Men:	BP decreased in groups 1 and 2 (both men and women)
		(2) Diet (as above) + exercise (60%–80% of maximal physical capacity, 25–45 min, three times per week)		(2) 90/81	(1) BW –5.1 kg	Cholesterol decreased in groups 1 and 2 (women)
		(3) Control		(3) 87/79	(2) BW –8.7 kg	HDL cholesterol increased in group 2 (both men and women)
					(3) BW +1.7 kg	TG decreased in group 2 (men)
					Women:	
					(1) BW –4.2 kg (2) BW –5.5 kg (3) BW +1.3 kg	
Svendsen <i>et al.</i> , 1994 (300)	Women: 49–58 y; BMI 25–42 kg/m ²	(1) Diet (4.2 MJ/d = 1000 kcal/d)	2 wk with 6 mo follow-up	(1) 51/47	12 wk:	TG decreased and
		(2) Diet (as above) + exercise (submaximal aerobics and body building)		(2) 49/47	(1) BW –6.6 kg	HDL cholesterol increased
		(3) Control		(3) 21/16	(2) BW –10.9 kg (3) BW 0.0 kg	There was no effect from physical activity
					6 mo:	
					(1) BW –8.0 kg (2) BW –8.0 kg (3) BW 0.0 kg	

(Continued)

Table 5. Continued

Authors	Inclusion Criteria	Intervention Groups	Duration	No. Patients/ No. Follow-up	Results	Comments
Pritchard <i>et al</i> , 1997 (301)	Men: overweight mean BMI 29 kg/m ²	(1) Diet (−500 kcal/d) + low fat	12 mo	66/60	(1) BW −6.3 kg	Diet was “self-controlled”
		(2) Exercise (65%–75% of maximal physical capacity, 45 min, three to seven times per week)			(2) BW −2.6 kg	
		(3) Control			(3) BW +0.9 kg	
Irwin <i>et al</i> , 2003 (302)	Overweight nonsmoking postmenopausal women age 50–75 y with a BMI > 25 kg/m ² or BMI 24–25 and body fat > 33% by DXA who were sedentary at baseline (<60 min/wk of moderate to vigorous activity) and maximal oxygen uptake of <25 mL/kg/min	(1) Exercise [at least 45 min, moderate intensity, 5 d/wk, 12 mo (months 1–3 they attended three sessions per week; months 4–12 they attended one session per week)]	12 mo	(1) 87/84	(1) 3 mo:	Participants were advised to maintain usual diet
		(2) Stretching (weekly sessions of 45 min for 12 mo)		(2) 86/86	BW −0.5	
					12 mo:	
					BW −1.3 kg	
					Fat −1.4 kg	
					VAT −8.5 cm ²	
					(2) 3 mo:	
					BW 0.0 kg	
					12 mo:	
					BW 0.1 kg	
Donnelly <i>et al</i> , 2003 (303)	Overweight men and women age 17–36 y with a BMI of 25.0–34.9 kg/m ²	(1) Exercise (400 kcal/d, 5 d/wk with walking on a treadmill at 55%–70% of maximal physical capacity uptake)	16 mo of verified exercise	(1) 87/41	(1) Men	Exercise produced weight loss in men and prevented weight gain in women
		(2) Control		(2) 44/33	BW −5.2 kg	
					Fat −4.9 kg	
					VAT −22.4 cm ²	
					Women	
					BW +0.4 kg	
					(1) Fat −0.2 kg	
					VAT −3.2 cm ²	
					(2) Men	
					BW −0.5 kg	
					Fat −0.7 kg	
					VAT −6.3 cm ²	

(Continued)

Table 5. Continued

Authors	Inclusion Criteria	Intervention Groups	Duration	No. Patients/ No. Follow-up	Results	Comments
Slentz <i>et al.</i> , 2004 (304)	Men and women age 40–60 y and BMI of 25–35 kg/m ² and mild to moderate lipid abnormalities	(1) Exercise [high amount/ vigorous intensity, calorically equivalent to ~20 miles (32.0 km) of jogging per week at 65%–80% maximal physical capacity]	8 mo of observed exercise	(1) 44/17	Women	Subjects were counseled not to change diets and encouraged to maintain body weight.
					BW +2.9 kg	
					Fat +2.0 kg	
					VAT +3.1 cm ²	
					(1) BW −3.5 kg	
					(2) 52/24	
					Fat 4.9 kg	
					(3) 42/14	
					Waist −3.4 cm	
					(4) 44/7	
		(2) Exercise [low amount/ vigorous intensity, equivalent to ~12 miles (19.2 km) of jogging per week at 65%–80%]			(2) BW −1.1 kg	
					Fat −2.6 kg	
					Waist −1.4 cm	
					(3) BW −1.3 kg	
					Fat −2.0 kg	
					Waist −1.1 cm	
					(4) BW 1.1 kg	
					Fat 0.5 kg	
					Waist 0.8 cm	
		(3) Exercise [low amount/ moderate intensity, equivalent to ~12 miles (19.2 km) of walking per week at 40%–55%]			(2) BW −1.1 kg	
					Fat −2.6 kg	
					Waist −1.4 cm	
					(3) BW −1.3 kg	
					Fat −2.0 kg	
					Waist −1.1 cm	
					(4) BW 1.1 kg	
					Fat 0.5 kg	
					Waist 0.8 cm	
		(4) Control			(2) BW −1.1 kg	
					Fat −2.6 kg	
					Waist −1.4 cm	
					(3) BW −1.3 kg	
					Fat −2.0 kg	
					Waist −1.1 cm	
					(4) BW 1.1 kg	
					Fat 0.5 kg	
					Waist 0.8 cm	

Abbreviations: BW, body weight; DXA, dual x-ray absorptiometry; TG, triglyceride; VAT, visceral adipose tissue.
Adapted and updated from Östman *et al.*, 2004 (296).

Educational instruction (*i.e.*, information) alone is not sufficient to induce clinically meaningful weight loss.

These studies also suggest that the most successful Internet programs are those in which therapists provide weekly e-mail feedback to patients. However, on-site behavioral programs still provide better results (320).

The reduced efficacy of Internet programs, however, is offset by the potentially greater accessibility and affordability of this approach, compared with traditional behavioral treatment.

Despite their popularity, little is known about the effectiveness of smart-phone applications for weight management. A recent study that compared usual primary care with or without the MyFitnessPal

application revealed essentially no weight-loss difference between the two approaches during 6 months (321).

Medication in Managing Obesity

Early history

Medications for managing obesity have a long and checkered history (322). Treatment in the 18th century included soap (6, 17) and vinegar mixed with a number of purgatives (18). Some treatments also used tobacco, a strategy people still use today to prevent weight gain.

In the late 19th and early to mid-20th century, three major groups of medications came into use: thyroid hormone, dinitrophenol, and amphetamine. Clinicians prescribed both thyroid extract and dinitrophenol (a product of the aniline dye industry) until negative side effects became evident (19).

Amphetamine became popular after 1937 when Nathanson (323) noted that 10 of 40 patients treated with amphetamine for narcolepsy had marked loss of appetite and weight. However, the abuse potential of amphetamines soon became apparent (324), and clinicians stopped prescribing them as a way to manage obesity.

Aminorex, another member of the amphetamine-like group, emerged in Austria and Switzerland in 1968, but it was removed from the market in 1972 due to associated pulmonary hypertension (325). Table 7 lists several drugs for obesity management that were associated with significant detrimental side effects (326).

From the end of World War II through 1994, there was considerable research on monoaminergic drugs. Researchers discovered that injecting norepinephrine into the central nervous system of experimental animals reduced food intake and activated thermogenesis. This resulted in a search for thermogenic drugs that could work through monoaminergic receptors.

During this period, researchers also synthesized many derivatives of amphetamine for treating obesity (327), along with serotonergic drugs and multiple monoamine reuptake inhibitors.

More recent drug development: continuing difficulties

The discovery of leptin in 1994 (20) marks the beginning of modern approaches to identifying drugs for treating obesity. Leptin is a peptide made primarily in adipose tissue. Its absence is associated with massive obesity in animals and human beings. Treatment with leptin reverses the obesity caused by leptin deficiency, indicating that there is a clear-cut molecular-genetic mechanism and a highly effective treatment of at least one type of obesity. However, because leptin failed to show adequate weight loss in obese persons who are not leptin deficient, trials were stopped (328, 329). The discovery of leptin opened a flood of research to discover new treatments, some of which were withdrawn from the market due to health risks (22).

Medications approved by the FDA for treating obesity

In Table 8 (330) we list medications that are FDA approved for weight management in patients with obesity and divide them into two groups. First are the agents approved for long-term treatment of obesity. These include orlistat, lorcaserin, liraglutide, the combination of phentermine/topiramate extended

release (PHEN/TPM ER), and the combination of naltrexone and bupropion sustained release (SR).

The second group consists of older, sympathomimetic drugs that are FDA approved for short-term use, usually considered <12 weeks. The FDA did not use modern standards to evaluate these “short-term” medications for safety and efficacy. The FDA approved them using only data from small, short-term studies, and there are no cardiovascular outcome studies for these agents.

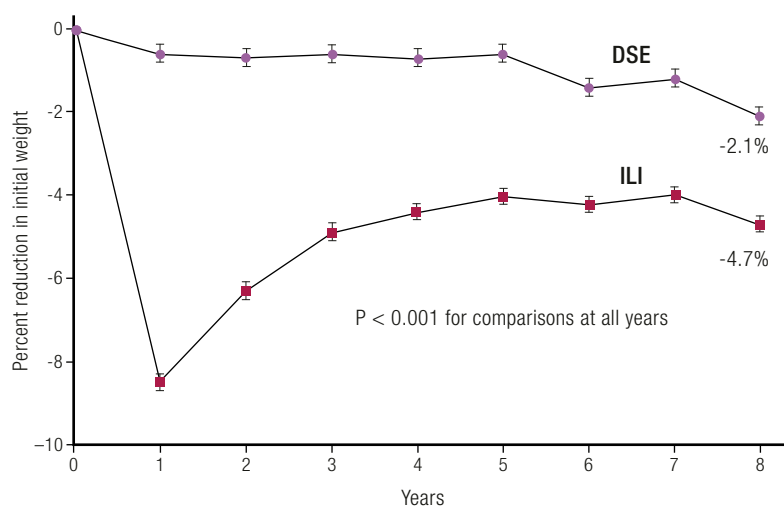
Importantly, note that in all the clinical trials evaluating these agents, the drug-vs-placebo study also included lifestyle interventions, such as diet and/or exercise, which contribute to the overall weight loss reported.

Also important to note, these drugs are all contraindicated for pregnant women, as is weight loss *per se*. Because weight loss can increase fertility, all women in a weight-management program that use medications should be cautioned about the need for contraception. If pregnancy does occur while a patient is taking any of these medications, the patient should immediately stop the medication and contact a medical professional.

