Part VI

Management
Health Benefits and Risks of Weight Loss

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Obese patients are at risk for developing a number of medical, psychological and behavioral problems. Medical conditions associated with obesity include insulin resistance and type 2 diabetes mellitus, hypertension, hyperlipidemia, cardiovascular disease, stroke, sleep apnea, gallbladder disease, hyperuricemia and gout, osteoarthritis, and certain types of cancer such as colon, rectum and prostate cancer in men, endometrial, breast and gallbladder cancer in women (1–6) (Table 29.1). Weight reduction results in an improvement or elimination of these obesity-related comorbid conditions (1,7–12). Weight loss as low as 5% has been shown to reduce health risks, while a greater degree of weight loss results in a better health outcome (13). Benefits maintain with the maintenance of weight loss. Generally, a calorie-reduced balanced diet and exercise that provide weight loss of 1–2 lb (0.45–0.91 kg) a week are very safe and effective. In patients who are unable to achieve weight loss goals, medical treatment such as a very low caloric diet (VLCD), medication, or gastric restrictive surgery may become necessary. The adverse effects of medical weight loss are usually mild, manageable, and do not outweigh the benefits. For example, gallstone formation and cholecystitis have been demonstrated with prolonged caloric restriction; however, they are successfully prevented by prophylactic use of ursodeoxycholic acid (8,14). Fluid, electrolyte abnormalities, and hyperuricemia may occur with VLCDs (8,15). A few years after gastric bypass surgery patients may develop digestive symptoms, vitamin and mineral deficiency (15). Certain preventive measures and close monitoring will significantly reduce these risks. In every case, with proper therapy, the benefit to risk should favor weight loss therapy (1). In particular, priority should focus on prevention of weight gain.

**HEALTH BENEFITS OF WEIGHT LOSS IN SPECIFIC DISEASES**

**Hypertension**

The prevalence of hypertension is significantly increased among obese subjects. Several cross-sectional studies have shown a linear relationship between blood pressure and body mass index (BMI) or body weight (16–18). For example, the data from the Third National Health and Examination Survey (NHANES III) showed the prevalence of hypertension among obese adults (BMI > 30) to be approximately two times that among normal weight adults (BMI < 25) (16). In the Swedish Obese Subjects Study, hypertension was present at baseline in 44–51% of subjects. In prospective longitudinal studies, a risk for a future development of high blood pressure is associated with weight changes, while weight gain increases and weight loss reduces the risks (19–21). Furthermore, in obese hypertensive persons, hypertension can improve with a reduction
Table 29.1  Relative risk of health problems associated with obesity

<table>
<thead>
<tr>
<th>Relative Risk</th>
<th>Health Problem</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 3</td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>2–3</td>
<td>Insulin resistance</td>
</tr>
<tr>
<td>1–2</td>
<td>Hypertension</td>
</tr>
<tr>
<td></td>
<td>Dyslipidemia</td>
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<td></td>
<td>Sleep apnea</td>
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<td>Gallbladder disease</td>
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<table>
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<tr>
<th>Relative Risk</th>
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<tr>
<td>2–3</td>
<td>Coronary heart disease</td>
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<tr>
<td>1–2</td>
<td>Osteoarthritis (knees)</td>
</tr>
<tr>
<td></td>
<td>Hyperuricemia and gout</td>
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<table>
<thead>
<tr>
<th>Relative Risk</th>
<th>Health Problem</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–2</td>
<td>Cancer (breast cancer in postmenopausal women, endometrial cancer, colon cancer)</td>
</tr>
<tr>
<td></td>
<td>Reproductive hormone abnormalities</td>
</tr>
<tr>
<td></td>
<td>Polycystic ovary syndrome</td>
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<td></td>
<td>Impaired fertility</td>
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<tr>
<td></td>
<td>Low back pain</td>
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<td></td>
<td>Increased anesthetic risk</td>
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<table>
<thead>
<tr>
<th>Relative Risk</th>
<th>Health Problem</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–2</td>
<td>Fetal defects from maternal obesity</td>
</tr>
</tbody>
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Reproduced with permission from Bray (3).

