

**AACE/ACE POSITION STATEMENT
ON THE PREVENTION, DIAGNOSIS,
AND TREATMENT OF OBESITY
(1998 Revision)**

AACE/ACE Obesity Task Force

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This report is not intended to be construed or to serve as a standard of medical care. Standards of medical care are determined on the basis of all the facts and circumstances involved in an individual case and are subject to change as scientific knowledge and technology advance and practice patterns evolve. This report reflects the views of the American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE) Obesity Task Force and reports in the scientific literature as of February 1998.

INTRODUCTION TO 1998 REVISION

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The goal of this revised document is to update the original statement (1), which was intended to provide physicians and associates with guidance on the treatment options for obesity and the procedures for selecting patients for these treatments.

During the past year, two antiobesity agents were withdrawn from the market because of findings of unusual, serious, and unexpected abnormalities of heart valves in patients treated with fenfluramine or dexfenfluramine, usually in combination with phentermine (2-8). Consequently, use of combined therapy with fenfluramine and phentermine was discontinued, a practice that evolved primarily as a result of the 1992 publication of a long-term study of this combination drug regimen (9). The recommendations for the care of patients who have taken fenfluramine or dexfenfluramine (alone or in a combination with other agents) are now widely known. Such patients are advised to request an assessment from their physician about the possible effects of the use of these antiobesity agents. Echocardiography should be performed on all patients who have cardiopulmonary signs (including a new heart murmur), who exhibit symptoms suggestive of valvular heart disease (for example, dyspnea or congestive heart failure), or who are anticipating any invasive procedure for which antimicrobial endocarditis prophylaxis is recommended by 1997 American Heart Association guidelines (10,11). Additionally, one new antiobesity agent (sibutramine) has been approved and marketed for use in appropriate patients, and another (orlistat) is expected to be approved soon.

Accordingly, these revised guidelines may serve as a useful reference to remind the reader of the essential elements of management of obesity—evaluation of the patient's risk and assignment of treatment based on these risks and the patient's preferences. Because obesity is a chronic disorder that is increasing in prevalence, involving the patient in all decisions is important; the patient must make a long-term commitment. Moreover, physicians and support staff should have a compassionate view of this stigmatized condition (12).

The importance of providing guidance for physicians, nonphysician therapists, and regulatory agencies dealing with the problem of obesity has become widely recognized. One of the first documents to address this problem was "Weighing the Options" from the National Academy of Sciences (13). This document was instrumental in promoting the step-by-step approach used in the guidance

provided by Shape Up America and the American Obesity Association (14). The first European recommendations for management of obesity were published by the Scottish Intercollegiate Guidelines Network (15). Furthermore, the National Institutes of Health has established a National Task Force on the Prevention and Treatment of Obesity (16), which has recently reported on the use of long-term pharmacotherapy in the management of overweight patients and is developing an evidence-based approach to treatment recommendations. The World Health Organization (WHO) has published the results of an international consultation held in 1997 (17). The National Heart, Lung, and Blood Institute also recently released Clinical Guidelines for Treatment of Adult Obesity (18). Finally, a monograph on obesity, which should be of interest to endocrinologists and other physicians, was published recently (19), as was a handbook of obesity (20). Clearly, more information will continue to be published as completed studies provide new insights.

The guidance provided herein by the American Association of Clinical Endocrinologists and the American College of Endocrinology (AAACE and ACE) is designed to help manage the problem of obesity in patients. Of importance, guidelines can help provide direction, but critical decisions should be made by the physician and the patient. No hard-and-fast, one-strategy-fits-all approach is available. Appropriate experience and clinical judgment, in combination with help from the patient, are critical. Successful weight loss is primarily the patient's responsibility. Physicians can help, but long-term weight-loss maintenance necessitates continuing management, and only the patient can ensure a good outcome.

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AACE OBESITY STATEMENT

INTRODUCTION

In this era of constrained health-care resources, a critical need exists for efficient, measurable systems of disease management that strike a balance between social responsibility and patient welfare. Clinical guidance is an important component of these systems because it addresses elements of care that are efficacious and that minimize the degree of variability in physicians' approaches to disease management.

This report addresses the prevention, diagnosis, consequences, and treatment of obesity—one of the most prevalent public health problems in the United States. Dietary factors and activity patterns that are too sedentary have key roles in obesity and contribute to approximately 300,000 deaths a year, making it second only to smoking as a cause of death (1,2). According to the National Health and Nutrition Examination Surveys (NHANES), the crude prevalence of overweight and obesity (body mass index [BMI] ≥ 25) for age ≥ 20 years is now 59.4% for men and 50.7% for women, totaling more than 97 million adults in America. For BMI ≥ 30 , the crude prevalence is 19.5% for men and 25.0% for women, involving a total of almost 40 million people. Furthermore, the incidence of obesity is increasing dramatically (3-6).

The treatment of obesity and its primary comorbidities costs the US health-care system more than \$99 billion each year (7-9), and consumers also spend in excess of \$33 billion annually on weight-reduction products and services (10). Moreover, obesity is associated with an increased prevalence of socioeconomic hardship due to a higher rate of disability, early retirement, and widespread discrimination (11-13). Efforts to reduce overweight and prevent weight gain offer a considerable potential for reduction of health-care costs (14). Annual health-care costs for patients with BMIs of 20 to 24.9 were 20% lower than costs for patients with BMIs from 30 to 34.9 and almost 33% lower than for patients who had BMIs of 35 or more.

The objectives of this position paper are as follows:

- Document that obesity is a disease
- Review current knowledge of the prevention, diagnosis, consequences, and treatment of obesity
- Enhance the likelihood of successful obesity prevention programs and maximize the long-term effectiveness of obesity treatment programs
- Advance the importance of a physician-led, multidisciplinary team approach to the care of obese patients
- Encourage health-care providers and payers to engage in the care and payment of services for obese patients
- Reduce the prevalence of obesity

The American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE) recognize that a multidisciplinary team

can improve the treatment of obesity and believe that such a team is best led by a physician. Obesity is, in part, an endocrine and metabolic disorder that is clearly associated with several endocrine and metabolic comorbidities that require ongoing medical management, including type 2 diabetes mellitus, hypertension, dyslipidemia, and gout.

This position paper has been designed to provide guidance to endocrinologists and other physicians who wish to treat obesity. In this publication, we outline what we believe are the best currently available treatment methods. Nevertheless, we present this information with the understanding and precaution that current approaches to prevention and treatment of obesity are far from ideal and with the expectation that new and better strategies are likely to be forthcoming. As the treatment of obesity advances, this position statement will be updated periodically and will be available on the AACE home page on the Internet. Please visit our web site at <http://www.aace.com>.

DEFINITION

Obesity is a complex, multifactorial condition characterized by excess body fat. It must be viewed as a chronic disorder that essentially requires perpetual care, support, and follow-up. Obesity causes many other diseases, and it warrants recognition by health-care providers and payers (see "Weight-Management Strategies," p. 308).

Generally, men with more than 25% body fat and women with more than 35% body fat are considered obese. A person may be within the desirable norm for body weight relative to height and frame size, yet still have a high percentage of body fat. In contrast, body weight can exceed the ideal standard because of large muscle mass; in such a case, the person is not considered obese.

Standards

Typically, the obese adult also has a body weight that exceeds the standard, and weight in relationship to height (BMI) is the most commonly used criterion for classifying the degree of obesity. (For further information on the use of BMI in clinical practice, see "Diagnosis" [p. 306] and Table 1.)

The 1995 healthy weight ranges for men and women issued by the Dietary Guidelines Advisory Committee of the US Department of Agriculture Food and Nutrition Center are useful and widely accepted body weight standards for adults (Table 2) (15). Within each range, a mid-weight goal may represent the most appropriate standard because several studies suggest that the risk of mortality increases in both overweight and underweight persons (16).

Types of Obesity

Two basic patterns of fat distribution have been noted in obese persons: central abdominal (android obesity) and

gluteofemoral (gynoid obesity). A generally useful method for distinguishing android versus gynoid obesity is to determine waist and hip measurements and calculate a waist/hip ratio. A ratio of less than 0.8 in women and less than 1.0 in men indicates lower risk (17). Android obesity is closely associated with comorbidities (see “Associated Health Risks,” p. 303). A waist circumference that exceeds 40 inches (102 cm) in men or 38 inches (97 cm) in women is also considered central obesity.

ETIOLOGY AND PATHOGENESIS

Each day, a person expends energy through basal or resting metabolism plus the thermal effects of meals and physical activity (Fig. 1). Obesity occurs as the result of an imbalance between energy expenditure and caloric intake.

Although the causes of this imbalance are not completely understood, they are thought to be both physiologic-genetic and environmental. A review of certain proposed causes follows, although many other factors may also influence food intake and energy expenditure (18).

Physiologic-Genetic Mechanisms

Dysmorphisms

In dysmorphic types of obesity—such as Prader-Willi syndrome, Bardet-Biedl syndrome, Simpson-Golabi-

Behmel syndrome, Cohen’s syndrome, Carpenter’s syndrome, and lipodystrophy—genetic mechanisms are the primary cause. These disorders are rare, and in affected persons, obesity may be moderate or severe.

Genetic Predisposition

More commonly, obesity results from an interaction between an underlying genetic predisposition and environmental factors. Animal and clinical studies suggest that genetic mechanisms can regulate food intake, alter energy expenditure, and control patterns of fat distribution (19-22). Early studies estimated heritability to be the major determinant of obesity. More recent adoption studies and complex segregation analyses, however, show that approximately a third of the variance in adult body weights results from genetic influences (23). Genetic factors are clearly important in the variance in obesity seen in the population (24), and estimates of heritability seem higher for weights within the normal range than for obesity (25).

Leptin is an adipocyte- and placenta-derived circulating protein that communicates the magnitude of fat stores to the brain. A deficiency of leptin (*ob/ob*) or a defective leptin receptor (*db/db*) seems to be responsible for obesity in *ob/ob* and *db/db* mice and obese Zucker rats. Leptin can cause weight loss not only in *ob/ob* mice but also in normal mice and in mice made obese through a high-fat diet. Investigators have theorized that a high-fat diet may

Table 1
Body Mass Index (BMI), Stratified by Height and Weight

	Good weights					↓	Increasing risk							
Height*	BMI⇒19	20	21	22	23	24	25	26	27	28	29	30	35	40
	Weight (lb)													
4 10	91	96	100	105	110	115	119	124	129	134	138	143	167	191
4 11	94	99	104	109	114	119	124	128	133	138	143	148	173	198
5 0	97	102	107	112	118	123	128	133	138	143	148	153	179	204
5 1	100	106	111	116	122	127	132	137	143	148	153	158	185	211
5 2	104	109	115	120	126	131	136	142	147	153	158	163	191	218
5 3	107	113	118	124	130	135	141	146	152	158	163	169	197	225
5 4	110	116	122	128	134	140	145	151	157	163	169	174	204	232
5 5	114	120	126	132	138	144	150	156	162	168	174	180	210	240
5 6	118	124	130	136	142	148	155	161	167	173	180	186	216	247
5 7	121	127	134	140	146	153	159	166	172	178	185	191	223	255
5 8	125	131	138	144	151	158	164	171	177	184	190	197	230	262
5 9	128	135	142	149	162	162	169	176	182	189	196	203	236	270
5 10	132	139	146	153	160	167	174	181	188	195	202	209	243	278
5 11	136	143	150	157	165	172	179	186	193	200	208	215	250	286
6 0	140	147	154	162	169	177	184	191	199	206	213	221	258	294
6 1	144	151	159	166	174	182	189	197	204	212	219	227	265	302
6 2	148	155	163	171	179	186	194	202	210	218	225	233	272	311
6 3	152	160	168	176	184	192	200	208	216	224	232	240	279	319
6 4	156	164	172	180	189	197	205	213	221	230	238	246	287	328

*In feet and inches.
Source: George A. Bray, M.D.

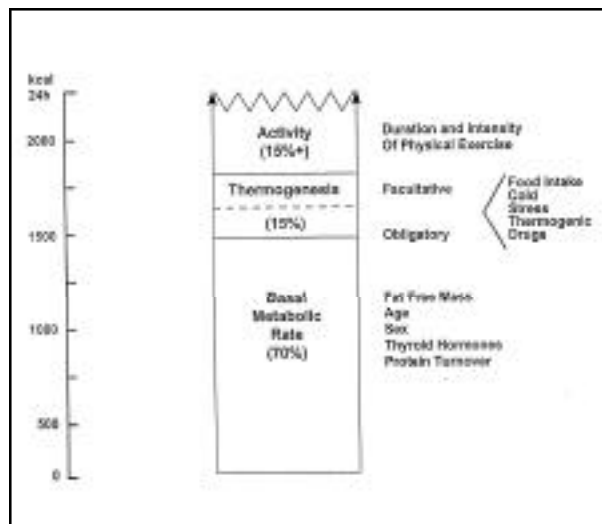


Fig. 1. Estimated daily energy needs. (From Bray GA, Gray DS. Obesity: part 1—pathogenesis. *West J Med.* 1988;149:429-441. With permission.)

change the set-point for body weight by limiting the action of leptin (26). A rare genetic mutation in the *ob* or leptin gene that produces leptin was recently reported in two obese cousins (2 and 8 years of age) in the United Kingdom. Consanguinity was present in this first report of a gene mutation in humans in which leptin regulation seemed related to the obesity (27). Body fat is the main determinant of serum leptin levels in obese persons (28,29). Clinical safety and efficacy testing for obesity treatment with leptin is now under way. (For more information on the set-point theory, see the subsequent paragraph.) Two other brain hormones, glucagon-like factor-1 and urocortin, have also been identified as appetite suppressants (30). A recent report described the discovery of still another peptide (orexin), which affects eating behavior in rats. It is produced in two forms by cells in the lateral hypothalamus (31). Elimination of melanocortin-4 receptor in mice produces massive obesity; thus, melanocyte-stimulating hormone may also be important in regulating food intake (31,32).