Listed below are brief assessments of these drugs' action, efficacy, and safety. More detailed information is in Figs. 7 (331) and 8 and Table 8.

Orlistat

Orlistat is a potent and selective inhibitor of pancreatic lipase that reduces intestinal digestion of fat. One clinical trial resulted in weight loss of 9% of body weight at 1 year, compared with ~5.5% in the placebo



Abbreviations: DSE, diabetes support and education; ILI, intensive lifestyle intervention

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Figure 6. Mean (\pm SE) weight losses during 8 years for participants randomly assigned to an intensive lifestyle intervention or diabetes support and education (usual-care group). Differences between groups were significant ($P < 0.001$) at all years. DSE, diabetes support and education; ILI, intensive lifestyle intervention.

Table 6. Key Components of Comprehensive Behavioral Weight-Loss Interventions to Achieve a 7% to 10% Weight Loss

Component	Weight Loss	Weight-Loss Maintenance
Frequency and duration of treatment contact	<ul style="list-style-type: none"> Weekly contact, in person or by telephone, for 20–26 wk (Internet/e-mail contact yields smaller weight loss) 	<ul style="list-style-type: none"> Every-other-week contact for 52 wk (or longer)
	<ul style="list-style-type: none"> Group or individual contact 	<ul style="list-style-type: none"> (Monthly contact likely adequate)
		<ul style="list-style-type: none"> Group or individual contact
Dietary prescription	<ul style="list-style-type: none"> Low-calorie diet (1200–1500 kcal for those <250 pounds; 1500–1800 kcal for those ≥250 pounds) 	<ul style="list-style-type: none"> Consumption of a hypocaloric diet to maintain reduced body weight
	<ul style="list-style-type: none"> Typical macronutrient composition: ≤30% fat (≤7% saturated fat), 15%–25% protein, remainder from carbohydrate (diet composition based on individual needs or preferences) 	<ul style="list-style-type: none"> Typical macronutrient composition similar to that for weight loss
Physical activity prescription	<ul style="list-style-type: none"> 180 min/wk of moderately vigorous aerobic activity (e.g., brisk walking), strength training also desirable 	<ul style="list-style-type: none"> 200–300 min/wk of moderately vigorous aerobic activity (e.g., brisk walking), strength training also desirable
Behavior therapy prescription	<ul style="list-style-type: none"> Daily monitoring of food intake and physical activity by use of paper or electronic diaries 	<ul style="list-style-type: none"> Occasional to daily monitoring of food intake and physical activity by use of similar diaries
	<ul style="list-style-type: none"> Weekly monitoring of weight 	<ul style="list-style-type: none"> Twice weekly to daily monitoring of weight
	<ul style="list-style-type: none"> Structured curriculum of behavior change (e.g., Diabetes Prevention Program) 	<ul style="list-style-type: none"> Curriculum of behavior change, including relapse prevention and individualized problem solving
	<ul style="list-style-type: none"> Regular feedback from an interventionist 	<ul style="list-style-type: none"> Periodic feedback from an interventionist

group (332) (Fig. 8). Another study achieved a weight loss of 11% compared with 6% in the placebo-treated group and a reduction of 37% in the development of T2DM in patients who had impaired glucose tolerance (333). In a meta-analysis of 31 studies using orlistat (Table 9), the maximal weight loss (by modeling) was −6.65 kg, and half the maximal effect occurred by 35.4 weeks (334).

Orlistat is the only medication the FDA approved for weight management in adolescents with obesity (335). Adherence to orlistat use falls off rapidly after initial prescription (336). Orlistat can cause small but significant decreases in fat-soluble vitamins, and clinicians should advise patients to take vitamin supplements. Rare cases of severe liver injury have been reported with patients taking orlistat. A causal relationship has not been established, but patients who take orlistat should contact their health care provider if itching, jaundice, pale color stools, or anorexia develop (330).

Lorcaserin

Lorcaserin selectively targets the serotonin-2c receptors to reduce food intake (337), but it has low affinity for the serotonin-2b receptors on heart valves.

The three clinical studies that provided the data for lorcaserin's approval reported modest weight loss (see Fig. 8 for one of these trials). In a meta-analysis of five

studies using lorcaserin (Table 9), the maximal weight loss (by modeling) was −5.39 kg, and half the maximal effect occurred by 19.3 weeks (334). They also showed improvements in cardiovascular risk factors (338–341).

In preclinical toxicology studies in rats, there were more brain and mammary tumors. This may reflect the fact that the drug does not reach the high concentrations in the central nervous system of human beings that is does in rats (341).

Liraglutide

Liraglutide is a GLP-1 agonist that has a 97% homology to GLP-1. The molecular change extends the circulating half-life from 1 to 2 minutes to 13 hours. Clinicians prescribe this drug in combination with a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with an initial BMI of >30 kg/m² or in adult patients with a BMI of >27 kg/m² who have T2DM, hypertension, or dyslipidemia.

One study (342) that administered daily subcutaneous injections of liraglutide at 1.2, 1.8, 2.4, or 3.0 mg produced mean weight losses of 3.8, 5.4, 6.1, and 7.8 kg, respectively, after 1 year of treatment, compared with a loss of 2.0 kg in the placebo-treated group and 3.9 kg in the orlistat-treated comparator group. Another larger trial reported that after 56 weeks, liraglutide reduced body weight by 8.4 kg

compared with 2.8 kg in the placebo-treated group (on average) (343) (see Fig. 8). In another trial (344), those receiving liraglutide for weight maintenance (after initially losing weight from a low-calorie diet) lost an additional 6.8 kg compared with no additional weight loss in the placebo group. Furthermore, only about half of the placebo group was able to maintain the weight they lost due to diet. In a meta-analysis of three studies using liraglutide (Table 9), the maximal weight loss (by modeling) was -7.68 kg, and half the maximal effect occurred by 12.7 weeks (334).

Liraglutide is contraindicated in people with a family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2. Clinicians should not prescribe liraglutide for patients with a history of pancreatitis and should discontinue liraglutide if acute pancreatitis develops. If weight loss does not exceed 4% by 16 weeks, patients should stop taking liraglutide. Two cardiovascular outcome trials studied liraglutide (1.8 mg/d) (345) and the long-acting version, semaglutide (0.5 or 1.0 mg weekly) (346). In patients with T2DM, liraglutide lowered the rate of the first occurrence of death from cardiovascular causes,

nonfatal myocardial infarction, or nonfatal stroke (345). Semaglutide lowered the rate of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke (346).

PHEN/TPM ER

PHEN/TPM ER has lower doses of phentermine than clinicians usually prescribe for phentermine alone. Phentermine acts to reduce appetite through increasing norepinephrine in the hypothalamus. Topiramate may reduce appetite through its effect on GABA receptors.

Two clinical studies (347, 348) provided the efficacy and safety data for the approval of PHEN/TPM ER (341) (see Fig. 8 for one of these trials). The patients in these two studies had higher risk profiles due to excess weight. PHEN/TPM ER produced weight losses of 9.3% and 10.7% with the middle and high doses, respectively, compared with 2.2% in the placebo group. This weight loss is larger than observed in clinical trials with single drugs (349). In a meta-analysis of six studies using phentermine/topiramate (Table 9), the maximal weight loss (by modeling) was 15.6 kg, and

Table 7. Some Medications Used in the Past for Managing Body Weight That Were Withdrawn or Are Not Approved in the United States

Drug	Year Introduced or Withdrawn	Comments
Thyroid	1892	Mimics endogenous thyroxine/triiodothyronine Associated with tachycardia and increase in metabolic rate
Dinitrophenol	1932	Uncouples oxidative phosphorylation Associated with cataracts, neuropathy, and death
Amphetamine	1937	Noradrenergic-dopaminergic drug Associated with recreational abuse and pulmonary hypertension
Aminorex	1965	Noradrenergic drug Associated with pulmonary hypertension
Fenfluramine, dexfenfluramine	1997	Serotonergic drugs Both associated with cardiac valvulopathy and primary pulmonary hypertension
Phenylpropanolamine	1998	Noradrenergic agonist Associated with strokes and cardiovascular deaths
Ephedra alkaloids	2003	Noradrenergic drugs Associated with heart attacks, strokes, and death
Rimonabant	2008	Cannabinoid receptor antagonist Associated with depression and suicidality
Sibutramine	2010	Norepinephrine-serotonin reuptake inhibitor Associated with elevated BP and death

half the maximal effect occurred by 29.8 weeks (some of which was related to the titration schedule) (334).

Improvements in BP, glycemic measures, HDL cholesterol, and triglycerides occurred with both the recommended and the top doses of the medication in these trials (347, 348). Improvements in risk factors were related to the amount of weight loss. In patients with OSA, this combination reduced the severity of symptoms (349).

Taking topiramate in the first trimester of pregnancy may increase risk of cleft lip/cleft palate in infants. Therefore, clinicians must inform women of childbearing potential of this risk and conduct a pregnancy test before prescribing PHEN/TPM ER. Glaucoma is a rare side effect of topiramate, and the drug is contraindicated in glaucoma. PHEN/TPM ER is also contraindicated in hyperthyroidism within

14 days of treatment with monoamine oxidase inhibitors and in patients with hypersensitivity to any of the ingredients in the medication. Topiramate is a carbonic anhydrase inhibitor that often produces tingling in the fingers and may change the taste for carbonated beverages. Other potential issues include risk of kidney stones (associated with topiramate) and increased heart rate in patients susceptible to phentermine.