in weight (22–24). In the Nurses’ Health Study, BMI at age 18 years and at mid-life were positively associated with the occurrence of hypertension (19). At age 18, for every 1 kg/m² increase in BMI, risk of hypertension increased 8%. After age 18, the risk for hypertension was reduced by 15% for a long-term (12–50 years) weight loss of 5.5 to 9.0 kg and by 26% for a long-term weight loss of 10 kg or more. In contrast, a five-fold increase in risk was noted in women who gained more than 25 kg after age 18 years. It was estimated that a 1 kg increase in weight was associated with a 5% increase in risk for hypertension. In the Framingham Study, a 15% decrease in weight was associated with a 10% decrease in systolic blood pressure (20).

Obesity and Hypertension: Pathophysiology

The pathophysiologic mechanisms underlying the association of obesity and hypertension are poorly understood. However, in obesity-related hypertension the cardiovascular abnormalities characterized by sodium retention, intravascular volume expansion, which induces an increase in venous return and cardiac output, and an increase in peripheral vascular resistance are well described (1,25,26). The maintenance of hypervolemia in hypertension implies a resetting of pressure natriuresis toward higher blood pressure (26). These changes in the cardiovascular system and the kidneys are believed to be related to insulin resistance, the enhancement in sympathetic nervous activity, and the activation of the renin–angiotensin system. In addition, interstitial cell proliferation and deposition of non-cellular matrix, histological changes seen within the renal medulla of obese persons, can lead to compression of tubules and vasa recta, and hence increased sodium reabsorption (26). Weight loss is associated with a reduction in total circulating and cardiopulmonary blood volumes, cardiac output, and peripheral vascular resistance, an improvement in insulin resistance, and inhibition of sympathetic activity and of the renin–angiotensin system (27–29).

Effect of Different Modes of Weight Loss on Blood Pressure

1. Weight loss produced by lifestyle modification. Lifestyle modification, which includes diet intervention, physical activity, behavior therapy, or combination therapy, can cause a significant reduction in blood pressure in both hypertensive and non-hypertensive obese persons (1,30–44). The Trial of Antihypertensive Interventions and Management (TAIM) (30), a randomized, multicenter placebo-controlled trial of antihypertensive drug and diet treatment in 787 patients with mild hypertension, reported a mean drop in diastolic blood pressure of 11.6 mmHg at 6 months in patients who lost 4.5 kg or more. This was significantly greater than the drop in blood pressure in patients who lost less than 2.5 kg or were on placebo. This reduction in blood pressure was as effective as 25 mg chlorthalidone or 50 mg atenolol. Moreover, the effect of antihypertensive drugs was potentiated by weight loss (30). In phase II of this trial, 587 patients continued to be followed for a mean of 4.5 years. Of those receiving placebo, low dose diuretic, or beta blocker, the need for additional antihypertensive medications was reduced by 23% with a 2–3 kg weight loss (31). A meta-analysis by MacMahon (32), which covered five randomized controlled trials, supported the benefit of dietary intervention on blood pressure.
Weight loss of 9.2 kg in hypertensive patients resulted in a reduction of 6.3 mmHg systolic and 3.1 mmHg diastolic blood pressure compared with controls (32).

In the Dietary Intervention Study in Hypertension (DISH) (33) and the Hypertension Control Program (HCP) (34), overweight patients with uncomplicated, well-controlled hypertension were withdrawn from drug treatment. Subsequent modest weight loss by diet therapy resulted in a significant reduction in the redevelopment of hypertension over 1 year (33,34) and 4 years (34) (Figure 29.1).

The reduction in blood pressure with weight loss is demonstrated regardless of sodium intake (28,35). One study showed greater benefit with weight loss than salt restriction for blood pressure reduction (36). In this study, the weight loss group lost an average of 6.9 kg with an 11.5 mmHg reduction in systolic and 7 mmHg reduction in diastolic blood pressure, whereas the salt restriction group lost no weight with only a 6.5 mmHg reduction in systolic and a 5 mmHg reduction in diastolic blood pressure.