Low Energy Output

Some researchers believe that the body attempts to maintain the metabolic rate around a specific set-point, which may be controlled by the sympathetic nervous system, and that this point may be set at a higher-than-desirable weight in some people (33). This theory may be evidenced by the finding that, with very-low-calorie diets (VLCDs), the resting metabolic rate seems to decrease by as much as 30% (34). Energy expenditure also increases with overeating; this response may be an attempt by the body to prevent storage of surplus calories (34). Investigators have also theorized that some people may have a high set-point—not only for body weight but also for total adipose tissue (35,36).

Table 2
Healthy Weights for Men and Women,
Stratified by Height*

Height (ft and inches)	Weight (lb)	
	Range	Middle (target)
4 10	91-119	105
4 11	94-124	109
5 0	97-128	112
5 1	101-132	116
5 2	104-137	120
5 3	107-141	124
5 4	111-146	128
5 5	114-150	132
5 6	118-155	136
5 7	121-160	140
5 8	125-164	144
5 9	129-169	149
5 10	132-174	153
5 11	136-179	157
6 0	140-184	162
6 1	144-189	166
6 2	148-195	171
6 3	152-200	176
6 4	156-205	180
6 5	160-211	185
6 6	164-216	190

*Weight ranges correlate with the following body mass index range: 19-25 kg/m².

Modified from Dietary Guidelines Advisory Committee of the USDA Food and Nutrition Center. Report of the Dietary Guidelines Advisory Committee on the Dietary Guidelines for Americans. Washington, DC: US Dept of Agriculture, Food and Nutrition Center, 1995 (9).

Regulation of Peptides and Neurotransmitters

Various gastrointestinal peptides (such as cholecystokinin, enterostatin, and glucagon) and neurotransmitters (serotonin) that influence communication among the brain, gastrointestinal tract, and adipose tissue may have an etiologic role in obesity. Serotonin seems to be especially important in suppressing hunger and food intake; serotonin antagonists increase appetite and food intake (37).

Hypothalamic Abnormalities

Stimulation or a lesion of the ventromedial region of the hypothalamus causes decreased satiety or increased appetite, which manifests as hyperphagia, decreased physical activity, and obesity (38). Lesions of other hypothalamic regions may also promote obesity (38).

Environmental Mechanisms

A person with no family history of obesity can become obese. Thus, environmental factors can assume a primary role in the development of obesity. Primary environmental contributors include pharmacologic agents, social factors, high-calorie and high-fat diets, inactivity, and psychologic factors.

Drugs

Several drugs can increase body weight. Some antipsychotic drugs, certain antidepressants, some anti-epileptic agents, insulin, glucocorticoids, and sulfonylureas have been reported to increase body weight.

Social Factors

A 1989 literature review that cited two large longitudinal studies demonstrated a cause-and-effect relationship between low socioeconomic status and obesity (39). Cultural and ethnic factors are also related to obesity. For example, the incidence of obesity is high in female African-American, Native American, and Latino populations.

High Energy and Fat Intake

Hyperphagia and high dietary fat intake are associated with obesity (40-42). Dietary fat content is directly correlated with energy intake, produces only weak satiation in comparison with protein and carbohydrates, and is thought to be processed efficiently by the body (42). The caloric content of fat is also more than twice that of protein or carbohydrate (9 versus 4 calories per gram, respectively). The fat content of the American diet (in contrast with carbohydrate and protein content) increased during the first half of this century (43), but fat consumption in the United States has now begun to decline (44).

Inactivity

In populations such as ours, food generally is readily available, few persons are obligated to engage in manual labor, and devices that minimize energy expenditure have proliferated. Thus, use of personal computers, portable telephones, televisions, clothes washers and dryers, leaf blowers, and riding lawnmowers has substantially decreased the energy expenditure involved in both work and play activities. This sedentary lifestyle promotes overweight (2) and is a risk factor for poor health (45). Furthermore, leisure time physical activity is associated with reduced mortality, even after genetic and other familial factors are taken into account (46). Recent evidence suggests that recommendations for physical activity levels should be adjusted for age, increasing to prevent undesirable weight gain in older adults (47).

Psychologic Factors

Emotional distress—including poor mood or depression and low self-esteem—may exacerbate overeating (38,48). Women who are overly concerned about their eating behaviors may engage in “restrained eating,” which

may lead to overeating after a period of caloric restraint (49). Some obese patients report addictive eating behaviors and anxiety-triggered overeating (49). Psychiatrists have also characterized binge eating as a disorder that may contribute to obesity in 20 to 30% of obese patients who seek treatment (49).

Obesity may also be the result of psychologic distress induced by difficult life events, such as sexual or nonsexual childhood abuse, early parental loss, parental alcoholism, chronic depression, and marital or family dysfunction (48). Obese patients have reported using obesity as a sexually protective mechanism (48).

ASSOCIATED HEALTH RISKS

The relationship between BMI and mortality appears curvilinear (50,51). Excess body weight increases the risk of death from many causes (5). One quantitative analysis of existing studies that was adjusted for cigarette smoking and early mortality showed that, when a relationship exists, mortality increases as BMI rises (16). A BMI >40 is also associated with an increased risk of sudden death (1). Undoubtedly, obesity is associated with numerous disorders and serious diseases that contribute to mortality. These health risks result from a positive energy balance attributable to excess caloric intake or decreased physical activity (1).

Physical Manifestations

Not every obese person has complicating medical conditions, both because the total body fat can differ and because the location of fat on the body is a primary determinant of health risk (52-54). Patients with android obesity with an intra-abdominal collection of fat tend to have a quartet of metabolic complications known as the *metabolic syndrome*—insulin resistance, hyperinsulinemia, dyslipidemia, and hypertension (53,55). Studies have also shown a correlation between android obesity and increased risk for coronary artery disease, stroke, hypertension, diabetes mellitus, and mortality (52-54). Because these risks increase as obesity worsens and decrease as obesity diminishes, prevention as well as successful long-term treatment of obesity should be emphasized. The primary comorbidities of obesity are diabetes mellitus type 2, cardiovascular disease (CVD), hypertension, reproductive disorders, certain cancers, gallbladder disease, and respiratory disease.

Diabetes Mellitus Type 2

Although patients in whom insulin resistance or diabetes mellitus type 2 develops are not necessarily obese, weight gain before the development of diabetes mellitus type 2 is common (53). In studies of twins, concordance is so high (>90%) that genetic factors almost always have a role. Obesity is the most powerful environmental risk factor for diabetes mellitus type 2 (56), and the prevalence of diabetes is 2.9 times higher in overweight (BMI 27.8 in men and 27.3 in women) than in nonoverweight

subjects 20 to 75 years of age (50). When this age range is narrowed to between 20 and 45 years, this risk is 3.8 times that of the comparable nonoverweight population (57).

Weight gain is associated with an increased demand for insulin and an increased likelihood of insulin resistance, which may lead to hyperinsulinemia and, ultimately, diabetes mellitus type 2 (1,53). Several pathologic processes may promote the development of insulin resistance (58). Obese patients have increased plasma free fatty acid levels, and this finding may interfere with insulin sensitivity in the muscles (59). Accumulation of fat in the intra-abdominal tissues, particularly those drained by the portal circulation, may also lead to high portal vein concentrations of free fatty acids. These are highly sensitive to lipolysis (59). This condition, in turn, may inhibit hepatic clearance of portal insulin (59). Obesity is also clearly associated with abnormalities of steroid hormones—primarily increased secretion of cortisol and hyperandrogenicity—which have an important role in the regulation of insulin sensitivity in muscle tissue and liver (59). Physical and chronic psychologic stress may also exacerbate insulin resistance or diabetes mellitus type 2 (59).

Clinical risk factors for diabetes mellitus type 2 include high waist-to-hip ratio (android obesity), large waist circumference (visceral adiposity), overall obesity, insulin resistance, dyslipidemia—increased triglycerides, hypercholesterolemia, increased low-density lipoprotein cholesterol (LDL-C), and decreased high-density lipoprotein cholesterol (HDL-C)—lack of physical activity, and gestational diabetes mellitus (60). The combination of obesity and diabetes mellitus type 2 is especially prevalent among African-Americans, Hispanic Americans, and American Indians (61-64).

Cardiovascular Disease

Obesity, particularly android obesity (50), increases the risk of CVD (65)—including essential hypertension, stroke, left ventricular hypertrophy, arrhythmias, congestive heart failure, myocardial infarction, angina pectoris, and peripheral vascular disease—in both men and women. Mortality due to CVD is almost 50% higher in obese patients than in those of average weight and is 90% higher in those with severe obesity (38).

Obesity, especially android or visceral obesity, is associated with a dyslipidemic state that exacerbates a genetic predisposition to coronary artery disease (54). Insulin resistance and hyperinsulinemia may regulate plasma lipid transport in obese patients, and this relationship is summarized in Figure 2. Dyslipidemia, in combination with the increased demand that obesity imposes on the heart to supply blood to peripheral organs, helps explain the increased risk of CVD and heart attack in obese patients (1).

Essential Hypertension.—Sixty percent of obese patients have hypertension (66), and epidemiologic data show a direct relationship among android obesity,

hyperinsulinemia, and hypertension. Insulin may mediate sympathetic nervous system stimulation and cause renal sodium retention and associated increased blood pressure (67,68). Weight loss reduces the risk for hypertension (69).

Stroke.—Obesity and high waist-to-hip ratio are associated with stroke (70-72). This relationship is not as strong or as consistent as that between obesity and diabetes mellitus type 2 or obesity and hypertension—probably because stroke is also associated with confounding variables, including cigarette smoking and thinness caused by deteriorating health (70).

Cardiomyopathy.—Fatty infiltration of the myocardium, right ventricular hypertrophy, excess epicardial fat, abnormalities of ventricular function, and increased left ventricular filling pressure all seem closely related to the duration of obesity (66,73). Abnormalities in cardiac structure and function occur more commonly in patients who have been obese for 15 years than in patients who have been obese for a briefer period (73).

Primary CVD risk factors include high waist-to-hip ratio (abdominal adiposity), large waist circumference (visceral adiposity), insulin resistance (with associated hyperinsulinemia), dyslipidemia, and diabetes mellitus type 2 (53,74).

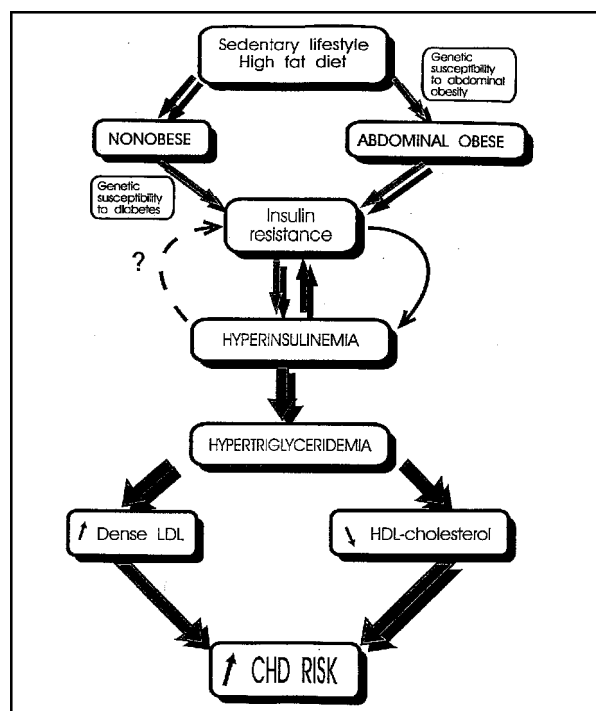


Fig. 2. Insulin resistance, dyslipidemia, and coronary heart disease (CHD) risk. HDL = high-density lipoprotein; LDL = low-density lipoprotein. (From Després JP. Abdominal obesity as important component of insulin-resistance syndrome. *Nutrition*. 1993;9:452-459. With permission.)

Reproductive Disorders

Obesity has a detrimental effect on female reproductive function (75). Obesity is frequently associated with hyperandrogenism in women because adipose tissue is an important site of active steroid production and metabolism (76). Hyperinsulinemia may also cause increased ovarian production of androgen, and insulin inhibits the synthesis of sex hormone-binding globulin; therefore, free testosterone levels are increased in obese women (38). As a result, obese women can experience hirsutism, anovulatory cycles, amenorrhea, decreased fertility, early menarche, and delayed menopause (38,56,77). These reproductive disorders are more pronounced in women with android obesity than in those with gynoid obesity (78) and are more prevalent in women with higher degrees of obesity (79).

Certain Cancers

In comparison with normal-weight women, obese female patients have a higher mortality rate from cancer of the gallbladder, biliary passages, breast (postmenopausally), uterus (cervix and endometrium), and ovaries (50,80). Obese men have a higher rate of mortality from rectal and prostate cancer than do nonobese men (50,80). Both obese men and obese women have an increased risk of colon cancer. Distinguishing between the effects of diet and obesity has been difficult, however, because dietary composition (high fat, high calorie), rather than simply the degree of obesity, may directly influence some cancers, such as those of the colon and breast (52).

Endometrial Cancer.—In women of all ages, endometrial cancer is strongly associated with obesity, an association that is most dramatic in severely overweight women (56). The risk of endometrial cancer increases up to 20-fold in the most obese women (56), and in an American Cancer Society prospective study, women with a BMI >35 had more than a 4-fold increase in mortality (81).

Breast Cancer.—For postmenopausal women with a BMI >35, the mortality ratio due to breast cancer is 1.53 (81). Obesity is associated with breast cancer only in postmenopausal women; this finding may be due, in part, to production of estrogen in adipose tissue (especially abdominal fat deposits) that is unopposed by progesterone (56,82). If this is a mechanism for breast cancer, the absolute fat mass, rather than weight in relationship to height, may be a more accurate predictor of risk of breast cancer (56). The cause of breast cancer, however, is complex; genetic factors, reproductive history, insulin, and nutritional factors (especially dietary fat and fiber intake) may all contribute (83,84). Women who avoid weight gain during adulthood, especially those who do not use postmenopausal hormones, may have reduced breast cancer risk (85).