Naltrexone/bupropion combination

Bupropion is approved as a single agent for depression and for smoking cessation. It reduces food intake by acting on adrenergic and dopaminergic receptors in the hypothalamus. It has a modest effect on weight loss. Bupropion stimulates the pro-opiomelanocortin neurons in the hypothalamus to produce pro-opiomelanocortin, which is further processed to

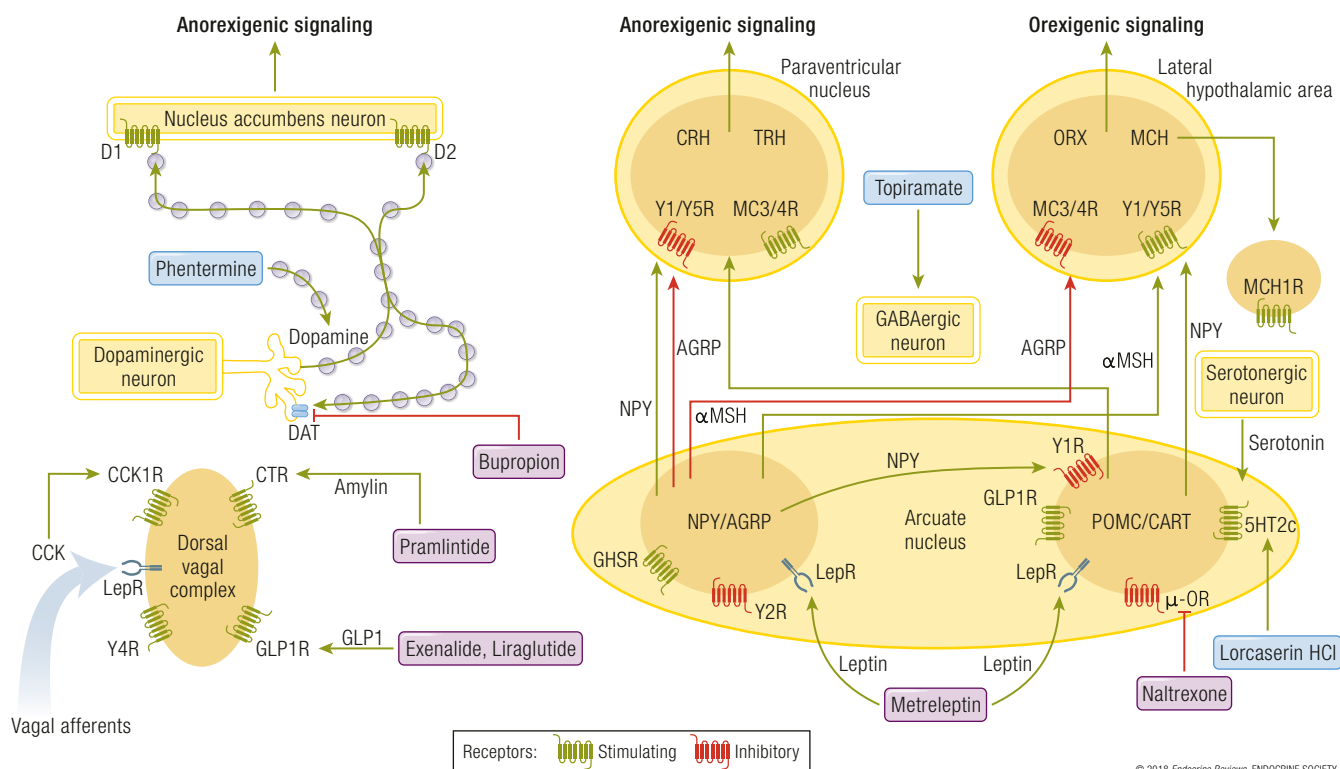
Table 8. Drugs Approved by the FDA for Managing Patients With Obesity

Generic Name (Year of Approval)	Trade Name(s)	Dosage	DEA Schedule
Pancreatic lipase inhibitors FDA approved for long-term use			
Orlistat (1999)	Xenical	120 mg, three times daily before meals	Not scheduled
Orlistat (2007)	Alli (over-the-counter)	60 mg three times daily before meals	Not scheduled
Serotonin-2C receptor agonists FDA approved for long-term use			
Lorcaserin (2012)	Belviq	10 mg, two times daily or 20 mg/d	IV
Glucagon-like peptide-1 agonists FDA approved for long-term use			
Liraglutide (2015)	Saxenda	3 mg/d; begin at 0.6 mg/d for week 1 and increase by 0.6 mg/d each week to reach 3 mg/d at week 4	Not scheduled
Combination drugs FDA approved for long-term use			
PHEN/TPM ER (2012)	Qsymia	3.75 mg/23 mg	IV
		7.5 mg/46 mg	
		11.25 mg/69 mg	
		15 mg/92 mg	
Naltrexone SR/bupropion SR (2014)	Contrave	8 mg/32 mg tablets: one in AM for week 1, one in AM and one in PM for week 2, two in AM and one in PM for week 3, two in AM and two in PM for week 4	Not scheduled
Noradrenergic drugs FDA approved for short-term use			
Diethylpropion (1959)	Tenuate	25 mg, three times daily	IV
	Tenuate dospan	75 mg, every morning	
Phentermine (1959)	Adipex and many others	15–30 mg/d	IV
Benzphetamine (1960)	Didrex	25–50 mg, three times daily	III
Phendimetrazine (1959)	Bontril	17.5–70 mg, three times daily	III
	Prelu-2	105 mg/d	

Abbreviation: DEA, Drug Enforcement Agency.

See Bray and Ryan, 2012 (330).

Figure 7. Diagram of the sites within the central nervous system where medications can have their effects. See Apovian *et al.*, 2015 (331).



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produce both α -melanocyte stimulating hormone (which reduces food intake) and β -endorphin (which stimulates feeding). Naltrexone blocks this effect of β -endorphin, thus allowing the inhibitory effects of α -melanocyte stimulating hormone to reduce food intake by acting on the melanocortin-4 receptor system (350).

Three studies of the combination drug naltrexone/bupropion provided the basis for its approval.

In one study (351), weight loss at 56 weeks was 5.0% for a lower dose of naltrexone/bupropion (16 mg per day/360 mg per day) and 6.1% for a higher dose (32 mg per day/360 mg per day), compared with placebo. Treatment also improved waist circumference, fasting glucose, fasting insulin, homeostasis assessment model of insulin resistance (HOMA-IR), and HDL cholesterol, but there was a transient increase in BP.

In a second study that included an intensive behavioral modification program (352), weight loss at 56 weeks was about 9% for naltrexone/bupropion (32 mg per day/360 mg per day) vs about 1.8% (Fig. 8) for placebo. The study also reported significant improvements in weight, waist circumference, insulin, homeostatic model assessment of insulin resistance, HDL cholesterol, triglycerides, and quality of life.

In a third study, weight loss at week 56 was 6.4% with naltrexone/bupropion (32 mg per day/360 mg per day) compared with 1.2% with placebo (353). As in the other studies, there were improvements in

cardiometabolic risk markers, weight-related quality of life, and control of eating.

Finally, naltrexone/bupropion use in patients with T2DM resulted in significantly greater weight reduction (5.0% vs 1.8% in the placebo group) and significantly greater reductions in HbA1c (-0.6 vs -0.1% ; $P < 0.001$) (354). There was also improvement in triglycerides and HDL cholesterol compared with placebo.

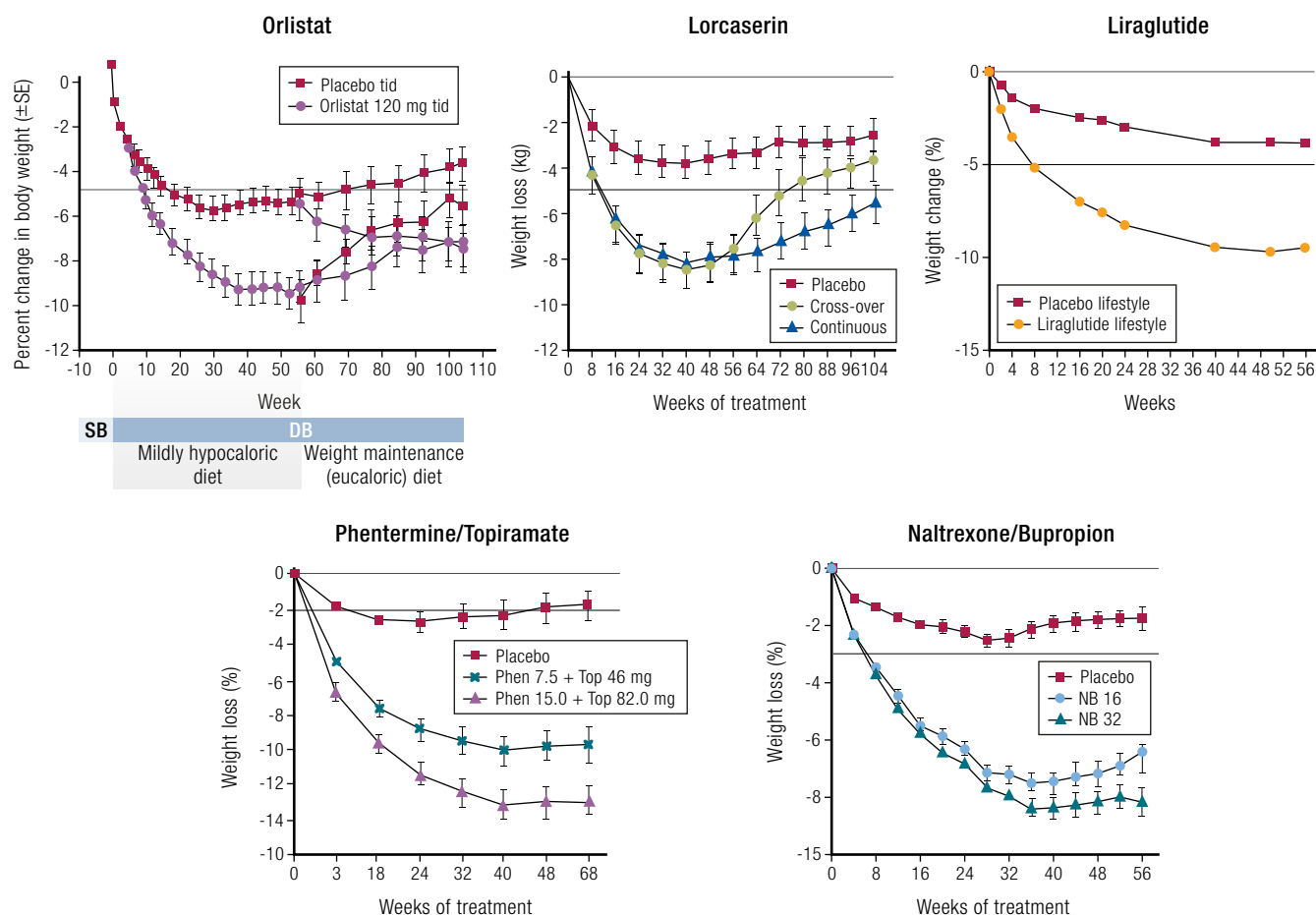
Efficacy of weight loss with the naltrexone/bupropion combination at 1 year is higher than lorcaserin but not as high as PHEN/TPM ER and is associated with improvements in risk factors (350, 351, 355). In a meta-analysis of six studies using naltrexone/bupropion (Table 9), the maximal weight loss (by modeling) was -13.2 kg, and half the maximal effect occurred by 35.2 weeks (probably related to the titration schedule) (334).

Because bupropion increases pulse and both bupropion and naltrexone increase BP, an ongoing study is examining cardiovascular outcomes (345).

Comparison of medications approved for chronic weight management

There are no head-to-head comparisons of these medications. However, there is an analysis of 28 RCTs of weight-loss medications that included trials with orlistat, lorcaserin, liraglutide, naltrexone/bupropion, and PHEN/TPM ER. The inclusion criteria and

Figure 8. Randomized controlled trial data showing weight loss with orlistat, lorcaserin, liraglutide, phentermine/topiramate, and naltrexone/bupropion. NB, naltrexone/bupropion; Phen, phentermine; SE, standard error; SR, sustained release; tid, three times a day; Top, topiramate.