For non-hypertensive obese persons, weight loss is a very effective way to prevent hypertension. Cutler reviewed four randomized controlled clinical trials in which 872 non-hypertensive subjects engaged in weight loss programs, using dietary intervention and/or exercise (37). Three of these trials were conducted in adults (38–40) and one in adolescents (41). Weight loss of 1 kg in adults resulted in approximately 0.45 mmHg reduction in both systolic and diastolic blood pressure, while weight loss of 1 kg in adolescents, resulted in a 5 mmHg reduction in blood pressure. During one 5-year study, weight reduction (mean 2.7 kg) in conjunction with low salt and alcohol intake and increased physical activity reduced the incidence of hypertension by 52% (40). The Trial of Hypertension Prevention Phase I (TOHP I) (42) and Phase II (TOHP II) (43) are two large collaborative, randomized controlled trials designed to determine the efficacy of non-pharmacologic intervention in preventing an increase in blood pressure. In TOHP I, 664 overweight adults between 30–54 years of age with high normal diastolic blood pressure (80–89 mmHg) were recruited from 10 centers in the United States then followed for 18 months. Participants in weight loss intervention groups attended group meeting and received behavior therapy. At the conclusion of the study, the weight loss intervention group produced 3.9 kg weight loss, 2.3 mmHg diastolic, and 2.9 mmHg systolic blood pressure reduction compared with controls (42). In TOHP II, more patients (2382) were enrolled and followed for a longer period of time (up to 3–4 years). At 36 months, blood pressure decrease remained greater in the intervention group, even though they regained some weight (2 kg weight loss, 0.9 mmHg diastolic, and 1.3 mmHg systolic blood pressure reduction) (43). In addition, weight loss reduced the incidence of hypertension at 18 months by 20–50% (42) and at 3 years by 19% (43) (Figure 29.2).

Secondary analyses from phase I showed sex-related differences in blood pressure response (44). When compared with controls, the blood pressure reduction was significant for men but not for women. This was due to the smaller amount of weight loss by women which could be accounted for by the differences in baseline body weight. However, regression analyses showed a linear relationship between blood pressure reduction and weight loss in both sexes, and when men and women lost an equivalent amount of weight, they experienced a similar degree of blood pressure reduction (44). In this study, other factors, such as sodium intake, alcohol use and exercise frequency, were not found to predict changes in blood pressure.
2. Weight loss produced by medications. Most of the studies have shown that weight loss medications (except for those that act on the sympathetic nervous system), when combined with lifestyle modification, are associated with a reduction in blood pressure. Since these medications are usually used in conjunction with lifestyle modification, there is very little data on the effect of drug therapy alone on this cardiovascular risk. It appears likely that the beneficial effect on blood pressure is due to the weight loss itself, and is not a drug-related effect. Generally, serotonergic drugs such as fenfluramine and dexfenfluramine (which have now been withdrawn from the market) produce similar or better weight loss than that seen in behavioral therapy alone (control) or placebo drug, and a similar or better reduction in blood pressure (1,45–47). In contrast, sibutramine, a serotonin and norepinephrine (noradrenaline) reuptake inhibitor, and other sympathomimetic drugs such as phentermine can be accompanied by an increase, decrease or no change in blood pressure as the action on the sympathetic nervous system would offset the effect of weight loss. A recent multicenter study showed an overall increase in blood pressure in patients on six different doses of sibutramine (1–30 mg), although the only statistically significant change was for diastolic blood pressure at the 20 mg dosage level (48). Individual variability of blood pressure response to medication was also noted, with some patients experiencing a decrease in diastolic blood pressure of 18–26 mmHg while other patients experienced an increase of 26–40 mmHg.