Prostate Cancer.—Men with a BMI >31 have a 20 to 30% increase in prostate cancer-related mortality (81). Although estrogen receptors have been found in neoplastic prostate tissue, the mechanism for this association is uncertain (56).

Colon Cancer.—Men and women with a BMI >35 have increased mortality from colon cancer (81). Colon cancer has been linked to dietary patterns, including high-fat and low-fiber intake, although the relationships of BMI and resting metabolic rate with risk of colon cancer are undetermined (86).

Gallbladder Disease

Gallstones occur approximately 3 times more often in obese than in nonobese persons (52). Dieting and rapid weight loss also increase the risk of occurrence of gallstones (87-89).

Respiratory Disease

Obesity is a common cause of sleep apnea, and from one-half to two-thirds of patients diagnosed with sleep apnea are obese (90,91). Sleep apnea, a syndrome in which the patient's breathing is obstructed during sleep because of collapse of the upper airway, causes the patient to awaken repeatedly during the night. The result is sleepiness and impaired cognitive performance during the day. Obese patients with sleep apnea tend to have fat deposits adjacent to the pharyngeal airway and in the soft palate and uvula, which narrow the nasopharyngeal airway (90). Most patients with sleep apnea are men, and androgens may also have a role in the pathogenesis of this syndrome (90).

Sleep apnea is associated with an increased risk of vehicular accidents and cardiovascular and cerebrovascular incidents (90,91). The syndrome increases pulmonary arterial pressure in about 25% of patients (90). In severe cases, obesity-hypoventilation syndrome (pickwickian syndrome) and cor pulmonale can occur (52). Pickwickian syndrome is considered a medical emergency because it is frequently fatal (50). Besides obesity and male sex, risk factors for sleep apnea include older age, craniofacial anomalies, and familial risks (90,91). Weight reduction is key to the successful treatment of sleep apnea (91,92), although nocturnal continuous positive airway pressure can relieve the symptoms.

Other Comorbidities

Cross-sectional studies have repeatedly shown that the prevalence of osteoarthritis increases with increasing weight (52,93-96). Moreover, the literature consistently reports that the uric acid level increases with increasing weight (97). Obese patients may also have edema, gastroesophageal reflux, urinary stress incontinence, idiopathic intracranial hypertension, or venous stasis disease of the lower extremities. Other medical complications associated with obesity are acanthosis nigricans, fragilitas cutis inguinalis, hepatic steatosis, impaired cell-mediated immunity, Blount's disease, pseudotumor cerebri, and obstetric complications including toxemia, hypertension, increased frequency of cesarean section, and longer labor (25).

Implications of Weight Cycling

Whether weight cycling (losing and regaining weight) further compromises an obese patient's health is unclear.

Some studies have reported that weight cycling increases upper-body fat, hinders weight-loss efforts because of altered metabolic rate, and may increase mortality rates, although more recent studies contradict these reports (23,98).

Psychologic Manifestations

Although most studies have found no differences in psychologic function between obese and nonobese people, clinical impressions, reports from obese patients (48), and a strong cultural bias against obesity (99) suggest that obese people suffer distress (38). Weight gain is associated with reduced self-esteem (100), and obesity is associated with a higher rate of disability, early retirement, and discrimination against the obese person (11-13).

PREVENTION

Because obesity is influenced by highly variable and complex behavioral, sociodemographic, and cultural relationships, its prevention presents a major challenge. To date, efforts at widespread prevention have been largely unsuccessful (69,101). Nevertheless, one attractive and hopeful view maintains that “obesity is potentially a preventable condition and that, in the long-term setting, humans must learn to optimize their health in the presence of a global food energy surfeit” (102).

Interventions for Prevention

Some promising early results have been reported for “indicated” preventive strategies that target persons who show minimal but detectable signs of obesity (Fig. 3) (103). At the very least, current research suggests that preventive efforts must be targeted toward a high-risk subgroup and designed to be effective within one population that has a homogeneous cultural or belief system—for example, African-American women (104,105). Another factor that seems important to successful prevention of obesity is early intervention during childhood or adolescence when genetic, cultural, environmental, and socioeconomic factors can be modified early (104,106).

In clinical practice, the physician should encourage all patients, particularly those who are at risk, to follow a healthful lifestyle that includes regular, moderate physical activity and a balanced, low-fat diet based on the US Department of Agriculture *Dietary Guidelines for Americans* (15). At-risk individuals may also benefit from some intervention, including behavior therapy (101).

Risk Factors

The following are known risk factors for obesity:

- *Age.* Developmental periods associated with weight gain (early childhood, prepuberty, and the 25- to 35-year age window) and critical life events such as pregnancy, menopause, and the period after successful weight

reduction may pose substantial risk for weight gain (101,103).

- *Mother with gestational diabetes.* Children born to women with gestational diabetes have an increased risk of obesity and glucose intolerance during adulthood (107).

- *Overweight family members.* Children with two overweight parents have a twofold to threefold increased risk of becoming obese (108).

- *Psychosocial factors.* A family history of depression, substance abuse, or sexual abuse may increase the risk of obesity (48).

An overweight condition is most prevalent in adult non-Hispanic black women, Mexican-American men and women, and Hispanic male subjects (3,105). Black women, in particular, have twice the rate of obesity as do white women (109). Abdominal deposition of fat is also common in black women, and the rates of hypertension, stroke, coronary artery disease, and diabetes among black women are reported to be 1.5 to 2.5 times those among white women (109). Unfortunately, few behavioral strategies and programs have been targeted to black Americans (109).

DIAGNOSIS

The physician should perform a comprehensive medical evaluation—including elicitation of a comprehensive patient history, performance of a comprehensive physical examination, appropriate laboratory testing, assessment of overweight and related health risks, and a psychologic-mental status evaluation. This comprehensive evaluation helps the physician achieve the following objectives:

- Diagnose the degree of obesity
- Determine the patient’s level of health risk because of obesity
- Identify any psychologic conditions (such as depression, substance abuse, or sexual abuse) that

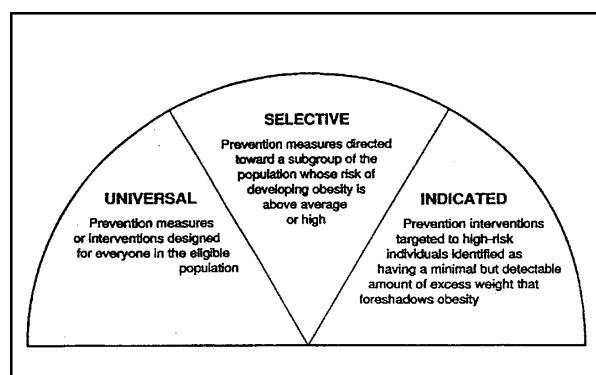


Fig. 3. Strategies for prevention of obesity. (From Institute of Medicine Food and Nutrition Board Committee to Develop Criteria for Evaluating the Outcomes of Approaches to Prevent and Treat Obesity. Thomas PR, ed. *Weighing the Options: Criteria for Evaluating Weight-Management Programs*. Washington, DC: National Academy Press, 1995. With permission.)

must be treated along with the obesity or that may contraindicate obesity therapy

- Identify other substantive contributing factors, such as genetic traits or neurologic disorders—for example, Prader-Willi syndrome, Bardet-Biedl syndrome, or lipodystrophy
- Identify endocrinologic correlates—for instance, insulin resistance or hyperandrogenism
- Determine the most appropriate weight-management strategy

Comprehensive Patient History

Family history should be assessed, including obesity, height, weight, shape (for example, gynoid or android), thyroid disease, CVD, hypertension, cancer, diabetes, and dyslipidemia.

Patient history demands a thorough investigation: eating habits, physical activity habits, stress factors, and psychosocial disorders (that is, poor self-esteem, negative body image, seasonal affective disorder, or binge-eating disorder). Patients with suspected eating disorders should be referred to a psychiatrist or psychologist for further evaluation and treatment. In addition, the following factors should be assessed: history of previous weight-loss attempts, weight history (minimal weight, maximal weight, weight changes, and current weight), use of tobacco, alcohol consumption, drug use, use of medications, and level of motivation.

To determine the best strategy for weight management, the physician must gauge each patient's likelihood for success. Patients who approach a physician about obesity for the first time may benefit from a straightforward program of slightly reduced caloric intake (primarily by decreased fat intake), increased physical activity, and some behavior therapy. Occasionally, a patient may have a reduced resting metabolic rate and edema as the primary cause of overweight. More typically, however, the patient is overweight or obese for other reasons and has engaged in numerous weight-loss efforts. Such a patient is a candidate for more aggressive intervention and should be assessed for motivation and ability to accept and understand realistic goals for weight control. A patient readiness checklist for assessing the patient's dieting history and motivation is presented in Appendix A. (For a further explanation of "realistic goals for weight control" and detailed intervention recommendations, see "Weight-Management Strategies," p. 308.)

Screening should be done for conditions that contraindicate participation in an exercise program or compromise the patient's ability to exercise—for example, recent myocardial infarction, angina pectoris, disabling osteoarthritis of the knees (degenerative joint disease), severe obesity, pulmonary disease, or traumatic injury.

Psychologic-Mental Status Evaluation

The physician should evaluate the state of the patient's self-image, assess general mental health, and

screen for binge-eating disorder (110). Appendix A can be used as a guide for conducting this evaluation (see "General Well-Being Schedule," Appendix A). Patients with a suspected eating disorder should be referred to a psychiatrist or psychologist.

Comprehensive Physical Examination

The physician should conduct a comprehensive physical examination, with special attention to potential comorbidities—for example, evidence of hyperinsulinemia, diabetes mellitus type 2, hypertension, dyslipidemia, and sleep apnea. Of importance, the blood pressure should be measured with use of a sufficiently large cuff to allow an accurate reading and with the patient in a stable, resting state. Pregnant and lactating women are not candidates for a weight-loss program. A screening checklist for sleep apnea is also included in Appendix A.

Laboratory Tests

The following laboratory tests may be useful:

- Lipid profile (total cholesterol, HDL-C, LDL-C, and triglycerides)
- Fasting blood glucose level
- Metabolic and chemistry profile (for example, liver tests and uric acid)
- Thyroid function tests—for example, thyroid-stimulating hormone (thyrotropin)
- Urine free cortisol measures to detect hypercortisolism in patients with signs of possible Cushing's syndrome

Assessment of Body Fat and Related Health Risk

Methods for estimating body fat are outlined in Table 3, although the physician should assess each patient as an individual. Currently, the healthy weight ranges for men and women (Table 2), BMI (Table 1), waist-to-hip ratio, and waist circumference are clinically effective and economic tools for assessing overweight. All four methods (as well as any other valid methods) may be used in clinical practice, in combination with visual inspection, to assess the degree of body fat and the associated medical risk.

The BMI is valuable because it correlates with total body fat. BMI does not indicate distribution of body fat; BMI is $\text{weight (kg)} \div [\text{height (m)}]^2$ and can be easily determined by using Table 1. The health risk increases as the BMI increases beyond the desirable range (and when the patient has at least one comorbidity) (Fig. 4). Some patients with a BMI <25, however, are at increased medical risk because of visceral accumulation of fat. The waist-to-hip ratio and waist circumference measurements should be used to determine the extent of abdominal adiposity.

The ratio of abdominal circumference to gluteal circumference is an indicator of location of body fat and is therefore a valuable determinant of health risk. The correct method for determining the waist-to-hip ratio is outlined

in Table 4. A nomogram for determining the waist-to-hip ratio and the degree of health risk associated with this measure are shown in Figures 5 and 6, respectively. Alternatively, the physician may measure the waist, abdominal, buttocks (hip), and thigh circumferences, as described by Lohman et al. (111).

The waist circumference correlates with the absolute amount of visceral adiposity (53,112), and a waist circumference of 40 inches (102 cm) in men and 35 inches (89 cm) in women may represent the critical threshold above which metabolic complications are more likely to develop (53). A waist circumference of 37 inches (94 cm) for men and 31.5 inches (80 cm) for women identifies patients with a

BMI of 25 and patients with lower BMIs but high waist-to-hip ratios (113). A waist circumference of 40 inches (102 cm) for men and 34.5 inches (88 cm) for women identifies patients with a BMI of 30 and patients with lower BMIs but high waist-to-hip ratios (113).

WEIGHT-MANAGEMENT STRATEGIES

Success in treatment of obesity has, in the past, been measured by how rapidly weight is lost and the amount of

weight loss (114,115). Today, success should be measured by the ability to achieve **and maintain** a clinically helpful and significant weight loss and by the salutary effects of weight loss on comorbidities of obesity, such as diabetes mellitus type 2, hypertension, and dyslipidemia. Acceptance of this concept by both the patient and the physician is essential to successful treatment of obesity (116).