Abbreviations: NB, naltrexone/bupropion; Phen, phentermine; SE, standard error; SR, sustained release; tid, three times a day; Top, topiramate

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background lifestyle interventions differed across studies, so we must interpret results with caution.

Attrition rates were 30% to 45% across these trials. All five agents were associated with significantly greater weight loss at 1 year than placebo. Collectively, these studies reported a weight loss of >5% in 23% of patients treated with placebo, 44% of patients treated with orlistat, 49% of patients treated with lorcaserin, 55% of patients treated with naltrexone/bupropion SR, 63% of patients treated with liraglutide, and 75% of patients treated with PHEN/TPM ER. The highest odds ratio for treatment-related discontinuation of the trial was with liraglutide and naltrexone/bupropion (356).

Drugs approved by the FDA for short-term treatment of patients with obesity

We group the sympathomimetic drugs benzphetamine, diethylpropion, phendimetrazine, and phentermine together, because they are noradrenergic

drugs that the FDA tested and approved before 1973. The U.S. Drug Enforcement Agency classifies phentermine and diethylpropion as schedule IV drugs and benzphetamine and phendimetrazine as schedule III drugs. This regulatory classification indicates the government's idea that these drugs have the potential for abuse, although this potential appears to be low (322). These drugs are approved for only a "few weeks" (usually 12 weeks).

Phentermine

Efficacy of phentermine. The FDA approved phentermine as a single agent in 1959, and it remains the most commonly prescribed drug for weight loss in the United States (350). There are few current data to evaluate its long-term efficacy.

A 6-month study of phentermine reported that 15 mg/d resulted in 4.6% weight loss at 6 months compared with 2.1% for placebo (341). In another

6-month study of phentermine, weight loss was 5.5% for phentermine at 7.5 mg/d and 6.1% for phentermine at 15 mg/d compared with 1.7% for the placebo group (357). Finally, a study from Korea (358) reported that after 12 weeks, mean weight loss for phentermine was 8.1 ± 3.9 kg vs 1.7 ± 2.9 kg for placebo patients. Weight loss with phentermine may not be greatly enhanced by increasing doses beyond 15 mg (353).

Safety of phentermine. Phentermine is part of a group of drugs called sympathomimetic drugs. These drugs produce central excitation, manifested as dry mouth, insomnia, or nervousness. This effect is most obvious shortly after the drug is started and wanes substantially with continued use. Sympathomimetic drugs may also increase heart rate and BP. The prescribing information usually recommends that the drugs not be given to individuals with a history of CVD (358–360).

Lacking good quantitative measures of the effects of sympathomimetic drugs on heart rate and pulse, we recommend caution in prescribing drugs in this group. According to the Endocrine Society Guidelines (331), clinicians should not prescribe sympathomimetic drugs to persons with a history of CVD and elevated BP.

Best practices for medications approved for weight management

The 2013 American Heart Association/American College of Cardiology/The Obesity Society “guideline for the management of overweight and obesity in adults” (39) and the 2015 Endocrine Society clinical practice guideline on obesity pharmacotherapy (331) both agree that clinicians may consider prescribing weight-reducing drug therapies for patients who: (1) struggle to achieve weight goals, (2) meet label indications ($\text{BMI} > 30 \text{ kg/m}^2$ or $\text{BMI} > 27 \text{ kg/m}^2$ with comorbidity), and (3) need to lose weight for health reasons (such as osteoarthritis, prediabetes, fatty liver, or other conditions). Furthermore, the American Association of Clinical

Endocrinologists/American College of Endocrinology “comprehensive clinical practice guidelines for medical care of patients with obesity” from 2016 (60) indicate that clinicians may consider pharmacotherapy as a first-line treatment of weight reduction if patients present with one or more severe comorbidities and would benefit from weight loss of $\geq 10\%$. Those guidelines do not require that patients fail lifestyle therapy before clinicians prescribe medications.

Medicating the patient for other chronic conditions who is also overweight or obese

For patients who are overweight or obese, the 2015 Endocrine Society clinical practice guidelines on obesity pharmacotherapy (331) recommended that providers consider body weight when prescribing medications for other chronic health conditions, so that at-risk patients can avoid medications that promote weight gain. The guideline recommends that patients use medications that are weight neutral or associated with weight loss.

In managing patients with obesity, the guideline also advises that providers review medications at every visit and discuss weight effects with patients, so that patients at risk for weight gain can share in the decision process when choosing medications. Additionally, the guideline cautions against prescribing medications known to be associated with weight loss if they have no proven beneficial effect on the patient’s other identified health issues (331).

What is the current status of clinical adoption of medications for chronic weight management?

According to the Awareness, Care and Treatment in Obesity Management study (345), there are a number of misconceptions regarding obesity shared by providers and patients alike, specifically that obesity is not a disease, that patients have the primary responsibility for their problem and for its treatment, that prevention is more important than treatment, and that the risks of treatment should be low.

Table 9. Weight Loss Associated With Use of Orlistat, Lorcaserin, Liraglutide, Topiramate/Phentermine, and Naltrexone/Bupropion

Drug/Placebo	No. of Trials	Maximal Weight Loss (kg)	Weeks to Half Maximal Weight Loss (wk)	Drop Rate (%)
Orlistat	31	−6.65	35.4	29.0
Lorcaserin	5	−5.39	19.3	40.9
Liraglutide	3	−7.68	12.7	24.3
Topiramate/phentermine	6	−15.6	29.8	34.9
Naltrexone/bupropion	6	−13.2	35.2	49.1
Placebo	51	−2.71	12.3	

Maximal weight loss is the modeled maximal effect and does not contain the placebo effect.
Data are from Dong *et al.*, 2017 (334).

Table 10. Complementary and Over-the-Counter Products Used for Weight Loss

Ingredient	Proposed Mechanism of Action	Evidence of Efficacy	Safety Concerns
Chromium	Increases lean muscle mass; promotes fat loss; and reduces food intake, hunger levels, and fat cravings	Several clinical trials of varying methodological quality	No safety concerns reported at recommended intakes (25–45 µg/d for adults)
		Research findings: minimal effect on body weight and body fat	Reported adverse effects: headache, watery stools, constipation, weakness, vertigo, nausea, vomiting, and urticaria (hives)
β -Hydroxy β -methylbutyrate	Metabolite of leucine, produced in 0.3 g/d, but taken in doses of 30–60 g/d	Used in conditions of muscle wasting and to augment muscle in athletes	In humans, no reported adverse in young adults or older adults when β -Hydroxy β -methylbutyrate is taken in doses of 3 g/d for up to 1 y
		β -Hydroxy β -methylbutyrate supplementation can preserve lean muscle mass in older adults (according to a 2015 meta-analysis)	
Pyruvate	Increases lipolysis and energy expenditure	Few clinical trials of weak methodological quality	Few safety concerns reported
		Research findings: possible minimal effect on body weight and body fat	Reported adverse effects: diarrhea, gas, bloating, and (possibly) decreased HDL levels
Conjugated linoleic acid	Promotes apoptosis in adipose tissue	Several clinical trials	Few safety concerns reported
		Research findings: minimal effect on body weight and body fat	Reported adverse effects: abdominal discomfort and pain, constipation, diarrhea, loose stools, dyspepsia, and (possibly) adverse effects on blood lipid profiles
Calcium	Increases lipolysis and fat accumulation, decreases fat absorption	Several large clinical trials	No safety concerns reported at recommended intakes (1000–1200 mg/d for adults)
		Research findings: no effect on body weight, weight loss, or prevention of weight gain based on clinical trials	Reported adverse effects: constipation, kidney stones, and interference with zinc and iron absorption at intakes >2000–2500 mg for adults
Green tea (<i>Camellia sinensis</i>) and green tea extract	Increases energy expenditure and fat oxidation	Several clinical trials of good methodological quality studied green tea catechins with and without caffeine	No safety concerns reported when used as a beverage
	Reduces lipogenesis and fat absorption	Research findings: possible modest effect on body weight	Contains caffeine
			Some safety concerns reported for green tea extract Reported adverse effects (for green tea extract): constipation, abdominal discomfort, nausea, increased BP, liver damage
Green coffee bean extract (<i>Coffea arabica</i> , <i>Coffea canephora</i> , <i>Coffea robusta</i>)	Inhibits fat accumulation	Few clinical trials, all of poor methodological quality	Few safety concerns reported but not rigorously studied
	Modulates glucose metabolism	Research findings: possible modest effect on body weight	Contains caffeine
			Reported adverse effects: headache and urinary tract infections

(Continued)

Table 10. Continued

Ingredient	Proposed Mechanism of Action	Evidence of Efficacy	Safety Concerns
Caffeine (as added caffeine or from guarana, kola nut, yerba mate, or other herbs)	Stimulates central nervous system	Short-term clinical trials of combination products	Safety concerns not usually reported at doses <400 mg/d for adults, significant safety concerns at higher doses
	Increases thermogenesis and fat oxidation	Research findings: possible modest effect on body weight or decreased weight gain over time	Reported adverse effects: nervousness, jitteriness, vomiting, and tachycardia
Forskolin (<i>Plectranthus barbatus</i>)	Activates the enzyme adenylyl cyclase	One clinical trial	Forskolin should be used with caution or avoided altogether in women who are pregnant
	Increases intracellular levels of cyclic adenosine monophosphate	Research findings: oral ingestion of forskolin (250 mg of 10% forskolin extract twice a day) for a 12-wk period was shown to favorably alter body composition while concurrently increasing bone mass and serum free testosterone levels in overweight and obese men	
Fucoxanthin	Increases energy expenditure and fatty acid oxidation	Studied only in combination with pomegranate seed oil in one trial in humans	No safety concerns reported but not rigorously studied
	Suppresses adipocyte differentiation and lipid accumulation	Research findings: insufficient research to draw firm conclusions	Reported adverse effects: none known
Hydroxycitric acid (<i>Garcinia cambogia</i>)	Inhibits lipogenesis	Several short-term clinical trials of varying methodological quality	Few safety concerns reported
	Suppresses food intake	Research findings: little to no effect on body weight	Reported adverse effects: headache, nausea, upper respiratory tract symptoms, and gastrointestinal symptoms
Yohimbe (<i>Pausinystalia yohimbe</i> , yohimbine)	Has hyperadrenergic effects	Very little research on yohimbe for weight loss	Significant safety concerns reported
		Research findings: no effect on body weight; insufficient research to draw firm conclusions	Reported adverse effects: headache, anxiety, agitation, hypertension, and tachycardia
Hoodia (<i>Hoodia gordonii</i>)	Suppresses appetite	Very little published research in humans	Some safety concerns reported, increases heart rate and BP
	Reduces food intake	Research findings: no effect on energy intake or body weight based on results from one study	Reported adverse effects: headache, dizziness, nausea, and vomiting
Raspberry ketone	Alters lipid metabolism	Studied only in combination with other ingredients	No safety concerns reported but not rigorously studied
		Research findings: insufficient research to draw firm conclusions	Reported adverse effects: none known
Guar gum	Acts as bulking agent in gut, delays gastric emptying	Several clinical trials of good methodological quality	Few safety concerns reported with currently available formulations
	Increases feelings of satiety	Research findings: no effect on body weight	Reported adverse effects: abdominal pain, flatulence, diarrhea, nausea, and cramps
Bitter orange (synephrine)	Increases energy expenditure and lipolysis	Small clinical trials of poor methodological quality	Some safety concerns reported
	Acts as a mild appetite suppressant	Research findings: possible effect on resting metabolic rate and energy expenditure; inconclusive effects on weight loss	Reported adverse effects: chest pain, anxiety, and increased BP and heart rate