Almost 4 decades ago, appreciable weight loss in the obese patient was unusual, and in the few patients who did succeed, weight loss was almost always transient (117). Today, patients who complete traditional programs designed to produce short-term weight loss lose approximately 10% of body weight but tend to regain two-thirds of it within 1 year and almost all of it within 5 years (Fig. 7) (43,103,118-121). This relapse occurs because treatment of obesity does not cure the condition. When treatment stops, weight is regained. This relapse results from a complex interaction of biologic and psychologic factors that influence the energy balance (122). These factors include failure to maintain regular physical activity, which would promote energy consumption; undereating, which can trigger excess energy intake; patient demotivation; and a reduced resting energy expenditure (REE) due to

Table 3
Methods of Estimating Body Fat and Distribution

Method	Cost	Ease of use	Accuracy	Measure regional fat?
Height and weight	Low	Easy	High	No
Skin folds	Low	Easy	Low	Yes
Circumferences	Low	Easy	Moderate	Yes
Density				
Immersion	Moderate	Moderate	High	No
Plethysmograph	High	Difficult	High	No
Heavy water				
Tritiated	Moderate	Moderate	High	No
Deuterium oxide or heavy oxygen	Moderate	Moderate	High	No
Potassium isotope	High	Difficult	High	No
Conductivity, total body electrical	High	Moderate	High	No
Bioelectric impedance	Moderate	Easy	Moderate	No
Fat-soluble gas	Moderate	Difficult	High	No
Computed tomography	Very high	Difficult	High	Yes
Ultrasonography	High	Moderate	Moderate	Yes
Neutron activation	Very high	Difficult	High	No
Magnetic resonance	Very high	Difficult	High	Yes
Dual energy x-ray absorptiometry	Moderate	Moderate	High	Yes

Modified from (primary source): Bray GA, Gray DS. Obesity: part I—pathogenesis. *West J Med.* 1988;149:429-441. With permission.

Additional sources: Wang ZM, Heschka S, Pierson RN, Heymsfield SB. Systematic organization of body-composition methodology: an overview with emphasis on component-based methods. *Am J Clin Nutr.* 1995;61:457-465.

Jensen MD, Kanaley JA, Roust LR, et al. Assessment of body composition with use of dual-energy x-ray absorptiometry: evaluation and comparison with other methods. *Mayo Clin Proc.* 1993;68:867-873.

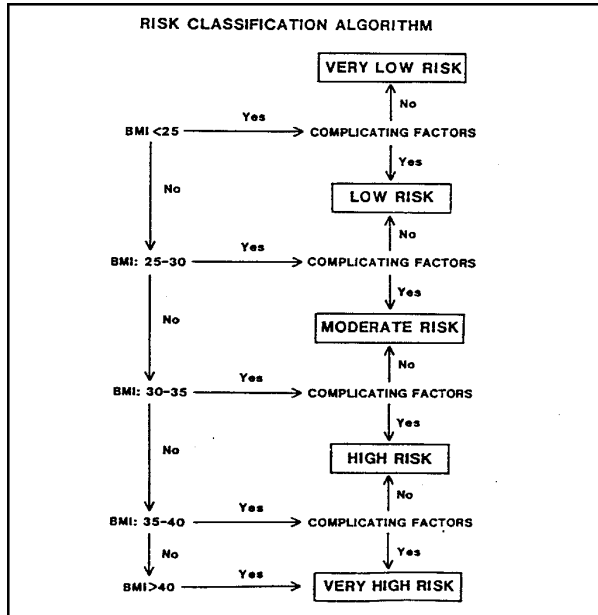


Fig. 4. Determination of medical risk, based on body mass index (*BMI*) and presence of comorbid conditions. (Source: George A. Bray, M.D.)

weight loss, which may be below that normally associated with the new body weight (123,124).

Even when a modest weight loss of 5 to 10% can be maintained, however, many patients with comorbidities will experience substantial health benefits (23,125). Such patients are likely to have decreased blood pressure measurements, improved blood glucose levels, improved lipoprotein profiles (reduced triglycerides, decreased total cholesterol, and increased HDL-C), ameliorated sleep apnea symptoms, decreased pain from osteoarthritis, and increased self-esteem (125). Patients on weight-loss programs, especially programs that promote rapid weight loss such as VLCDs, may also experience some adverse effects—such as low serum sodium or potassium levels, cholelithiasis, and liver dysfunction. Except for the rare occurrence of arrhythmia or sudden death, these adverse effects are relatively minor and do not outweigh the benefits of sensible weight loss (126).

Weight-loss management strategies can be classified into three broad categories: basic treatment, pharmacotherapy, and surgical treatment. The criteria for selecting an appropriate strategy are outlined in Table 5.

AACE and ACE believe that, after assessment of an overweight patient by the physician, an appropriate weight-management program should be offered. For the patient requiring medication or surgical intervention for weight control or medication for treatment of comorbidities, physician management is essential. Note that the *Guidance for Treatment of Adult Obesity* document, produced by Shape Up America! and the American Obesity Association, does not place the physician in the central management role of a weight-loss or weight-maintenance

Table 4
Accurate Measurement
of the Waist-to-Hip Ratio

1. *Locate the waist.* The waist is the smallest circumference of the torso and is not necessarily at the umbilicus. In obese patients in whom the waist is not present, measure the smallest horizontal circumference between the 12th rib and the iliac crest
2. *Measure the waist.* The patient should be unclothed at the waist and standing with abdomen relaxed, arms at sides, and feet together. Use nonstretchable tape measure, and do not compress the skin
3. *Locate the hip.* The hip is the maximal posterior extension of the buttocks. In obese patients, the anterior abdominal wall may sag and must be included in the measurement
4. *Measure the hip.* The patient should be wearing underwear and should stand tall but relaxed with arms at sides. Use nonstretchable tape measure, and do not compress the skin
5. *Calculate the waist-to-hip ratio.* Divide the waist circumference by the hip circumference

From Yanovski SZ. A practical approach to treatment of the obese patient. *Arch Fam Med.* 1993;3:309-316. With permission.

program. It is incumbent on the physician to adhere to the following principles.

- *Treat the patient with sensitivity and respect.* Many obese persons report disrespectful treatment by the medical profession (121). The office environment should be friendly to the severely obese patient—for example, use armless chairs and a blood pressure cuff sufficiently large to allow an accurate determination (123).

- *Conceptualize obesity as a heterogeneous group of chronic disorders.* This approach helps the physician to maintain emphasis on the heterogeneous nature of obesity, recognize the need to treat each patient individually (for example, as is done for hypertension therapy), and remember the long-term nature of the disorder (123). The concept that obesity is a chronic disorder that requires long-term—perhaps lifelong—treatment is similar to that applied to hypertension or diabetes mellitus and has been well described (123,127).

- *Consider consultation or concomitant therapy for the patient with coexisting psychologic conditions* (for example, depression) that can stem from difficult life events (such as childhood abuse). Obesity treatment is unlikely to be successful if these conditions are not addressed.

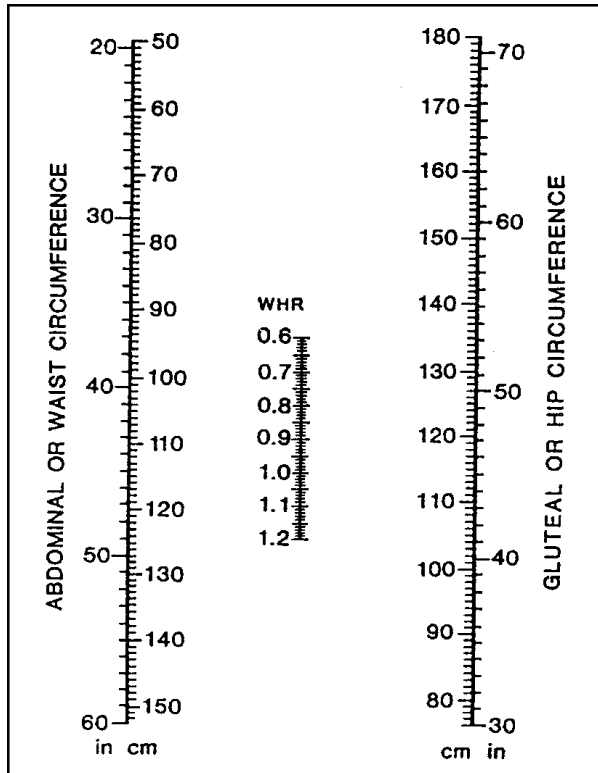


Fig. 5. Waist-to-hip ratio (WHR) nomogram. (Note: In lieu of the nomogram, use a calculator and divide the waist circumference by the hip circumference.) (From Bray GA, Gray DS. Obesity: part 1—pathogenesis. *West J Med.* 1988;149:429-441. With permission.)

Basic Treatment

All obese patients—whether or not they are candidates for pharmacotherapy or surgical treatment—should undergo basic treatment. Basic treatment should include counseling, caloric restriction, behavior therapy, and physical activity. The goal of any basic treatment program is to integrate positive eating and physical activity behaviors into the patient's life. The program should be well supervised.

AACE and ACE recommend only programs that actively encourage lifestyle changes (for example, proper nutrition and regular physical activity) and require participation (preferably in a group setting) in an ongoing, well-supervised weight-maintenance program. Many placebo-controlled studies have shown that such basic treatment can successfully yield weight loss of approximately 1 pound per week in some patients, without the aid of pharmacotherapy or surgical treatment (114,118).

Nevertheless, patients often revert to old behaviors and regain weight. Therefore, a structured weight-maintenance program with indefinite, continual contact is also needed to help the patient sustain weight loss (see "Maintenance of Weight Loss," p. 321).

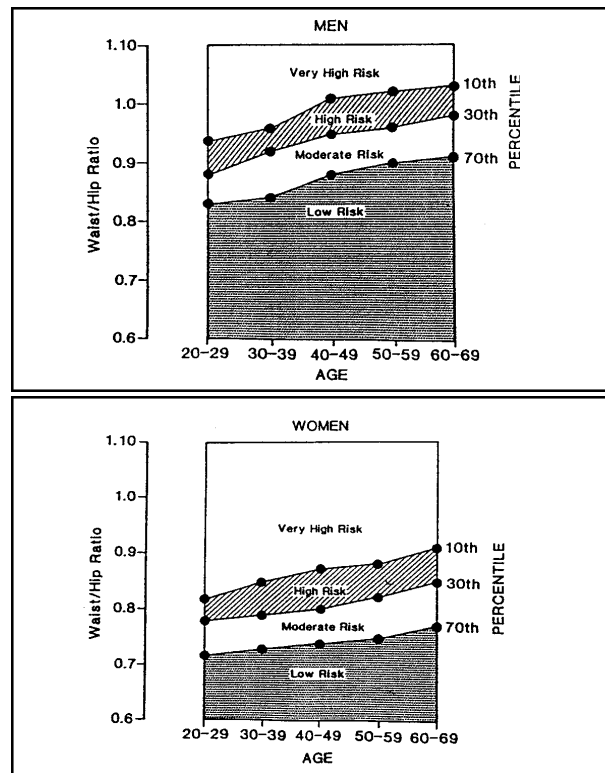


Fig. 6. Health risk associated with waist-to-hip ratios for men (top) and women (bottom). (From Bray GA, Gray DS. Obesity: part 1—pathogenesis. *West J Med.* 1988;149:429-441. With permission.)

Essential Components

All basic programs for treatment of obesity have several essential components.

- **Attainable weight-loss goals.** Both the desired rate of weight loss and the ultimate weight-loss goal must be reasonable and achievable. When the projected rate of weight loss is determined, gradual weight reduction should be emphasized. For most obese patients, a weight-loss goal of 10 to 15% is reasonable. The mean weight-loss goal after the initial month of treatment should approximate 1 pound per week. A person with a strong family and personal history of obesity should not strive for weight in the normal range (128).

Attempts to achieve goals defined by external criteria such as desirable body weight usually fail (115). This outcome is likely to be viewed by the patient as a personal failure and can result in lowered self-esteem, explosive weight regain, and a reduced chance for future weight-loss success.

- **Regular contact.** In any basic treatment program, the patient should have consultations regularly (initially, weekly to biweekly; subsequently, monthly) for at least 1 year. These visits should include the physician and other

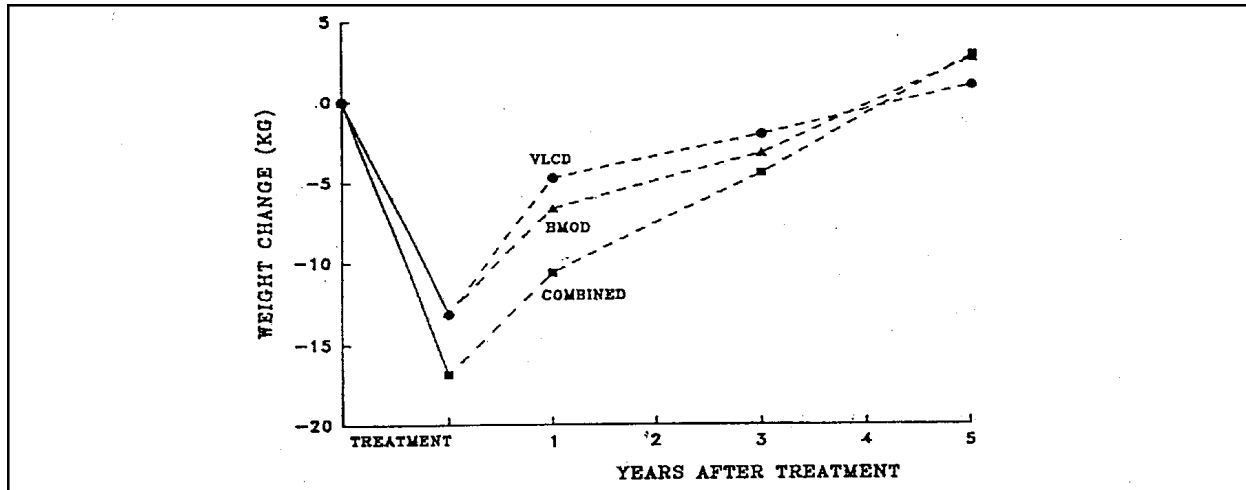


Fig. 7. Five-year pattern of weight change in obesity treatment, based on a prospective study of 76 women. VLCD = very-low-calorie diet alone. BMOD = behavior therapy combined with 1,200 kcal/day diet of conventional foods. Combined = very-low-calorie diet combined with behavior therapy. No statistically significant differences were noted among the three groups at 3- or 5-year follow-up. (From Wadden TA, Sternberg JA, Letizia KA, Stunkard AJ, Foster GD. Treatment of obesity by very low-calorie diet, behavior therapy, and their combination: a five-year perspective. *Int J Obes.* 1989;13[Suppl 2]:39-46. With permission.)

members of the multidisciplinary team. Such monthly sessions should provide nutrition education, identify causes of weight excess (for example, inactivity, high energy and fat intake, psychologic factors, and hereditary factors), help patients determine and discuss personal situations and risk factors, clearly communicate the complications associated with obesity, and provide guidance on lifestyle changes (see "Lifestyle Changes," p. 314). A physician should monitor patients who are consuming VLCDs (see "Restriction of Calories," below) and patients with comorbid conditions that necessitate close medical supervision every week during the first month of treatment and as clinically indicated thereafter.

For all patients, the value of group sessions, which provide mutual support and sharing, cannot be underestimated. Support ("buddy") relationships are often key to continued success when the patient has an eating disorder, just as they are for those with other behavioral disorders (for example, alcohol abuse) (129).

- **Emphasis on weight-loss maintenance.** Subsequent participation in a program designed to help the patient maintain the weight loss is also essential (see "Maintenance of Weight Loss," p. 321).

- **Informed consent.** The patient must be aware of the level of commitment required, the program content, and the past program success rates, if available. A sample informed consent form is shown in Appendix B.

- **Physician role.** Basic treatment should always be conducted by a physician.

Essential Modes of Therapy

Counseling.—Before initiating treatment, the physician should prepare the patient by clearly communicating the medical reason (or reasons) for weight loss tailored to the patient's specific problems. This approach enables

patients to accept the concept of a healthful lifestyle, while de-emphasizing weight loss as the primary goal. It also helps the patient understand the physician's role in the program and realize that even modest weight loss can be beneficial. The physician should also explain the importance and benefits of realistic weight loss as well as emphasize the importance of good, basic nutritional principles. Furthermore, potential physiologic and psychologic changes that the patient may experience should be identified—especially if a rapid weight-reduction phase is planned (that is, with a VLCD or surgical treatment of obesity). Finally, the need for regular, moderate physical activity should be explained (see "Physical Activity," p. 314).

Worksheets that may help guide the initial counseling session and encourage patient commitment are included in Appendix C. A detailed list of potential complications or side effects of VLCDs and counseling advice are provided in Appendix D.

Restriction of Calories.—Caloric restriction can be moderate to severe, depending on the patient's health risk. A moderate caloric deficit or low-calorie diet (LCD; 800 or more calories daily) is indicated for most patients, whereas more severe caloric restriction (VLCD; 250 to 799 calories daily) is limited to patients who face major health risks.

A moderate caloric deficit or LCD is a first-line approach for obese patients who are attempting to lose weight for the first time. This regimen is also indicated for patients with BMI from 25 to 35 who have a good diet history (that is, may have failed at one attempt but are motivated to lose weight).

Although a LCD is traditionally defined as a diet that provides caloric intake of approximately 1,200 kcal/day

Table 5
General Criteria for Selecting a Weight-Management Strategy*

Basic treatment with LCD	Basic treatment with LCD or VLCD†	Basic treatment with LCD or VLCD† and pharmacotherapy	Surgical treatment
BMI 25 Good diet history	BMI 35 BMI 30 with comorbid conditions Poor diet history	BMI 35 BMI 30† BMI 27-29 with comorbid conditions‡ Poor diet history	BMI >40 BMI 35 with life-threatening or disabling comorbid condition(s) Obesity history 5 yr No history of alcoholism or major psychiatric disorders 18 yr old

*BMI = body mass index; LCD = low-calorie diet; VLCD = very-low-calorie diet.
†VLCDs are reserved for nonelderly adults with high health risk due solely to BMI or BMI with serious comorbid condition(s).
‡In combination with LCD only.

for women or 1,500 kcal/day for men, an individualized approach is more likely to succeed in clinical practice. For instance, an obese woman with an energy expenditure of 1,500 kcal/day would lose 1 pound a week on a 1,000 kcal/day diet, whereas an obese woman with a daily energy expenditure of 2,500 kcal/day would lose approximately 3 pounds a week on the same diet (118). Therefore, the physician and dietitian should determine caloric requirements for each patient based on daily energy intake, daily energy expenditure, and an average weight-loss goal of approximately 1 pound per week after the first month (128).

To determine initial caloric requirements, calculate daily caloric intake based on a daily caloric deficit of 500 kcal, with use of the resting energy expenditure (REE) equation recommended by Mifflin et al. (130):

$$\text{REE} = [9.99 \times \text{weight (kg)}] + [6.25 \times \text{height (cm)}] - [4.92 \times \text{age (yr)}] + [166 \times \text{sex (male = 1; female = 0)}] - 161$$

Multiply REE by an activity factor of 1.5 for women and 1.6 for men (131), and then subtract 500 kcal to determine the caloric intake needed to achieve a weight loss of approximately 1 pound per week (103).

Alternatively, the physician may use the Harris-Benedict equation to calculate REE or basal metabolic rate (BMR). This equation, however, overpredicts REE by 5 to 24% (130). The Harris-Benedict equation follows (132,133):

$$\text{BMR for males} = 66 + 13.8 (\text{weight in kg}) + 5 (\text{height in cm}) - 6.8 (\text{age in yr})$$

$$\text{BMR for females} = 655 + 9.6 (\text{weight in kg}) + 1.8 (\text{height in cm}) - 4.7 (\text{age in yr})$$

For otherwise healthy patients, the basic nutritional proportions should be consistent with the recommendations outlined in the US Department of Agriculture *Dietary Guidelines for Americans* (15). The diet must be realistic—that is, based on dietary modification and practical changes in eating habits. For example, nutritional recommendations should be based on the patient's current eating habits, lifestyle, ethnicity and culture, other coexisting medical conditions, and potential nutrient-drug interactions. The patient should also drink at least 1.5 to 2.0 quarts of water daily (128), unless cardiac disease (such as congestive heart failure), edema, or renal insufficiency is present. For patients with renal disease, diabetes, or other metabolic disorders, the physician should determine protein requirements. Energy restriction and weight loss may also necessitate changes in scheduling or dosage of medications such as orally administered glucose-lowering agents or insulin.

The diet, which should be prescribed by the physician and implemented by the dietitian, is most likely to succeed when it is the patient's first attempt at weight loss. LCDs are safe for patients with comorbid conditions such as diabetes mellitus, hyperlipidemia, or hypertension; in such cases, the physician should be actively involved in patient

management. The assistance of a dietitian can be invaluable, inasmuch as energy intake should be evaluated monthly. Food logs or record books should be completed by the patient and adjusted, if necessary, to ensure that the rate of average weight loss does not exceed or fall short of the weekly goal. Of importance, changes in body weight may not reflect changes in body fat if the patient has edema, and the rate of weight loss can be expected to decline as the patient's energy requirements decline. If energy intake must be adjusted below 1,200 kcal/day, daily supplementation is indicated to ensure adequate vitamin and mineral intake (128).

Potential complications include the following (134): ketosis (if the diet contains <100 g of carbohydrate daily), excessive loss of lean body mass, arrhythmias, dehydration, and a tendency for recidivism. On the average, LCDs result in a total weight loss of 13 to 17 pounds during a period of 20 to 24 weeks (135). Some patients, however, need to lose more weight and may need to lose it more rapidly; in such cases, a VLCD may be necessary.

A VLCD is a liquid formulation or food diet that provides <800 kcal/day (136). A daily caloric intake of <800 kcal is not usually recommended because little evidence exists to show that VLCDs providing less energy will increase weight loss (135). Just as with standard LCDs, the exact number of calories in the VLCD should be individualized (137).

A VLCD is appropriate only when the patient faces a major health risk and the physician has determined that such a diet can be used safely. *Indiscriminate use is a serious mistake.* VLCDs are indicated for patients who meet specific criteria. They should have a high or very high health risk due to BMI alone (BMI 35) or BMI 30 in association with serious comorbid conditions (for example, congestive heart failure). The physician should not prescribe a VLCD to patients who have a BMI 30 because such patients have an increased risk of negative nitrogen balance and loss of lean body mass (118,137). Candidates for VLCDs should have failed prior weight-loss attempts and should demonstrate motivation to adhere to the VLCD, with commitment to participate in a lifestyle change program to maintain the weight loss (see "Maintenance of Weight Loss," p. 321). VLCDs can be considered in adults 65 years of age, unless circumstances are extenuating (for example, cardiopulmonary failure). Because of the reduction in anabolic hormones—such as insulin, insulin-like growth factors, and growth hormone—with aging, nitrogen loss associated with hypocaloric dieting increases with advancing age (137). The risks of obesity in elderly persons are also unclear (137). The contraindications to use of VLCDs are listed in Table 6.

Historically, "liquid protein" VLCDs were associated with at least 58 deaths because these diets contained protein of poor biologic value, usually did not contain other nutrients, and were often taken without supervision (138). The VLCD should provide daily protein of at least 1 g/kg of desirable body weight. This protein must be of high

biologic value—from lean meat, fish, or fowl or, in the case of liquid diets, from dairy sources, soy, or albumin—to maximize preservation of lean body mass. Most liquid formulations provide between 0.8 and 1.5 g of protein per kilogram of desirable body weight per day, up to 100 g of carbohydrate, a minimum of essential fatty acids, and the recommended allowances of vitamins, minerals, and electrolytes.

Clearly, VLCDs are still associated with more side effects and greater risk for potentially serious complications than are LCDs. Usually, however, they are associated with only minor complications when administered to carefully selected patients by experienced physicians (139). With use of a VLCD, patients receiving drugs to treat diabetes or hypertension require close surveillance because doses of both types of medication will probably have to be reduced or discontinued. Cholelithiasis is the most frequent complication of VLCD therapy. It occurs in up to 25% of patients on VLCDs (140) and is most common when weight loss consistently exceeds 3 to 5 pounds per week. It is not associated with more conservative weight-loss approaches that rely primarily on behavior modification. Serious complications can include excessive loss of lean body mass (141) and sudden death in medically vulnerable persons who have comorbidities, especially if daily caloric intake is <600 kcal. A complete review of the potential complications and side effects associated with VLCDs, as well as patient counseling recommendations, is presented in Appendix D.

Table 6
Contraindications
to Very-Low-Calorie Diets

Recent myocardial infarction
Cardiac conduction disorder
History of cerebrovascular, renal, or hepatic disease
Type 1 diabetes mellitus
Major psychiatric disorders
Gallbladder disease
Alcoholism
Cancer
Infection
Acute substance abuse
Anorexia
Human immunodeficiency virus

Modified from Pi-Sunyer FX. The role of very-low-calorie diets in obesity. *Am J Clin Nutr.* 1992;56:240S-243S. Wadden TA, Van Itallie TB, Blackburn GL. Responsible and irresponsible use of very-low-calorie diets in the treatment of obesity. *JAMA.* 1990;263:83-85.

Patients who receive a VLCD require close medical supervision (43). A physician should see such patients in consultation weekly during the rapid weight-loss period and every 2 to 4 weeks thereafter. At each visit, patients should undergo a basic serum chemistry evaluation—including electrolytes and liver function tests. This fairly intensive medical monitoring will help the physician detect the small minority of patients who may react adversely to the VLCD (139). The physician must often discontinue administration of diuretics because of an increased risk of dehydration and electrolyte imbalance (142).

The duration of use of a VLCD should not exceed 12 to 16 weeks (137). Longer-term VLCD programs can lead to excessive nitrogen loss (as the patient continues to lose weight), gallstone accretion, and relapse or recidivism. Relapse or recidivism can stem from patient demotivation because the transition back to food can be psychologically difficult after long periods of consumption of a liquid diet, especially when substantial and unrealistic weight loss has occurred (137). After the diet has been discontinued, the daily caloric intake should be gradually increased during a 3-month period because the decline in resting metabolic rate usually persists for about 3 months (142).

VLCDs can yield 2 to 3 times more weight loss than LCDs (118), and the rate of weight loss is usually greater. VLCDs usually produce weight loss of 3.3 pounds per week in women and 4.4 pounds per week in men, with the total loss after 12 to 16 weeks averaging 44 pounds. Improvements in glycemic control, decreases in systolic and diastolic blood pressure, and decreases in serum concentrations of total cholesterol, LDL-C, and triglycerides often occur within 3 weeks (103). Investigators have hypothesized that the short-term success of VLCDs, in comparison with LCDs, is attributable more to the structure of the diet rather than to the difference in caloric intake. Obese patients, when asked to consume a conventional diet, underestimate caloric intake by as much as 40% (40,118). In contrast, portion- and calorie-controlled servings and liquid diets may promote adherence (118).

Although few long-term studies are available, long-term success with VLCDs seems no better than that with LCDs (98,143). As with any other type of caloric restriction, combining behavioral therapy and physical activity with the VLCD seems to improve maintenance of weight loss (129,135).

Lifestyle Changes.—Counseling for lifestyle changes should be provided. This enables patients to evaluate and modify eating practices, habits of physical activity, and emotional responses to weight (118). Sessions should be conducted weekly (118), or at least monthly, and should include a structured program with long-term follow-up. The LEARN manual is one of several useful guides to help patients with behavior changes (144).

A lifestyle change program should include *self-monitoring*. Patients should keep daily logs or records of physical activity, food intake, and problems. These diaries, which should be reviewed at clinical visits (118), help the

physician, counselor, and dietitian identify behaviors that need to be changed. Patients should be taught *portion control*, should participate in the weighing of food, and should learn to gauge the size portions they eat.

Stimulus control helps the patient identify and avoid environmental cues associated with unhealthful eating and sedentariness, such as holidays, dining out (cafeteria or buffet style), travel, exhaustion, and missed meals. Strategies for modifying these cues include limiting eating to specific times and places, purchasing food when not hungry, and laying out physical activity clothing to encourage regular participation (103).