(Continued)

Table 10. Continued

Ingredient	Proposed Mechanism of Action	Evidence of Efficacy	Safety Concerns
Chitosan	Binds dietary fat in the digestive tract	Small clinical trials, mostly of poor methodological quality	Few safety concerns reported, could cause allergic reactions
		Research findings: minimal effect on body weight	Reported adverse effects: flatulence, bloating, constipation, indigestion, nausea, and heartburn
Glucomannan	Increases feelings of satiety and fullness	Several clinical trials of varying methodological quality, mostly focused on effects on lipid and blood glucose levels	Significant safety concerns reported with tablet forms, which might cause esophageal obstructions, but few safety concerns with other forms
		Research findings: little to no effect on body weight	Reported adverse effects: loose stools, flatulence, diarrhea, constipation, and abdominal discomfort
White kidney bean (<i>Phaseolus vulgaris</i>)	Interferes with breakdown and absorption of carbohydrates by acting as a “starch blocker”	Several clinical trials of varying methodological quality	Few safety concerns reported
		Research findings: possible modest effect on body weight and body fat	Reported adverse effects: headache, soft stools, flatulence, and constipation

See National Institutes of Health, Office of Dietary Supplements, 2015 (365).

At present, the FDA has approved nine agents (five for long-term use and four for short-term use). For newer drugs, the time since approval of these medications is too short to know whether and how they will be used. However, older data (which predate the current medication landscape) indicate there are some serious concerns about how diet medications are used, such as: patients using prescription weight-loss pills who do not meet the BMI criterion for these medications; family, friends, and other nonphysicians providing medications; the use of nonprescription diet products; using pills after they were withdrawn from the market; low 1-year persistent use rates; and co-using narcotic and antidepressants (35, 336, 361, 362).

Dietary supplements, over-the-counter products, and other treatments with unproven efficacy and unknown safety

The Dietary Supplement Health Education Act of 1994 provided the framework for an expansion in the use of non-FDA-approved, over-the-counter products in the United States billed as “dietary supplements.” As a result, there has been a proliferation in the use of these products.

This legislation helped undercut the credibility of legitimate weight-management practices by allowing the promotion of agents that are often unsafe, ineffective, and have unproven health claims. As long as the claim is not for disease treatment *per se*, and products are generally recognized as safe, they can be promoted for health claims. These agents are regulated by the U.S. Federal Trade Commission but not by the FDA, and thus they do not undergo the rigorous testing and review exercised by the FDA when it

approves pharmaceutical preparations for patients who are overweight or obese.

Blanck *et al.* (363) reported that 15.2% of adults (20.6% of women and 9.7% of men) have used a weight-loss supplement, and 8.7% have used one in the past year (11.3% of women and 6.0% of men). Almost 10% (10.2%) used them for ≥ 12 months.

Pillitteri *et al.* (364) reported that females, the young, the less educated, and those with lower incomes are more likely to use these products. Many respondents thought that dietary supplements are safer than prescription drugs, and many overestimated the degree of regulatory screening of these products.

Clinicians should be aware and knowledgeable about these products when they begin discussing weight management with patients, since patients have likely taken them or may currently be taking them. Table 10 (365) provides a list of herbal and complementary medications and treatments that claim to improve weight loss. Evidence to support the effectiveness for weight loss or the safety of these preparations is usually nonexistent. Moreover, variability in the composition of these products adds an additional uncertainty to their use. We thus think that the public would be better served if the dietary supplements were held to a higher standard and were overseen by the FDA.

Drug targets

Effective drugs to treat obesity have been slow to arise, but efforts are still underway to develop novel, effective, and transformative medications that would have the effect on treating obesity that statins had for high cholesterol or thiazides had for hypertension (366).

Surgery in Managing Obesity

Introduction

Surgical strategies (including the use of medical devices) for the purpose of inducing and maintaining clinically significant weight loss have emerged and evolved during the last 50 years. Surgeons performed ~196,000 bariatric procedures in 2015 in the United States.

Sleeve gastrectomy (SG) is the most common procedure (53.8%), followed by Roux-en-Y gastric bypass (RYGB), 23.1%; laparoscopic adjustable gastric banding (LAGB), 5.7%; biliopancreatic diversion with or without duodenal switch, 0.6%; and revision and others, 16.8% (367). SG and RYGB together are the most popular procedures (77%), whereas LAGB has become less popular due to poor long-term results. We list the three most common surgical procedures in Fig. 9 (368).

Evidence now indicates that that some of these bariatric procedures (which were intended to either physically limit the ingestion of food or produce malabsorption of energy-containing nutrients) actually produce durable weight loss and health benefits by altering metabolic processes, reducing appetite, and inducing satiety early after meal ingestion.

Sleeve gastrectomy

In SG, surgeons use a linear cutting stapler to make a narrow gastric tube along the lesser curvature of the stomach and remove the remaining 75% to 80% of the gastric body and fundus (369, 370).

The lack of gastrojejunal anastomosis has theoretic benefits, such as reducing the risk of micronutrient deficiencies and peptic ulcer disease. Although some restriction of food intake may occur, gastric emptying is accelerated.

Roux-en-Y gastric bypass

RYGB refers to procedures in which a small (~30 to 60 mL) gastric pouch is created just distal to the gastroesophageal junction with a stapling device. Most of the stomach is therefore disconnected (but not excised) from the alimentary stream.

The small gastric pouch is the restrictive component of this procedure. RYGB permits ingested food to pass directly from the esophagus through the small stomach pouch and proceed directly into the jejunum, with little or no gastric or duodenal phase of digestion, because food never enters the body of the stomach or the duodenum.

RYGB became a predominant weight-loss procedure in the 1990s and is used worldwide today. The development and demonstration of the safety and efficacy of minimally invasive (laparoscopic) techniques, the recognition of severe obesity as a disease, and the health benefits of bariatric surgery have led to a progressive increase in the number of gastric bypass procedures performed (143, 160, 371, 372).

Laparoscopic adjustable gastric banding

LAGB constricts the upper stomach by placing a mechanical device encircling the stomach just

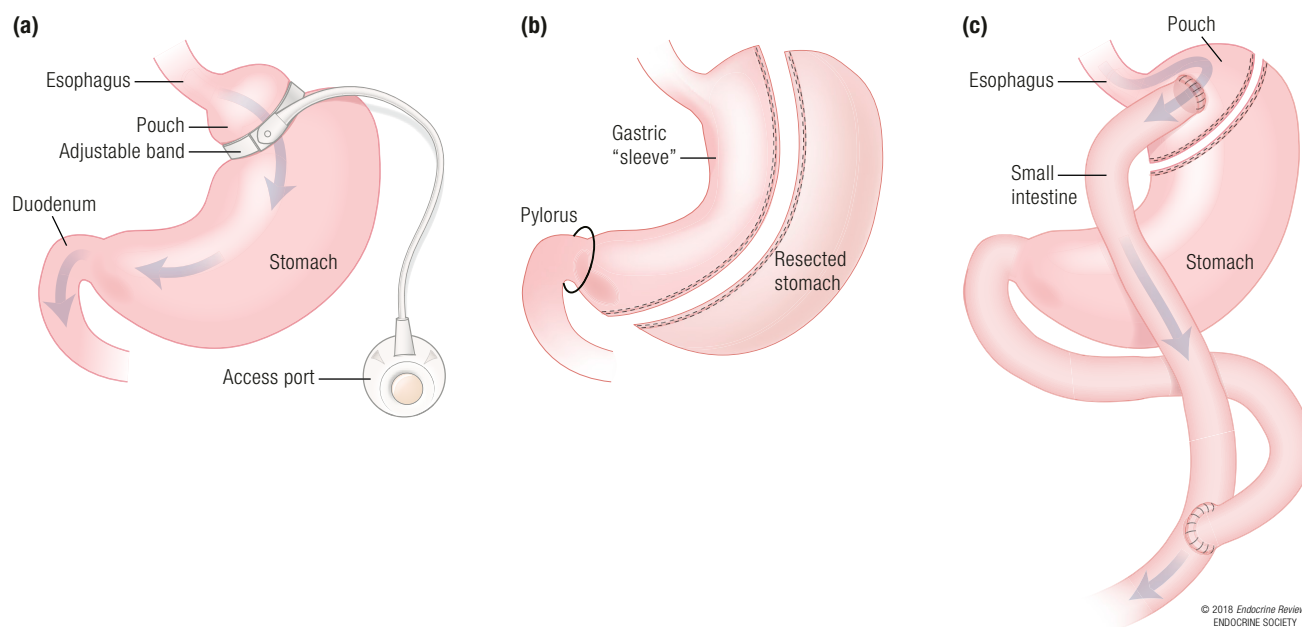


Figure 9. The three most commonly performed bariatric surgical operations. (a) The laparoscopic gastric band is placed around the upper stomach to restrict the transit of ingested food. (b) Laparoscopic sleeve gastrectomy involves separation of the greater curvature from the omentum and splenic attachments. (c) RYGB involves the rearrangement of the alimentary canal, such that ingested food bypasses most of the stomach, all of the duodenum, and a portion of the proximal jejunum. See Nielsen *et al.*, 2014 (368).

beyond the gastroesophageal junction, thus creating a small (30 to 60 mL) pouch. The tightness of the band is adjusted by inflating a linear balloon fixed within the wall of the band. The balloon is connected to a subcutaneous port, so clinicians can tighten the band via a relatively simple percutaneous injection procedure. The band is intended to reduce the amount of food consumed (373).