Contingency management includes the use of rewards for positive lifestyle changes such as reducing the grams of fat in the diet and increasing minutes of daily physical activity (103). Another aspect of treatment, *stress management*, includes meditation, relaxation techniques, and regular physical activity to cope with stress (103).

Cognitive-behavioral strategies, such as creative visualization, help to change a patient's attitudes and beliefs about unrealistic expectations and body image (103). This approach involves the regular use of positive self-statements and visual imagery—that is, seeing oneself eating and exercising appropriately.

Participation in weight-loss *support groups* tends to reduce uncertainty about self-worth (145). Generally, group programs, rather than couples' programs, are more effective in helping patients sustain weight-loss behavior. A disinterested or marginally involved spouse may actually increase the likelihood of failure (145).

Support sessions should be conducted in closed groups of 10 to 20 participants that form at the beginning of the program. Attrition rates average only about 13% in closed-group programs, whereas they are as high as 70% in open-group programs (103).

An overly ambitious program must be avoided. An incremental approach to lifestyle change is best. Greater success may be achieved if treatment focuses on a few crucial issues—such as eating in social situations and mechanisms for obtaining satisfaction from smaller intakes of food (slow eating methods and concentration on eating as a unique activity)—rather than on numerous, more global issues (115).

In a pilot study of lifestyle modification in patients participating in a basic weight-loss program and receiving pharmacotherapy, traditional group behavior modification by a nutritionist (32 sessions of 75 minutes each during a 1-year period) was compared with lifestyle modification by ten 15- to 20-minute structured physician visits throughout a year. The results were comparable, and the weight loss for the year correlated well with patient completion of daily food records and with the rate of weight loss during the initial 4 weeks (146).

Physical Activity.—Although regular, moderate physical activity alone results in a limited weight loss of 4 to 7 pounds over the long term (134), it is an essential and high-priority element of any weight-management program. Regular physical activity is the most important pre-

dicator of long-term weight maintenance (103,118,147). Correlational studies and randomized trials have shown that patients who diet and exercise regularly are much more likely to maintain weight loss than those treated by diet alone (118,147), and regular physical activity is especially beneficial for male patients with a high waist-to-hip ratio (148).

When performed in combination with restriction of calories, regular, moderate physical activity achieves the following results: increases energy expenditure; maintains or minimizes the loss of lean body mass (128,134) [for patients on a VLCD, physical activity may slow the loss of lean body mass, but results are inconclusive (118)]; reduces cardiovascular risk by producing beneficial changes in the lipid profile (149); has positive psychological effects, including stress reduction and an improved sense of well-being and optimism (150,151); reduces insulin resistance (152); and may provide other health benefits (some normalization of blood lipids, glucose, and insulin), even when the patient remains overweight. Some studies show lower mortality in active persons in comparison with those who are sedentary or physically unfit (148,153).

The goal of any weight-management program should be at least 30 minutes of moderate-intensity physical activity 5 to 7 times per week. In order to achieve this goal, emphasize consistency and comfort first; encouraging incorporation of physical activity into a person's lifestyle is important (128). At the onset, create a low-level workout, and recommend that the patient develop a consistent pattern of physical activity. Initially, several 10-minute periods of physical activity throughout the day—for example, a 30-minute daily aggregate of brisk walking (154), aerobic physical activity such as exercise tapes, or housework such as vacuuming—performed 3 days per week may be more important than 30 minutes of continuous physical activity performed 6 days per week (155).

Encourage appropriate, intermittent physical activity when needed. If a patient cannot perform 10 or 20 minutes of continuous physical activity, alternate work and rest intervals (155). The intensity, duration, and frequency of activity should be gradually increased; maintain each level of intensity and duration for at least 1 to 2 weeks (128). Identify opportunities for increased activity—such as using stairs rather than elevators, parking a distance from the mall rather than at the store entrance, and taking 10- to 15-minute walks after meals (128).

Self-documentation of the type and duration of physical activity is also important. Emphasize the importance of ample intake of water (1.5 to 2.0 quarts per day), but avoid water overload in patients with heart or renal disorders. Ensure that all patients can recognize and deal with abnormal physical responses to physical activity. Directly supervise patients with conditions such as diabetes or CVD. Make these patients aware of any warning signs of their disease that may manifest during physical activity, and provide guidance when needed. For example, patients with diabetes, vascular disease, degenerative joint disease,

traumatic injuries, rheumatoid arthritis, and pulmonary or cardiac limitations must be aware of the importance of excellent foot care (128).

The patient who needs to exercise but cannot do so because of a medical condition (for example, heart disease, pulmonary disease, severe degenerative joint disease, morbid obesity, or traumatic injury) should be referred to a physician, therapist, or exercise physiologist for a tailored program of physical activity.

Pharmacotherapy

AACE and ACE do not condone antiobesity agent therapy when used simply for cosmetic purposes or when weight loss can be achieved and maintained without pharmacotherapy. When needed to reduce a health risk, used in the context of long-term disease management, and prescribed and supervised by an *experienced* physician such as an endocrinologist, internist, or family practitioner, pharmacotherapy may increase the effectiveness of a basic weight-management program and should be used only in conjunction with such a program. Although antiobesity agents can improve weight loss, they may also be associated with adverse effects, including even the potential for a fatal outcome.

Generally, AACE and ACE recommend prescribing only Food and Drug Administration (FDA)-approved agents. AACE does not advocate the use of any antiobesity agent, prescription or otherwise, that has not undergone thorough clinical testing. Any administration beyond a few weeks (usually considered as 3 months)—except for sibutramine, which may be given for up to 1 year—is an “off-label” use. The physician should be aware of the recommended treatment duration, although long-term use of an appropriate antiobesity agent may be necessary for successful, long-term maintenance of weight loss. When long-term use is indicated, the patient should understand the benefits and possible risks of such treatment. Use of an informed consent form is advised because the long-term safety and efficacy of antiobesity pharmacotherapy are unknown (see Appendixes B and E for sample informed consent forms). AACE and ACE do not believe that formal Institutional Review Board approval is necessary for such long-term use unless a formal protocol has been implemented, although the physician should continue to monitor the patient for adverse effects.

Antiobesity agents that have been approved by the FDA affect the noradrenergic or serotonergic pathway (or both); they are listed in Table 7. Two previously available agents—fenfluramine and dexfenfluramine—have recently been withdrawn and are not included in the compilation. A recently approved agent (sibutramine) has been added to the list. All except one of these antiobesity agents affect the noradrenergic rather than the serotonergic pathway. Sibutramine has effects in both pathways.

Weight Loss

Patients who take active drug are more likely than those who do not to achieve a clinically significant weight

Table 7
Summary of Data on Available Antiobesity Agents*

Agent	Schedule	Trade name(s)	Dosage form (mg)	Administration
<i>Approved for use up to 1 year</i>				
Sibutramine HCl	IV	Meridia	5, 10, 15	Initial dose: 10 mg 1 ×/day Maximal dose: 15 mg 1 ×/day
<i>Approved for short-term use</i>				
Diethylpropion HCl	IV	Tenuate	25	25 mg 3 ×/day
		Tenuate Dospan	75	75 mg 1 ×/day
Mazindol HCl	IV	Sanorex	1, 2	Initial dose: 1 mg 1 ×/day Maximal dose: 1 mg 3 ×/day with meals
Phentermine resin†	IV	Ionamin	15, 30	15 mg/day (30 mg for less responsive patients)
Phentermine HCl†	IV	Adipex-P	37.5	37.5 mg/day in AM
		Obe-Nix 30	37.5	37.5 mg/day in AM
		Fastin	30	30 mg/day 2 h after AM meal
<i>Second-line agents</i>				
Benzphetamine HCl	III	Didrex	25, 50	Initial dose: 25-50 mg 1 ×/day Maximal dose: 25-50 mg 3 ×/day
Phendimetrazine tartrate	III	Prelu-2	105	105 mg in AM
		Plegine	35	35 mg before meals
		X-Trozine:		
		Standard	35	35 mg before meals
		Extended release	105	105 mg 30-60 min before morning meal
		Bontril:		
		PDM	35	35 mg before meals
		Slow-release	105	105 mg 30-60 min before morning meal
<i>Over-the-counter agents</i>				
Phenylpropanolamine	Unscheduled	Dexatrim Acutrim	25, 75	25 mg 3 ×/day

*Schedule II agents (for example, amphetamine, methamphetamine, and phenmetrazine) are not included because of abuse potential. Because fenfluramine and dexfenfluramine were withdrawn from the market in 1997, they are not included in this summary.

†The FDA's "Orange Book" classifies phentermine HCl and phentermine resin as two separate products that are not bioequivalent and cannot be substituted for each other. Although the clinical significance of these differences is unknown, they are sufficient for the two agents to be considered distinct entities (177).

loss of 10% of initial body weight (156). Approximately a third of the patients, however, do not respond to pharmacotherapy (115,157,158). Among responders, weight loss can vary widely (159), and the weight loss tends to plateau after approximately 6 to 8 months (103,114,115, 160-163). The reason for this variation is unclear, but tolerance does not seem to be the cause (114).

On average, antiobesity agents produce a weight loss of 4 pounds in 4 weeks in responders (115,160). When pharmacotherapy is initiated, a 3- to 6-week run-in period can often predict patient responsiveness, inasmuch as weight loss during this period is a major indicator of success (115). A recently published clinical study, in which response was defined as a loss of 1% of weight in the initial 4 weeks of pharmacotherapy, showed an 89% response rate in patients receiving the maximal dose of the active drug versus 61% in patients receiving placebo (164). If patients do not lose weight during the run-in period, the physician may discontinue pharmacotherapy because titration even to maximal levels apparently does not increase effectiveness (115). This approach will minimize unnecessary exposure and risks. Failure of antiobesity drugs to work in many patients may reflect the fact that such agents do not address the problem of the body's error in appropriately judging and regulating energy stores. Studies that have shown relatively better weight-loss results interestingly also have shown good weight loss in the placebo groups (160), in comparison with those of other studies. This outcome highlights the importance of lifestyle changes to maximize pharmacologic efficacy.

Maintenance of Weight Loss

Although their utility for weight loss has been recognized for many years, antiobesity agents have been noted only recently as useful for long-term maintenance of weight loss. A double-blind clinical trial addressed questions of safety and efficacy by demonstrating no difference in side effects between placebo and combination low-dose fenfluramine-phentermine therapy (165). Recent concerns about cardiac valvulopathy were not seen in this relatively small study population. The concept of obesity as a chronic disease that necessitates a treatment approach similar to that for hypertension or diabetes mellitus, however, gained acceptance only after publication of a 3.5-year study of this combination treatment by Weintraub et al. (115) in 1992. Obesity is no longer attributed primarily to behavioral disorders, and it may be responsive to a comprehensive program of treatment that includes long-term pharmacotherapy (166).

Studies that have investigated the long-term (1- to 3.5-year) effectiveness of the antiobesity agents (fenfluramine plus phentermine resin) have shown that these drugs helped maintain reduced body weight in a substantial number of patients (103,115,160,167). When pharmacotherapy was discontinued, patients regained weight, and when medication was reintroduced, patients achieved additional weight loss (103,115,160). Although dropout rates were as high as 39% at 1 year and 58% at 2 years in treatment groups, attributable at least in part to side effects

(167), dropout rates were consistently higher (to 92%) in placebo or control groups because patients were dissatisfied with their lack of weight loss (160,167). In the clinical study of the most recently approved antiobesity agent, sibutramine, maintenance of weight loss at 1 year was excellent in patients who had responded during the initial month of treatment (164).

Recommended Use of Available Agents

Pharmacotherapy, in conjunction with a basic weight-management program, is suitable for patients with a BMI 30 or for patients with a BMI of 27 to 29 and at least one major comorbidity. Pharmacotherapy is contraindicated in pregnant or lactating women; patients with unstable cardiac conditions; those with uncontrolled hypertension, serious medical conditions, or psychiatric disorders; or patients taking other incompatible drugs. When pharmacotherapy is associated with an overall weight loss of 10% during the initial 3 to 6 months of treatment, continued use may be appropriate to prevent regain, provided the physician and patient have considered the risks and benefits of long-term use. A realistic anticipation is a weight loss of 5 to 10% and the subsequent maintenance of that loss with its desirable benefits. Weight loss in excess of 10 to 15% of initial body weight should not be expected.

An overview of the AACE and ACE recommendations for use of approved antiobesity agents in clinical practice is provided in Table 8. Detailed information about the approved agents and their mechanisms of action, role

**Table 8
Summary of Recommendations for Use
of Antiobesity Agents in Clinical Practice:
From the American Association of
Clinical Endocrinologists and
American College of Endocrinology**

Agent	Role
Sibutramine HCl	Appropriate for use up to 1 yr as part of a basic weight-loss treatment program
Diethylpropion HCl Mazindol HCl Phentermine resin Phentermine HCl	Appropriate for short-term use as part of a basic weight-loss treatment program
Benzphetamine HCl Phendimetrazine tartrate Phenylpropanolamine	Second-line agents* for use as part of a basic weight-loss treatment program
Amphetamine Methamphetamine Phenmetrazine	Not recommended for use in a weight-loss treatment program

*AACE and ACE believe these are less desirable agents that may be used infrequently under physician supervision.

in clinical practice, efficacy, common and serious side effects, contraindications or precautions, dosage, and duration of treatment is summarized in Appendix F. Although “off-label” combination pharmacotherapy has been widely used, the risks and benefits of such combinations have not been established. Because of the lack of studies and the potential associated serious complications, combination pharmacotherapy should *not* be used until it can be evaluated further. A patient checklist of adverse effects associated with antiobesity agents is presented in Appendix G.

Antiobesity Agents Approved for Use Up to 1 Year

Sibutramine.—Sibutramine, a centrally acting antiobesity agent, was recently approved by the FDA. It blocks the reuptake of norepinephrine, serotonin, and dopamine in nerve terminals to produce substantial weight loss and maintenance of loss of weight. It does *not* stimulate serotonin, norepinephrine, or dopamine release (156,168), nor does it have an affinity for these receptors (168-170). Sibutramine acts primarily through active amine metabolites to reduce food intake and may increase energy expenditure.