Biliopancreatic diversion with (or without) duodenal switch

Biliopancreatic diversion with or without duodenal switch is a complex procedure in which ~80% of the body of the stomach is resected, creating a tubular stomach (SG) based on the lesser curvature of the

stomach. An anastomosis between the proximal duodenum and bypassed intestine creates a degree of malabsorption of nutrients. This procedure is infrequently performed because of a relatively high incidence of short-term and long-term complications, including micronutrient deficiencies (369).

Vagal blockade

In this procedure, leads are placed about the vagal trunks at the diaphragm to produce intermittent vagal blockade. Weight loss occurs by reducing appetite and inducing early satiety. The intermittent blockade is designed to avoid the neural adaptation that occurred with truncal vagotomy for peptic ulcer disease. Weight loss, although modest, is superior to sham-treated controls yet less successful than conventional surgical procedures, such as SG and gastric bypass (374). Despite a better safety profile than adjustable banding, intermittent vagal blockade has limited efficacy. This coupled with adverse events make it a less desirable intervention for resolving obesity and associated comorbidities (375).

Gastrointestinal endoscopic interventions or devices

Several devices, placed either by gastrointestinal endoscopy or suturing procedures, have become available. The FDA approved two gastric balloons in 2015 and another in 2016. Clinicians can fill the Orbera intragastric balloon system with 400 to 700 mL of saline. The ReShape integrated dual balloon system contains two connected, saline-filled balloons. In 2016 the FDA approved the Obalon balloon system, which expands with air after insertion. Technical improvements to these devices have resulted in a favorable safety profile (376). The present protocol requires removal of the intragastric balloon 3 to 6 months after placement, which is a limitation to the long-term efficacy of this intervention. The balloon can be replaced for those who regain weight (377). In August 2017, the FDA sent a letter to health care providers noting seven deaths associated with liquid-filled intragastric balloon systems used to treat obesity. Four of the reports involved the Orbera intragastric balloon system and one with the ReShape integrated dual balloon system. Two earlier deaths were also noted.

Researchers have also developed a specially designed percutaneous gastrostomy tube and apparatus, called the AspireAssist device, that allows patients to directly remove ingested food from the stomach (378). After 1 year with this device, patients lost 12.1% compared with 3.6% in the control group. This aspiration technique requires available facilities to discard the aspirated food and is not for everyone.

Additionally, endoscopic placement of a duodenal-jejunal luminal sleeve is under evaluation (379). In

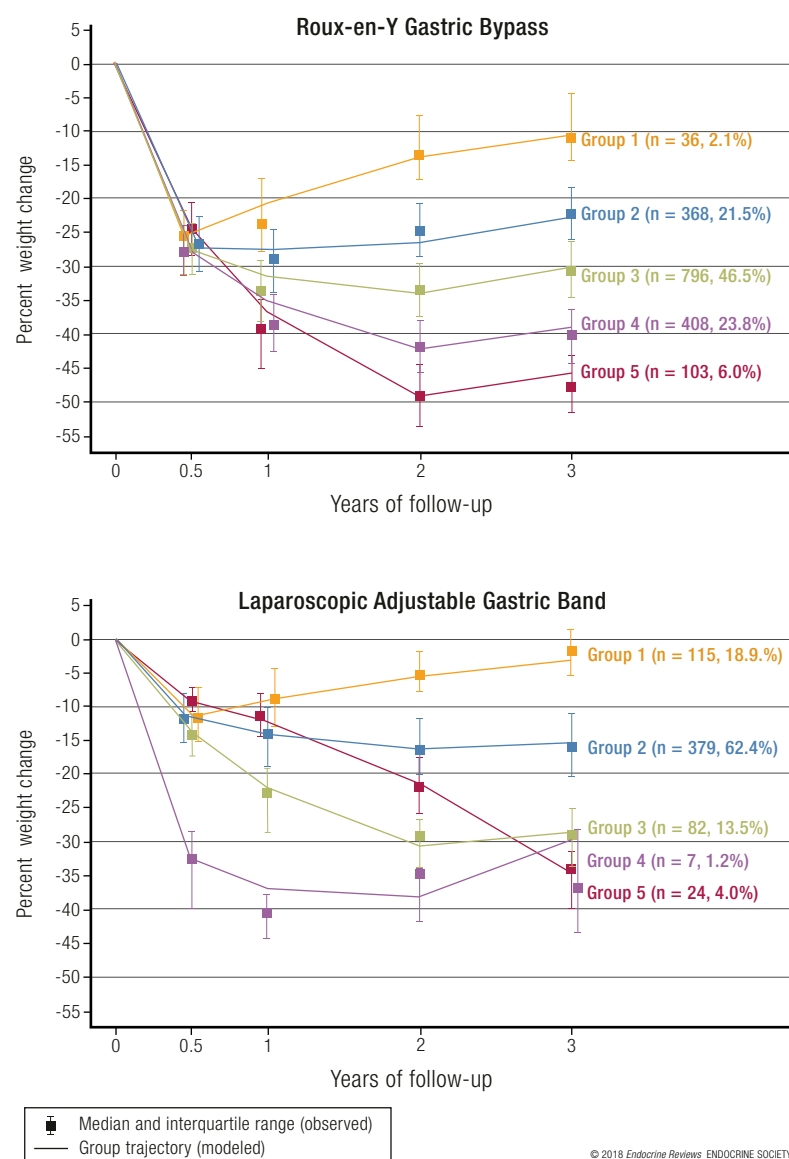


Figure 10. (a) Percentage weight trajectories. See Courcoulas *et al.*, 2013 (383). (b) Percentage of participants in the intensive lifestyle intervention and diabetes support and education groups who achieved different categorical weight losses at year 8. See Look AHEAD Research Group, 2014 (271).

a study that examined endoscopic ablation of duodenal mucosa to enhance glycemic control of T2DM (380), reduction of HbA1c persisted 6 months after ablation.

Liposuction

Liposuction (also known as lipoplasty or suction-assisted lipectomy) is the most common esthetic procedure performed in the United States, with >400,000 cases performed annually (381). Although not generally considered to be a bariatric procedure, clinicians remove and contour subcutaneous fat by aspiration after injecting physiologic saline. As techniques have improved, it is now possible to remove significant amounts of subcutaneous adipose tissue without affecting the amount of visceral fat. In a study to examine the effects of this procedure, Klein *et al.* (381) studied seven diabetic women who were overweight and eight women with normal glucose tolerance that were overweight before and after liposuction. One week after assessing insulin sensitivity, the subjects underwent large volume tumescent liposuction, which consists of removing >4 L of aspirate injected into the fat beneath the skin. There was a significant loss of subcutaneous fat, but no change in the visceral fat. Subjects were reassessed 10 to 12 weeks after the surgery. The non-diabetic women lost 6.3 kg of body weight and 9.1 kg of body fat, which reduced body fat by 6.3%. The diabetic women had a similar response with a weight loss of 7.9 kg, a reduction in body fat of 10.5 kg, and a reduction in percentage fat of 6.7%. Waist circumference was also significantly reduced. Despite these significant reductions in body fat, there were no changes in BP, lipids, or cytokines (tumor necrosis factor- α , interleukin-6), or C-reactive protein. There was also no improvement in insulin sensitivity, suggesting that removal of subcutaneous adipose tissue without reducing ectopic fat depots has little influence on the risk factors related to being overweight.

Indications for bariatric surgery

Criteria for bariatric surgery

The National Institutes of Health Consensus Panel in 1991 established the initial criteria for surgical interventions for obesity (382). The panel concluded that individuals with BMI ≥ 35 kg/m² with a related comorbidity or BMI ≥ 40 kg/m² were appropriate candidates for bariatric surgery. An additional criterion was failure of medical treatment to accomplish sustained weight loss. These criteria have been variably interpreted for many years but have remained essentially unchanged until the present.

In evaluating the outcome for any procedure, we need criteria for “successful” treatment. Weight loss is highly variable with all interventions. For example, intense lifestyle interventions in the Look AHEAD trial produced an average of 8.6% weight loss at 1 year and ~5% at 4 years. However, this average covers

considerable variability. In this study, the bottom 25% of participants lost <3% of their body weight in contrast to the top 25% who lost 12 kg (Fig. 10b) (383).

During active weight loss after surgery, BP decreases to a point where antihypertensive drugs may be discontinued. In addition, the requirement for hypoglycemic medications in patients with T2DM may also be diminished or discontinued. However, after weight stabilization, the results are less clear, as hypertension commonly reoccurs. Additionally, if weight is regained, comorbidities that were present at baseline may reappear. As a result, the question of what constitutes “successful medical therapy” is open to interpretation. Therefore, additional criteria for surgical interventions should include an understanding of operative risk and the ability to manage obesity and comorbid disease after surgery.

A recent joint statement by international diabetes organizations has indicated that bariatric or metabolic surgery procedures are a consideration for patients with poorly controlled T2DM and a BMI of 30 to 35 kg/m² (380). The Endocrine Society has also released pediatric guidelines for bariatric surgery (62).

Preoperative assessment

Preoperative assessment of potential bariatric surgical candidates includes confirming the patient’s understanding of the basic procedure(s) proposed and what he or she needs to do to help make the treatment successful. It also includes determining the patient’s dedication and motivation to make the behavioral changes necessary for a satisfactory outcome. Fig. 11 (384) contains a flowchart for managing bariatric patients with obesity.

The patient must also understand the risks associated with the procedure, and clinicians need to assess all related comorbid conditions and manage these conditions preoperatively. At a minimum, clinicians

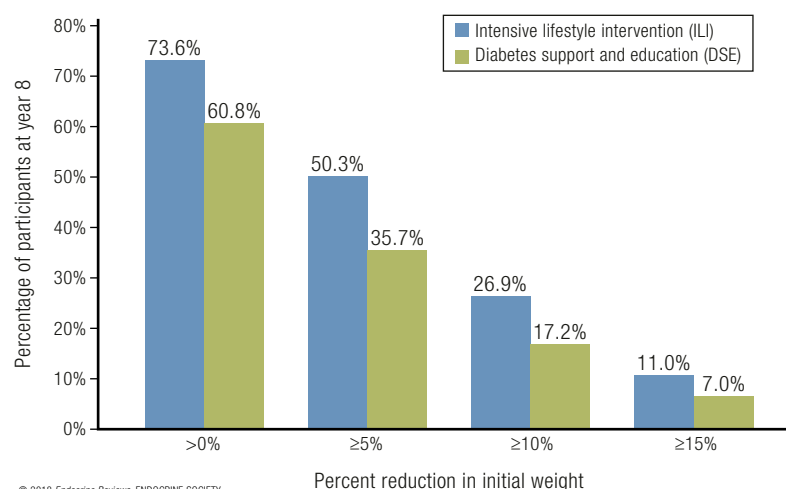
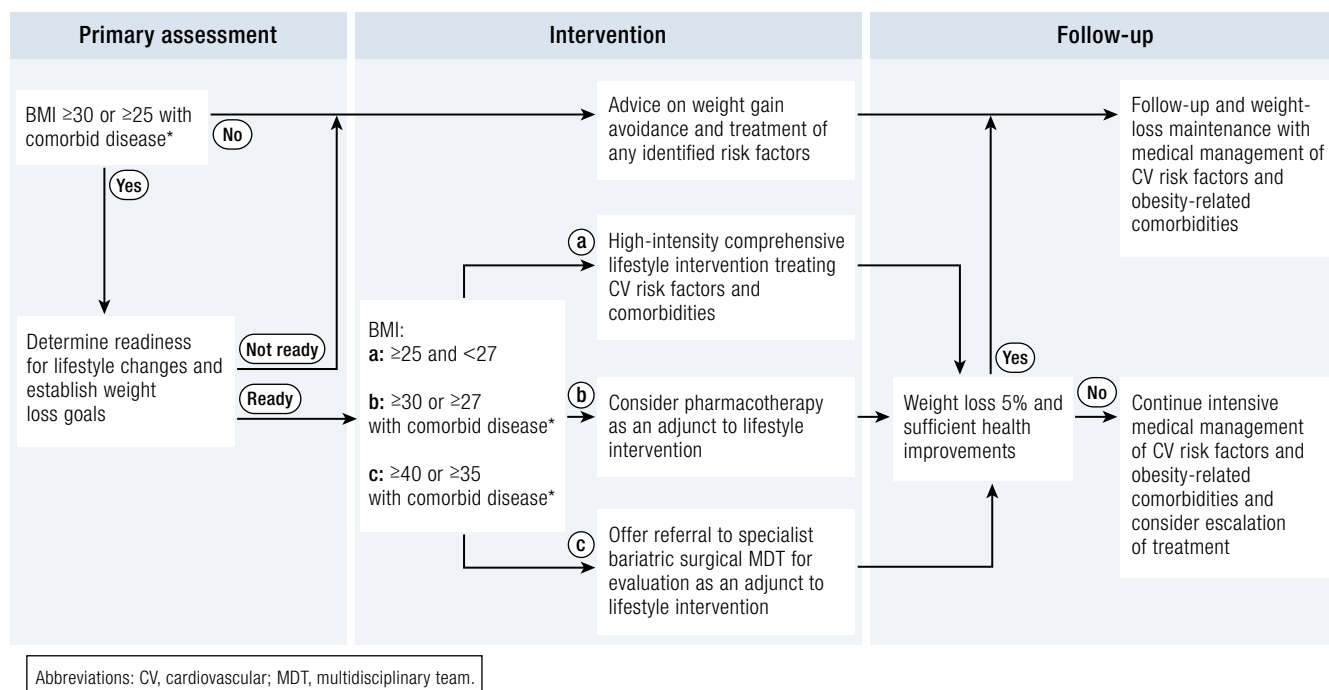


Figure 10. (Continued)

Figure 11. Obesity management flow. Summarized from the 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults (39). * refers to comorbid conditions. Reproduced with permission from Beamish *et al.*, 2016 (384).



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should meet standard guidelines for cancer screening, given the increased risk for common cancers in those with obesity (including breast and colon cancers). Clinicians should also identify and correct micronutrient deficiencies.

Many centers require preoperative weight loss, which may decrease the risk of perioperative medical complications of anesthesia and abdominal surgery. However, the role of preoperative weight loss in determining longer term outcomes (such as weight loss beyond 1 year) has not been demonstrated.

Outcomes of bariatric surgery

Safety

There is little or no disagreement about the benefits of weight loss among individuals with severe obesity, particularly those with comorbid conditions. These benefits, however, must be considered in the context of potential surgical complications. A population-based study in 2004 reported 2% mortality after RYGB (385). In response, the bariatric surgical community enacted several changes to improve safety. This included identifying the importance of surgeon experience and the experience of the particular surgical center; the establishment of pathways, care protocols, and quality initiatives; and the incorporation of all these aspects of care into the Metabolic and Bariatric Surgery Accreditation and Quality Improvement Program administered by the American Society for

Metabolic and Bariatric Surgery and the American College of Surgeons.

The addition of laparoscopic procedures also contributed to improved safety. Recently, the Longitudinal Assessment of Bariatric Surgery (LABORATORIES) (a multicenter bariatric surgery research consortium funded by the National Institutes of Health) reported a 30-day overall bariatric surgery mortality rate of 0.3%. For laparoscopic RYGB, it reported a 30-day mortality rate of 0.2% (386).

A serious complication occurred in 4.1% of all patients. Factors that predicted a major complication include high BMI, extreme OSA, inability to walk 200 feet, and a history of deep vein thrombosis. Other studies have reported different risk profiles. Studies consistently report that the experience of both the surgeon and the surgical center are predictors of safety (386).

Mid-term and longer term complications have been well described, although determining their incidence is limited by a progressively greater number of patients lost to follow-up (387). These include, but are not limited to, intestinal obstruction, marginal ulcer, ventral hernia, and gallstones. Metabolic complications reported include nephrolithiasis, osteoporosis, and hypoglycemia. Mineral and vitamin deficiencies and weight regain are reported in variable numbers of patients. Micronutrient deficiencies following gastric bypass include: iron, 33% to 55%; calcium/vitamin D, 24% to 60%; vitamin B₁₂, 24% to 70%; copper, 10% to

15%; and thiamine, <5% (388). Established guidelines recommend routine nutrient supplementation to include multivitamins, vitamin B₁₂, iron, minerals, calcium, and vitamin D (389, 390).

Perioperative complications specific to LAGB are less frequent, with near zero mortality. Longer term complications, however, continue to occur at a rate of ~2% per year. These longer term complications include erosion of the gastric wall by the band and slippage or herniation of the body of the stomach, thereby creating obstructions within the band. Inadequate weight loss is the most common cause of LAGB failure. Complications following other device placement procedures occur but are infrequent and generally less severe. However, there is a tradeoff between reduced complication rates and the severity of complications vs efficacy of weight loss.

In summary, both perioperative and longer term complications occur after all bariatric surgical procedures. Multiple steps have been taken in recent years to reduce perioperative mortality and serious complications. Prospective data collection, analysis, and reporting to individual centers through the accreditation program will continue to identify complications and stimulate appropriate quality improvement initiatives.

Weight loss

The high degree of variability of weight loss following all interventions (including intense lifestyle intervention, medications, and virtually all bariatric surgical procedures) speaks to the complexity of severe obesity (Fig. 10a and 10b). We can define obesity in terms of excess weight represented by BMI. However, the genetic, behavioral, and environmental factors that underlie excessive weight gain in life are exceedingly complex and variable.

The same factors influence variability observed in the weight-loss phenotypes following surgery. After RYGB, for example, the LABORATORIES Consortium reported patterns of similar and rapid weight loss among patients 6 months after surgery by stratifying weight loss into five separate trajectories, ranging from 12% to 45% total body weight loss 3 years after surgery (391) (Fig. 10a). These weight-loss trajectories persist through 7 years (391).

Weight loss following LAGB is similarly variable, but only one-half of the total body weight loss seen with RYGB is seen after LAGB (on average). Thus, the commonly reported mean weight loss among populations undergoing bariatric surgery is of limited use for predicting results for individuals who are contemplating surgical treatment.

There have been many efforts to identify preoperative clinical predictors of postoperative weight loss. However, although research has established some statistical correlations, the extent of the variability explained by a number of clinical covariates has been disappointing (391).

The single best predictors of sustained postoperative weight loss (identified by the LABORATORIES Consortium) are postoperative eating and lifestyle behaviors. Specifically, subjects who self-monitor (e.g., frequent weighing), avoid eating when full, and who avoid snacking between meals appear to experience the greatest weight loss (392). The weight loss following RYGB, compared with interventions other than surgery (Fig. 10a and 10b), demonstrates that even the poorest weight loss following gastric bypass is comparable to the best reported weight loss for nonsurgical interventions (393). A third study found changes from baseline after 5 years in the surgical groups were superior to the changes seen with medical therapy. Body weight decreased 23% with gastric bypass, 19% with SG, and 5% with drug therapies (161). We must interpret these outcomes with the caveat that the requirement for surgical intervention is the failure of patients to accomplish sustained weight loss via other means, thereby creating a selected population.

Related outcomes/remission of T2DM

The remarkable remission of T2DM following RYGB has generated much interest given the prevalence of T2DM and the severity of this disease (394, 395) (Table 11) (396, 397).

Analysis of the data from the LABORATORIES Consortium has demonstrated that both weight loss and the neuroendocrine effects specific to gastric bypass contribute to the remission of T2DM (159). The durability of the remission in many participants was sustained through year 7 (391).

The Swedish Obese Subjects study reported that ~50% of gastric bypass patients who were in T2DM remission at year 2 had recurrence by year 10 (160). Weight loss in these groups is shown in Fig. 12. Gastric banding was the predominant procedure in the Swedish Obese Subjects trial. This suggests that maintaining weight loss, as well as the incretin stimulation associated with RYGB, contributes to the durability of the remission. Reports of T2DM remission among patients with considerably less severe

Table 11. Weight Loss and Reversal of Diabetes Mellitus after Metabolic/Bariatric Surgery

Procedure	Excess Weight Loss (%)	Resolution of T2DM (%)
Gastric banding	46.2	56.7
Gastroplasty	55.5	79.7
RYGB	59.7	80.3
Biliopancreatic diversion	63.6	95.1

Including data from Buchwald *et al.*, 2009 (396) and Bray, 2011 (397).

obesity (BMI 27 to 40 kg/m²) have led to several RCTs in this patient population (398).

Most recently, SG has taken a dominant place in the spectrum of procedures used for weight loss worldwide (399, 400). Although the weight loss and T2DM remission following SG appear to be slightly less than that following gastric bypass, lower perioperative complication rates, shorter lengths of stay, and lower costs have made SG an attractive bariatric surgical procedure (395, 401). The mechanism and durability of this improved glycemic control, including the role of diet-induced weight loss, have not been determined (60).

Overall, there is considerable evidence favoring RYGB, LAGB, and now SG as superior methods for controlling or inducing remission of T2DM, vs intense medical treatment (380). As a result, the term “metabolic” surgery has become popular. The concept that clinicians should consider surgical intervention for patients with poorly controlled T2DM and patient with less severe obesity (class I) with T2DM (rather than having BMI be the primary indication for surgery) has gained widespread international support (380). Remission of dyslipidemia is also seen in most patients following effective surgical weight loss, whereas remission of hypertension is less frequent.

Bariatric/metabolic surgery in adolescents

Owing to the lack of effectiveness of nonsurgical options for treating severe obesity in young patients and the demonstrated safety and efficacy of bariatric surgery in adults, clinicians increasingly use surgical procedures to induce weight loss in selected adolescents with severe obesity. The rationale for and expectation of bariatric treatment in adolescents are to provide significant and durable weight reduction, correct existing health problems, and prevent expected comorbidities in those at risk.