The clinical efficacy of sibutramine has been evaluated in approximately 4,600 patients worldwide. When administered in conjunction with a reduced-calorie diet, sibutramine is effective for weight loss and maintenance of weight loss for up to 1 year (146,164,171-173). In placebo-controlled clinical trials, weight loss persisted for up to 6 months and was maintained with continued treatment. Clinical trials of up to 1 year demonstrated that a weight loss of at least 4 pounds (1.8 kg) during the first 4 weeks of sibutramine therapy was a predictor of significant weight loss and reductions in BMI (146), waist-to-hip ratio, waist circumference, plasma triglycerides, total cholesterol, and LDL-C as well as increases in HDL-C (164,174,175).

Sibutramine is generally well tolerated, has a low abuse potential, and has not been associated with cardiac valvulopathy, primary pulmonary hypertension (PPH), or neurotoxicity. Most adverse events, including dry mouth, anorexia, and constipation, were transient and mild to moderate in severity.

Sibutramine should not be used in patients with uncontrolled or poorly controlled hypertension. Sibutramine increases sympathetic nervous system activity through its norepinephrine reuptake inhibition. Thus, increases in blood pressure or pulse rate (or both) can be anticipated. In placebo-controlled trials of obese patients, sibutramine (5 to 20 mg daily) has been associated with mean increases in systolic and diastolic blood pressure from 1 to 3 mm Hg relative to placebo and increases in pulse rate of 4 to 5 beats/min relative to placebo. Larger increases were seen in some patients, particularly when sibutramine treatment was initiated at higher doses. For patients treated with sibutramine who have sustained increases in blood pressure or pulse rate, dose reduction or discontinuation of sibutramine therapy should be considered (176).

Routine vital sign monitoring is recommended. Sustained, potentially clinically significant increases in blood pressure are usually detectable within the first month of treatment (177).

Sibutramine, a potent serotonin and norepinephrine reuptake inhibitor, should not be used in patients receiving monoamine oxidase inhibitors (for example, selegiline, tranylcypromine, or phenelzine) or centrally acting appetite suppressants (such as phentermine). Caution is advised about potential drug interactions that may affect the metabolism and excretion of sibutramine and its metabolites. Sibutramine should not be used in patients with a history of narrow-angle glaucoma or seizures. Additionally, those patients with poorly controlled or uncontrolled hypertension, severe renal impairment, severe hepatic dysfunction, congestive heart failure, coronary artery disease, arrhythmia, or stroke should not be treated with sibutramine, nor should sibutramine be given to patients who are being treated with medications that regulate the brain neurotransmitter serotonin (such as fluoxetine, sertraline, venlafaxine, fluvoxamine, and paroxetine). “Serotonin syndrome,” a rare but serious condition, may develop in patients receiving other serotonergic agents (including sumatriptan succinate, dihydroergotamine, dextromethorphan, meperidine, pentazocine, fentanyl, lithium, or tryptophan) (178). To date, no cases of overdose or serotonin syndrome have been reported with use of sibutramine. Fourteen cases of overdose have been reported, however, with use of the structurally related compound venlafaxine. All patients recovered without sequelae (179).

Antiobesity Agents Approved for Short-Term Use

Diethylpropion.—An anorexiant agent considered one of the safest for patients with mild to moderate hypertension, diethylpropion is effective in producing weight loss and is indicated for use up to a few weeks (180). In a clinical trial for 24 weeks involving 200 patients, diethylpropion-related weight loss ranged from 14.5 to 25 pounds (6.6 to 11.3 kg), but 82% of the patients did not complete the trial (181). Side effects of the drug include mild restlessness, dryness of the mouth, and constipation. Less frequently, nervousness, excitability, euphoria, or insomnia may occur. Cases of psychologic and physical dependence have reportedly occurred with use of diethylpropion (182). Use in patients with severe CVD or pronounced hypertension is inadvisable, and occurrence of seizures may increase in patients who have seizures.

Mazindol.—Structurally related to the tricyclic antidepressant agents, mazindol seems to act by blocking norepinephrine reuptake and synaptically released dopamine. It is effective as an appetite suppressant (183). Loss of weight of 26.5 to 31 pounds (12 to 14 kg) versus 22 pounds (10 kg) for the placebo group of patients has been reported in a 1-year study (184,185). The effects of long-term use of mazindol were a 15-pound (6.8-kg) mean loss of weight and improvement in systolic blood pressure, liver function (serum glutamic-oxaloacetic transaminase), triglyceride

and cholesterol levels, and glucose tolerance. In the same study, 53% of obese subjects maintained weight loss by use of mazindol after loss of weight resulting from consumption of a VLCD, but only 20% maintained the loss of weight without use of mazindol. The same investigators reported inhibition of weight gain in two of three patients with Prader-Willi syndrome who received mazindol (186). In a recently published 12-week study in which a VLCD was used initially in patients with severe obesity, mazindol treatment enhanced the weight-reducing effect of conventional dietary therapy after a VLCD during the initial 2 to 4 weeks and prevented default from treatment. Mazindol treatment response was also associated with increased insulin sensibility (187). It can potentiate catecholamines, and caution is needed when used in conjunction with sympathomimetic amines. Adverse reactions include stimulant effects similar to amphetamines; however, mazindol does not seem to cause euphoria, and the abuse potential is low. Insomnia, agitation, and dizziness are common with use of mazindol. A small increase in heart rate (10 beats/min) is noted with orthostatic position change. Use in patients with severe hypertension or CVD is inappropriate (188).

Phentermine.—Phentermine has been evaluated in placebo-controlled and comparative studies, in which it was equal in efficacy to fenfluramine. The efficacy of phentermine used in combination with fenfluramine was well documented in the 3.5-year trial by Weintraub et al. (115). The FDA has approved phentermine for short-term use (that is, a few weeks). Weight loss does not seem to be related to plasma drug concentrations. Titration of the dosage beyond 30 mg/day is unnecessary (159).

Phentermine monotherapy has been evaluated in studies up to 36 weeks. No case reports have been published of heart valve abnormalities with use of phentermine alone. Few reports of PPH have been associated with phentermine used alone (189). Phentermine, however, was not one of the drugs investigated in the International Primary Pulmonary Hypertension Study, and large-scale data on its use as monotherapy are limited (190). Therefore, we cannot conclude that phentermine is completely without such risk.

Over-the-Counter Antiobesity Products

Phenylpropanolamine.—The FDA considers phenylpropanolamine, an over-the-counter drug, to be safe and effective as an aid in weight reduction. This agent acts on the α_1 -receptor and is classified as a direct α -adrenergic agonist with indirect catecholamine-releasing effects. Probably related to reduced lipid solubility, in comparison with amphetamine, it has little central nervous system stimulant effect, and its use has not been shown to result in development of dependence. It is used systemically as an appetite suppressant. In a comprehensive obesity-management program, phenylpropanolamine increased weight loss by 0.25 to 0.5 pound weekly in comparison with placebo in a 16-week controlled clinical trial (191). The anorexigenic effectiveness of phenylpropanolamine may diminish after 4 weeks (192). Although superior to placebo at producing weight loss, a modest difference was

seen (1.5 to 4 pounds during a 4- to 12-week period) (166). Use of phenylpropanolamine is sometimes associated with adverse effects such as confusion, headache, nervousness, tachycardia, palpitations, or sleeplessness. It is not addictive at recommended doses. Used in excessive doses, it may produce altered perception or psychosis. Currently, its labeling warns that use in patients with hypertension, depression, heart disease, diabetes, or thyroid disease should be under the supervision of a physician. Serious toxicity (for example, intracranial hemorrhage or severe hypertension) may occur in patients who receive doses above that recommended. Use with monoamine oxidase inhibitors should be avoided (193-196).

Other Products.—Besides phenylpropanolamine, most over-the-counter products promoted for weight control are bulk-producing agents such as methylcellulose, carboxymethylcellulose, psyllium hydrophilic colloid, polycarbophil, and natural fibers (for example, wheat and oat bran). They produce a transient sense of fullness and can temporarily lessen the desire to eat (for about 30 minutes). These products are not systemically absorbed, but they require large quantities of water and can increase peristalsis. Accumulation of mucilaginous bulk laxatives may also result in esophageal, gastric, small intestinal, or rectal obstruction, and they are not indicated in persons with preexisting intestinal problems, those with difficulty swallowing, or patients on carbohydrate-restricted diets.

Ephedrine is a sympathomimetic agent that has been shown to increase thermogenesis and promote weight loss, especially when combined with caffeine, in short-term studies of small numbers of patients. It is marketed as a nutrition supplement, “fat burner,” or energy booster. The current popular use involves combining it with St.-John’s-wort (a plant-derived serotonergic agent), and it is being called the “herbal fen-phen” and promoted as a weight-loss product (for example, ma huang).

Ma huang may have powerful stimulant effects on the heart and nervous system. The weight-loss claim has not been substantiated. Since 1994, the FDA has evaluated more than 900 reports of adverse effects (including several dozen deaths) associated with use of “ephedrine alkaloid-containing products.” Some products contain the herb *Hypericum perforatum* (known as St.-John’s-wort) or the compound 5-hydroxytryptophan, which is closely related to L-tryptophan. The actions and possible side effects of St.-John’s-wort have not been carefully studied. Finally, the L-tryptophan products were removed from the market after they were linked to more than 1,500 cases of eosinophilia-myalgia syndrome. AACE and ACE do not recommend the use of *any* over-the-counter products for treating obesity, primarily because efficacy data are lacking.

Antiobesity Agents, Obesity, and PPH

Although PPH has not been a major issue for most physicians, its occurrence in association with the use of fenfluramine, dexfenfluramine, and a combination of either of these with phentermine prompts the inclusion of

a brief summary of the issue. In the general population, PPH occurs in one to two persons per million each year. The incidence of PPH for patients who use some antiobesity agents longer than 3 months is estimated to be 23 to 46 cases per million patients per year (190). This result is similar to the risk of death associated with penicillin-induced anaphylaxis or oral contraceptive-related venous thromboemboli and myocardial infarction (197). The fenfluramine derivatives and other antiobesity agents, even with shorter term use, are associated with an increased risk of PPH (170,190,198,199). After considering the health benefits of weight loss and assuming a 50% mortality rate for patients with PPH, Manson and Faich (197) estimated that treatment with some antiobesity agents is associated with a 20:1 benefit:risk ratio (280 lives saved due to weight loss in comparison with 14 deaths caused by the drugs per million person-years of treatment).

Despite these estimates of a benefit:risk ratio that would argue for use of pharmacotherapy in high-risk patients with obesity, reasons exist for caution and further investigation of this and other possible consequences of drug treatment (for example, heart valvular changes) (200). New approaches that may be helpful in the treatment of patients with PPH have continued to appear (201-203). Of interest, a familial variant of PPH can now be identified by genetic testing (204).

Antiobesity Agents in Development

Many types of agents are under study as potential antiobesity agents (205). Research is under way on agents that inhibit digestion or absorption of fat and thereby decrease the energy available to the body. The following are examples of such agents.

Orlistat.—The lipase inhibitor orlistat is in the final stages of FDA review. It is to be called Xenical. The drug binds to pancreatic lipase in the gut and makes it ineffective. Thus, partial fat malabsorption is induced (206). Effects on the absorption of fat-soluble vitamins, particularly vitamins D and E, make vitamin supplementation advisable in some patients (206-208). The drug also may cause oily stools as a result of increased fat in the lower gastrointestinal tract (206,208). Reports of breast neoplasms have prompted further safety evaluation (207). Clinical trials of efficacy demonstrated clinically significant weight loss (5% more than with placebo) in slightly more than half the patients who received orlistat for up to 1 year (207). Weight loss in patients treated for 2 years was confounded by liberalization of caloric intake after 1 year, and in treated patients, results after 1 year were disappointing (207; personal communication). No studies of its use in combination with other antiobesity agents are available.

Acarbose.—An orally administered agent that acts as an amylase inhibitor, acarbose delays or inhibits digestion of diglycerides and complex carbohydrates. It has been approved for use in diabetes mellitus type 2. Clinical trials of efficacy in reducing energy availability have, to date, been unsatisfactory (209).

Olestra.—Olestra, a product of sucrose esterification with certain fatty acids scheduled to be marketed during 1998, is a nondigestible fat substitute that reduces cholesterol absorption. Clinical data supporting its role in weight loss are inconclusive, although it has been shown to reduce LDL-C (210,211). In one study (210), patients who received 30 g of their daily fat intake from this sucrose polyester lost a mean of 2.6 pounds (1.2 kg) during a period of 30 days. Olestra has been approved as a fat substitute in baked snack foods, but its role in prevention or treatment of obesity is unclear (212,213). Although fat replacers seem to be safe, their efficacy in treatment of obesity and contribution to improved health are entirely dependent on how patients use them as part of their diet (214). Use of these foods alone is not expected to result in weight loss or weight control; rather, long-term changes in eating behavior that produce a favorable energy balance are needed (214,215).

Other.—Agents that affect thermogenesis are also being studied. Genetic obesity and induced obesity in animal models are thought to depend on down-regulation of this mechanism, and the metabolic rate does decline in humans with weight loss. Thermogenic regulators under study include drugs that stimulate β_3 -adrenergic receptors, which enhance thermogenic activity and increase lipolysis and lean body mass. Clinical trials to date have not been promising, perhaps because this type of receptor differs in animals and humans (216). Thyroid hormone (the prototypical thermogenic agent) and growth hormone are not considered appropriate for treatment of obesity because of adverse effects (217).