Lifestyle modification and even pharmacotherapy in adolescents with severe obesity are associated with unsatisfactory outcomes, and any weight reduction seen may not be sustained. Conversely, growing evidence indicates that surgery results in 25% to 35% weight reduction in severely obese adolescents. In the Teen-LABORATORIES study, SG and RYGB were the most commonly performed procedures in adolescents, and 3-year outcomes demonstrated a similar weight loss of nearly 30% for these procedures (402).

The lower complexity of SG and the lower theoretical risk of at least some micronutrient deficiencies associated with RYGB make SG an attractive option for most adolescents, despite fewer published studies of SG in adolescent age groups.

In 2017, investigators in the United States (403) and Sweden (404) simultaneously reported long-term outcomes for weight loss and comorbidities in adolescents who underwent RYGB. Eight-year (United States) and 5-year (Sweden) post-RYGB surgery follow-up assessments indicated 30% and 28% BMI reductions, respectively. Both research groups documented important improvements in health.

In the U.S. study, remission of T2DM occurred in 88% (n = 7). The study did not report any incident T2DM during the 8 years. The study also reported dyslipidemia remission in 64% (n = 29) and incident dyslipidemia in four of eight subjects who did not have dyslipidemia at baseline. The study reported hypertension remission in 76% (n = 19) and incident hypertension in only 10% (3 of 29) participants without hypertension at baseline.

The Swedish study reported similar health improvements, with remission of comorbid conditions in 74% to 100% of participants. The study reported remission of T2DM in 3 of 3 participants, disturbed glucose homeostasis in 18 of 21, dyslipidemia in 43 of 52, elevated BP in 11 of 12, inflammation (high-sensitivity C-reactive protein ≥ 2 mg/L) in 45 of 61, and elevated liver enzymes in 19 of 19 participants.

Both studies also reported long-term nutritional effects. The U.S. study reported mild anemia in 46% (n = 25), hyperparathyroidism in 45% (n = 22), and low vitamin B12 levels in 16% (n = 8) at long-term follow-up. At 5 years in the Swedish study, 63% (46 of 73) had vitamin D (25-hydroxy vitamin D) insufficiency (<50 nmol/L) and 66% (51 of 77) had low ferritin and/or

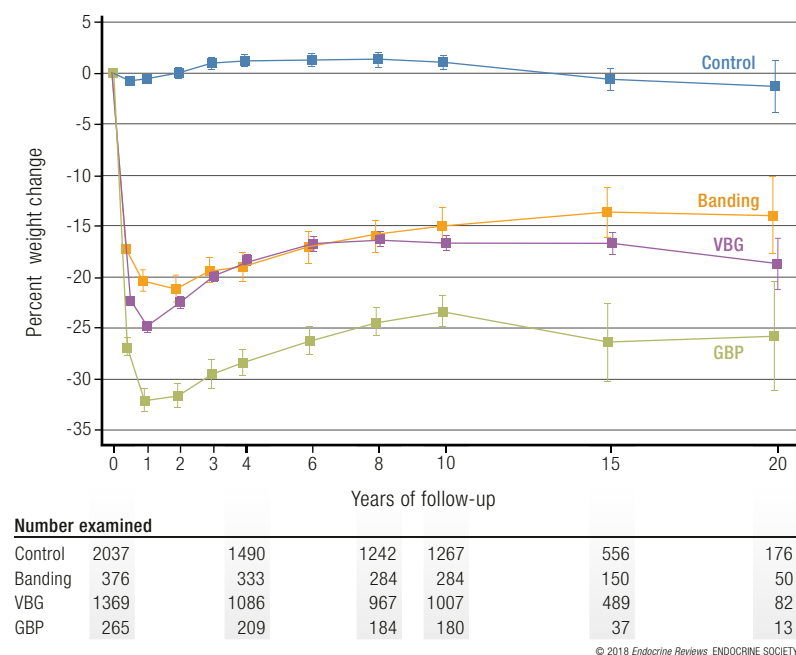


Figure 12. Mean weight change percentages from baseline for controls and the three surgery groups during 20 years in the Swedish obese subjects study. Data shown for controls obtaining usual care and for surgery patients obtaining banding, vertically banded gastroplasty, or gastric bypass at baseline. Percentage weight changes from the baseline examination and onward are based on data available on 1 July 2011. Error bars represent 95% CIs. Vertical error bars represent SEM. GBP, gastric bypass; VBG, vertically banded gastroplasty. See Sjöström *et al.*, 2012 (393).

iron levels. The prevalence of anemia rose from 10% (8 of 78) to 32% (25 of 77), and 22% had low vitamin B12 levels.

In summary, the two long-term, prospective studies demonstrate excellent durability of weight loss and response of comorbidities for adolescents who have RYGB surgery. These studies also reported the typical nutritional consequences of RYGB that we see in studies in adults, and this must be taken into consideration when counseling patients about long-term risks of RYGB.

Current expert opinion recommends that clinicians should use criteria similar to those used for adults when selecting adolescents for weight-loss surgery (399, 405). Surgery is generally recommended for adolescents with a BMI ≥ 40 kg/m² and a weight-related comorbid condition or impairment in quality of life. It is also recommended for those with a BMI of ≥ 35 kg/m² with significant current comorbidities, such as T2DM, dyslipidemia, OSA, hypertension, NASH, or pseudotumor cerebri (395, 400).

Where Do We Go From Here?

In this Endocrine Society Scientific statement titled “The Science of Obesity Management: An Endocrine Society Scientific Statement,” we have documented the rising prevalence of obesity in both men and women in the United States and worldwide with resultant hazardous health implications. The prevalence of obesity is correlated with income disparity both between developed countries and between the states of the United States (406).

Obesity results in part from environmental and behavioral factors, and both the public and health care professionals alike stigmatize the condition. The opportunity to move from a neighborhood with a high level of poverty to one with a lower level of poverty was associated with modest but potentially important reductions in the prevalence of extreme obesity and diabetes (120), supporting the relationship between income inequality and obesity. Because the prevalence of obesity has strong social and environmental components, this may provide a basis for future approaches. The study by Christakis and Fowler (407) showed that “friends” of an individual with obesity were more likely to also be obese.

Obesity is lower when there are more opportunities for physical activity as part of everyday life, as shown by the slower rise in obesity among more active individuals during 10 years (123). Sleep time is a modifiable behavior, and the observation that preschool-aged children with early weekday bedtimes were one-half as likely as children with late bedtimes to be obese as adolescents offers further opportunities for intervention in the environment

(408). These observations may provide the potential for more effective preventive strategies utilizing social engineering.

Genetic factors also play a role. Recently, insufficiency in the gene TRIM28 was shown to produce polyphenic obesity in both mice and humans. In this setting, both lean and obese phenotypes can arise from identical genotypes through dysregulation of an imprinted gene network (409). This finding and other genetic research into the mechanisms behind obesity may provide new genetic strategies for helping this segment of the population.

The hazards of obesity are many, including a shortened life span, T2DM, CVD, some cancers, kidney disease, OSA, gout, osteoarthritis, and hepatobiliary disease, among others. As might be expected, weight loss reduces all of these diseases in a dose-related manner.

The phenotype of MHO appears to be a transient state that progresses over time to an unhealthy phenotype, especially in children and adolescents. Understanding in more detail how complications of obesity develop will provide new opportunities for prevention of these negative outcomes.

Of particular interest are reports that two diabetes medications (liraglutide and empagliflozin) (345, 410) also produce weight loss and are cardioprotective. Particularly striking is the fact that these two drugs reduce cardiovascular death to a greater extent than statins. This opens a whole new paradigm for managing patients with obesity and diabetes in relationship to their complications.

One of the unexplained issues in all treatment strategies is the marked variability in response of any form of treatment of obesity. Efforts to understand the biological basis of this variability may provide new insights into its treatment. The POUNDS Lost Study population of 811 individuals randomized to one of four diets (20% vs 40% fat and 15% vs 25% protein) has provided many genetic clues to help us better understand factors that modulate dietary response (206, 411). The ability to combine several measures to predict responses to environmental factors may expand the option for personalized medicine. An algorithm that integrates blood parameters, dietary habits, anthropometrics, physical activity, and gut microbiota measured in a sample cohort (412) showed that these factors accurately predict personalized postprandial glycemic response to real-life meals. Similar strategies might well be developed for obesity. Many genes affect the response to diets, opening the possibility of “personalized medicine” for managing obesity.

The public commonly uses over-the-counter herbal preparations to manage obesity, but evidence documenting their efficacy or safety is usually absent. We think that the public would be well served by more regulatory requirements regarding sale and use of these products.

We can expect to see weight gain in all patients when they discontinue obesity treatments. When making treatment decisions, clinicians should consider body fat distribution and individual health risks in addition to BMI. Because all treatments have considerable variability in their outcome, it is important to know when to stop treatment as well as when to begin. Surgical strategies have demonstrated greater weight loss that outlasts other treatment options.

As the knowledge base underpinning obesity continues to expand, the options for treating patients with obesity should also expand, offering hope for future conquest of this problem. One fascinating new strategy is the combination of peptides acting on receptors in the gastrointestinal track into a single molecule acting on two or more receptors, called coagonists and triagonists. Using glucagon-like peptide-1, glucagon, and glucose-insulin peptide as the background for these molecules,

peptides have been shown to enhance weight loss and the decline in glucose, opening a fascinating new horizon (413, 414).

Finally, improved techniques for modulating food transit through the gastrointestinal track and its absorption also offer new strategies for dealing with the devastating epidemic posed by obesity. It is clear that food is more than calories and that dietary choices and diet quality play a role in long-term weight change (415), and this provides other opportunities for public health programs. The so-called “obesogens” in the food supply offer another opportunity for making the food supply less likely to contribute to obesity (416). Control of obesity is the most important public health strategy for the prevention of diabetes and its devastating consequences. With all of these opportunities on the horizon, we are optimistic about the future of treatment and prevention of obesity.

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Abbreviations

BMI, body mass index; BP, blood pressure; CDC, Centers for Disease Control and Prevention; CI, confidence interval; CVD,

cardiovascular disease; ECE, early care and education; ER, extended release; FDA, Food and Drug Administration; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; HR, hazard ratio; LAGB, laparoscopic adjustable gastric banding; LDL, low-density lipoprotein; MHO, metabolically healthy obesity; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; OSA, obstructive sleep apnea; PHEN/TPM ER, phentermine/topiramate extended release; RCT, randomized controlled trial; RYGB, Roux-en-Y gastric bypass; SG, sleeve gastrectomy; SR, sustained release; T2DM, type 2 diabetes mellitus; VLCD, very low-calorie diet; WHR, waist-to-hip ratio.