Surgical Treatment of Obesity

Two proven surgical options are available for the treatment of morbid obesity: (1) restrictive operations such as vertical banded gastroplasty (gastric stapling) or laparoscopic gastric banding and (2) gastric bypass operations such as Roux-en-Y gastric bypass or extensive gastric bypass (biliopancreatic diversion) (103,218-221). Other surgical options include intestinal bypass (effective but associated with major complications), jaw wiring (effective while used), and liposuction (cosmetic procedure). Gastric bubble and vagotomy have not been proved effective (158,222).

Surgical treatment of obesity may be considered only in carefully selected patients who meet the following criteria: (1) a very high medical risk exists (BMI >40 or BMI of 35 to 39 with life-threatening or disabling comorbid conditions such as diabetes mellitus, dyslipidemia, hypertension, or serious cardiopulmonary disorders) (223); (2) obesity has been present for at least 5 years; (3) no history of alcoholism or a major psychiatric disorder is noted (222); and (4) the patient is between 18 and 65 years of age (222,224).

For such patients, a gastric surgical procedure can induce rapid and substantial weight reduction within 1 year postoperatively (103,222). The accepted weight-loss

goal should not be greater than 150% of the desirable body weight (222). The decision to perform or undergo surgical treatment, however, must be considered carefully because serious complications can occur. The long-term maintenance of weight loss can be impressive. Maintenance of more than 50% of excess body weight loss was seen at 5 and 10 years in one study (225). Results from the extensive Swedish Obese Subjects (SOS) Study comparing surgical and nonsurgical interventions are expected soon (226). In appropriate patients, a VLCD prescribed as part of a closely monitored medical program may be an option before attempting surgical intervention (227,228). Further information on the two aforementioned currently favored gastric procedures—including brief descriptions, advantages, disadvantages, complication rates, efficacy, specific indications, and other considerations—is summarized in Appendix H.

Vertical banded gastroplasty results in weight loss for at least 2 years (222,229), but some of the weight lost may be regained within 5 years (103,229). Few reports have described longer follow-up (222). The weight loss associated with vertical banded gastroplasty can also considerably reduce the severity of comorbid conditions, including diabetes mellitus type 2, hypertension, respiratory distress, hyperlipidemia, and disability (7,222,223). Laparoscopic gastric banding has not yet received approval by the FDA (230).

Roux-en-Y gastric bypass produces more substantial weight loss than vertical banded gastroplasty (231,232). This procedure is a more complicated gastric bypass that successfully promotes weight loss and is associated with a risk for nutritional deficiencies (230). Some investigators, however, believe that it is a preferable procedure to gastric stapling alone because of long-term success rates (224,233). In summary, in patients with severe obesity, surgical treatment is the only well-studied option and may be appropriate when done by surgeons who regularly perform such procedures in properly selected patients.

Maintenance of Weight Loss

Maintaining weight loss seems to be more difficult than losing weight, particularly for patients who were treated with caloric restriction. It requires a lifelong commitment to a change in lifestyle, behavioral responses, and dietary practices. Accordingly, weight-maintenance programs must emphasize continued behavior therapy (103,234). A weight-maintenance program should probably last a lifetime.

The following guidelines will help maximize the duration of weight loss. The weight-maintenance program should have the following characteristics.

- *Offer well-supervised, closed-group classes.* Patients who are left to their own devices are unlikely to succeed at weight loss—even if they are enrolled in a weight-maintenance program (119,143).
- *Use a multidisciplinary team approach* that includes a physician, nurse, dietitian, and other members

qualified to provide counseling and behavior therapy and manage an individualized physical activity program (235).

- *Set positive, achievable patient goals* and use counseling that helps the patient progress toward a positive mind-set (236).
- *Use motivational aids* such as diaries and daily logs that promote and reinforce desirable lifestyle changes.
- *Maintain records*, beginning at the outset, including regular weigh-ins.
- *Encourage self-monitoring* of eating habits, calories, and physical activity.
- *Promote physical activity* as a fundamental lifestyle. Participation in physical activity is a strong predictor of maintenance of weight loss (103).
- *Teach nutritional principles*, including maintenance of low-calorie foods in the refrigerator, freezer, and pantry, low-calorie meal planning, and avoidance of alcohol.
- *Help the patient manage lapses.* Use cognitive therapy (positive “self-talk”) so patients can view lapses positively and improve coping skills during high-risk situations. Success usually ensues after several lapses (234).
- *Help patients incorporate other positive experiences into their lives*, including participation in mentally and physically stimulating activities such as hobbies, self-improvement projects, and volunteerism.

Continued program contact, physical activity, nutritional sophistication, and self-monitoring are four characteristics that were observed in men and women who successfully maintained a weight loss of 20% or more for 2 years (237). Individual factors such as self-confidence and the ability to confront problems have also been associated with maintenance of weight loss (238). Women who maintain weight loss also tend to assume responsibility for their need to lose weight by developing their own diets, physical activity programs, and maintenance plans and becoming more involved in business and other productive activities outside of the home (237).

The medical reasons for weight loss and its maintenance should be strongly emphasized. A patient who has experienced a reduction of comorbidities and an improved sense of well-being is more likely to be motivated to maintain weight loss (103). In addition, psychologic therapy should be encouraged for patients experiencing negative life events or family dysfunction, both of which are negative predictors of maintenance of weight loss (103).

PEDIATRIC AND ADOLESCENT OBESITY

Associated Health Risks

The most important consequences of childhood obesity are the psychosocial ramifications. Obese children report disturbances of body image that can last well into adulthood (1), frequently complain of teasing, and, even at a very early age, associate obesity with very negative

stereotypes (25). Obesity has also been shown to be associated with decreased acceptance rates into high-ranking colleges (25).

Most of the health consequences of obesity in adults occur much less frequently in children (perhaps they have not had time to develop in childhood), although several studies have also linked childhood android obesity with abnormal insulin levels, abnormal lipid levels, and increased blood pressure (25). In the young patient, however, obesity can alter bone growth. Obese children tend to be taller and have advanced skeletal growth (25). Young, severely obese boys also have a substantially increased incidence of slipped capital femoral epiphyses (25).

Perhaps the foremost concern is the potential for childhood obesity to persist into adulthood. In most reported samples, from 25 to 50% of obese children and adolescents become obese adults (25).

Risk Factors

Some of the primary risk factors for childhood obesity are the following (25):

- *Parental obesity.* This is the most important risk factor for childhood obesity.
- *Family inactivity.* Television viewing, in particular, displaces physical activity and influences eating patterns. Children whose parents are active tend to be leaner.
- *Region.* In the United States, childhood obesity is most prevalent in the Northeast, followed by the Midwest, South, and West.

Diagnosis

Diagnosis of childhood obesity requires special consideration. The most important clinical task is to distinguish children who are overweight because of frame size

from those who are overweight because of excess fat (25). Of note, the weight of children who are the same age, height, and gender can vary by as much as 20% solely because of frame size (25). Therefore, only children whose weight exceeds 120% of that expected for their height are considered obese. Making this distinction before counseling the child and the parents is important because an unjustified emphasis on weight can have damaging psychologic effects, especially in girls who are concerned about body image. Approximately 10 to 15% of the children and adolescents seen in consultation in an obesity clinic are overweight but not "overfat" (25).

The waist-to-hip ratio may not provide useful clinical information about children (25). Rather, the most practical diagnostic tool is the childhood weight-for-height plot (25,103). The 95th percentile represents children whose weight exceeds 120% of that expected for height. The percentile curves for young white male and female subjects based on NHANES I data are shown in Figure 8.

Weight-Management Strategies

Many of the same general counseling and behavioral therapy principles that apply to treatment of obesity in adulthood apply to childhood obesity treatment as well. Children do, however, require some special considerations. When treating children, the physician should consider the following guidelines.

- *Develop an alliance with the family.* Families are often defensive and hesitant to discuss obesity, and if the family does not feel comfortable discussing the issue, behavior will not change. Rather than taking an abrupt approach or one that assumes the family even perceives obesity as a problem, use a gentle, careful approach (25). Use the term "overweight" rather than "obese," and use open-ended questions designed to help you learn and understand the family's perspective (25).

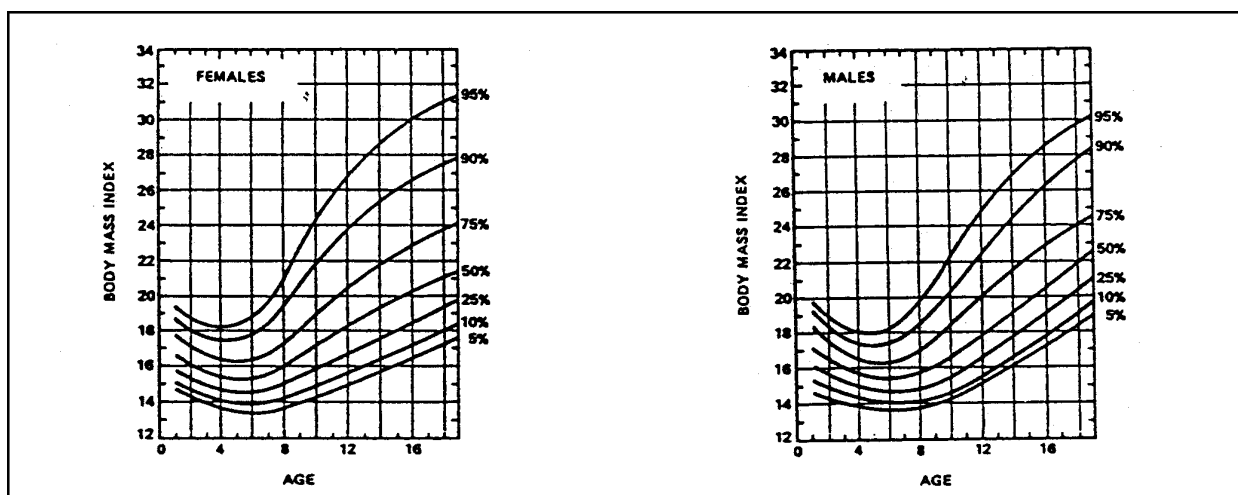


Fig. 8. Body mass index percentile curves for white males (left) and females (right) 1 to 19 years of age. (From Hammer LD, Kraemer HC, Wilson DM, Ritter PL, Dombusch SM. Standardized percentile curves of body-mass index for children and adolescents. *Am J Dis Child.* 1991;145:259-263. With permission.)

Families often believe that the child's obesity is primarily due to "low metabolism," and providers who directly challenge this belief will create an adversarial relationship (25). Children, in general, respond better than adults to weight-management programs. Evidence for significantly greater effectiveness of family-based behavioral treatment of obesity in children versus that in adults was found in a 10-year study involving parents and children from 113 families. Maintenance of weight loss in obese preadolescent children was strikingly better than results in adults (239). The physician should position obesity as a condition influenced by genetics, but one that can be modified by changing environmental factors that increase caloric intake and reduce energy expenditure. This approach successfully maintains the responsibility for treatment of obesity with the family.

- *Treat parents also.* For the very young child (1 to 5 years of age), focus on the parent who controls food selection, preparation, and availability. When adolescents are being treated, however, outcomes are better when the intervention is directed individually to both the patient and the parents (103). Family modeling, reinforcement, and support of eating and exercise behaviors were the basis of interventions in the care of obese 8- to 12-year-old children during a 10-year study. Two factors were particularly important to success in weight control: (1) direct involvement of at least one parent as an active participant in the weight-loss process, improving both short- and long-term weight regulation, and (2) increasing activity for long-term maintenance of weight control. The long-term outcome is related to support from family members and friends for behavior change (240). It is important to change behaviors of school-age children by emphasizing nutritional education and appropriate physical activity. A child who adopts appropriate eating and physical activity behaviors can prevent a future of poor health due to obesity.

- *Use positive reinforcement.* Ongoing positive reinforcement from the physician and the parents is critical. For example, the decision not to eat dessert should be positioned as a positive choice, not a form of deprivation (25). Use contractual agreements between parents and children, as well as stickers to reward good eating and physical activity behaviors.

- *Emphasize the importance of family involvement in a physical activity program.* Family-based physical activity programs in which parents are trained to reinforce their children's physical activity produce the best results (241,242).

- *Promote a conservative approach to caloric restriction for most patients.* Because children are growing, 1 to 2 years of weight maintenance can effectively compensate for each 20% increment in excess of desirable body weight (25). When weight loss is indicated, a reasonable initial goal is 1 pound per month (25,103), and the daily energy requirement should be calculated individually for each patient on the basis of this goal. This goal can be achieved through reductions in dietary fat intake. The effects of weight loss in a child are approximately doubled

because the usual weight gain does not occur (25). A child may also be more able to make small but permanent changes in food consumption than numerous, short-term changes (25).

- *Prescribe more restrictive diets only for patients with comorbidities.* More restrictive diets are a last resort for patients with at least one serious comorbidity who require immediate weight reduction. Restrictive diets, such as the protein-sparing modified fast that provides 600 to 800 kcal per day, have the potential to impair growth, and no available evidence supports any long-term benefit.

Liquid weight-loss diets are *not* recommended for children or adolescents. Rather, a carbohydrate-free diet that consists of meat and vegetables can be realistically sustained (25). Diets for obese children or adolescents must contain 2 g of high-quality protein per kilogram of desirable body weight per day to prevent or minimize nitrogen loss (25,243,244). The diet may also include at least 2 L of water, 2 to 4 cups of low-starch vegetables, and one multivitamin tablet containing iron, 800 mg of calcium, and 25 mEq of potassium.

The physician *must* closely supervise the patient for nitrogen loss, cardiac arrhythmias, and cholelithiasis (25). Restrictive diets are not indicated for patients with renal, hepatic, or cardiac disease (25).

For more information on childhood obesity, key resources are listed under Recommended Reading after the reference list. Another useful resource is the Weight-Control Information Network (WIN) on the Internet at <http://www.niddk.nih.gov/health/nutri/win.htm>.

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RECOMMENDED READING

Adult Obesity

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