3. Weight loss produced by surgery. Gastric restrictive surgery is the most effective treatment for morbid obesity. It is associated with both short-term and long-term weight loss and an improvement or resolution of obesity-related comorbidities (49,50). In one series of 289 patients followed for about 4 years after gastric surgery, 67 patients had preoperative hypertension. Of these, hypertension had resolved in 66% at the time of the last follow-up (51). In another study of 45 morbidly obese patients with diastolic hypertension who had undergone gastric surgery, 22 patients (54%) resolved, and 6 patients (15%) improved their hypertension at 12 months after surgery (52). The resolution of hypertension depended both on the severity of preoperative hypertension and on the amount of postoperative weight loss (51,52). Patients who required no antihypertensive medications preoperatively and patients who lost more weight tended to do better regardless of preoperative weight (51).

Dyslipidemia

The relationship between obesity and altered lipid metabolism is well established (53). In general, obese individuals tend to have elevated fasting plasma triglycerides and reduced plasma high density lipoprotein cholesterol (HDL-C) levels (7,8,53). Plasma cholesterol and low density lipoprotein cholesterol (LDL-C) levels are slightly elevated or normal, but the number of apo-B carrying lipoproteins is increased. The low HDL-C and high LDL-C to HDL-C ratio put the patients at greater risk for atherosclerosis. In addition, abdominal obesity is associated with an increased proportion of small, dense atherogenic LDL particles in plasma, hypertriglyceridemia, and insulin resistance. This type of obesity is a significant risk factor for cardiovascular disease, type 2 diabetes, and their related mortality (54).

Obesity and Dyslipidemia: Pathophysiology

Central obesity and the hyperinsulinemia that accompanies insulin resistance are thought to cause
an excess production of very low density lipoprotein (VLDL) which is triglyceride-rich in the liver (55). Since the lipolysis of visceral adipocytes appears to be insulin-resistant, this may cause an increased free fatty acid flux to the liver and stimulate VLDL secretion. Also, the lipoprotein lipase levels are decreased, resulting in a slower clearance of VLDL and a reduced production of HDL particles (53,55). In addition, alteration in VLDL metabolism can lead to production of smaller, denser LDL. With weight reduction, both free fatty acid levels and hyperinsulinemia decrease, resulting in decreased VLDL production and improvement of VLDL metabolism. Furthermore, weight loss improves lipoprotein lipase activity, greater triglyceride clearance and HDL production.

**Effect of Different Modes of Weight Loss on Plasma Lipid Levels**

1. **Lifestyle modification.** Modest weight loss induced either by dieting or by exercising is associated with an increase in HDL-C and a reduction in serum triglycerides. Serum total and LDL-C are also decreased (1,8). In 1992, a meta-analysis by Dattilo and Kris-Etherton showed that weight reduction was associated with significantly decreased LDL and VLDL cholesterol as well as triglycerides; during active weight loss, HDL increased by 0.007 mmol/L for every kilogram weight loss (56). Recently, National Institutes of Health and National Heart, Lung, and Blood Institutes (1) have reviewed 14 randomized controlled trials conducted to evaluate the effect of weight loss induced by diet and/or physical activity on plasma lipid levels. The data demonstrated that the intervention group when compared with the control has a 5–13% weight loss accompanied by changes in total cholesterol of 0 to 18%, triglycerides of −2 to −44%, LDL cholesterol of −3 to −22%, and HDL cholesterol of −7 to +27%. Most of these trials lasted for about 4–12 months excluding the result of acute caloric deprivation. At longer durations, this beneficial effect of weight loss has been shown to continue; the study by Waki et al. (57) demonstrated a decrease in serum total, LDL cholesterol and triglycerides as well as an increase in the ratio of HDL to total cholesterol in healthy obese women who lost weight (mean 16.7 kg) at 17 months follow-up.

2. **Weight loss medications.** While weight loss induced by lifestyle modifications significantly improves plasma lipid levels, available data on weight loss induced by medications appear to show no consistent effects. Dexfenfluramine, for example, has been shown both to increase and decrease total cholesterol and triglyceride levels (45–47,58,59). HDL cholesterol was reported to be increased in one study (46). The trial on sibutramine showed statistically significant changes in serum lipids in patients who lost weight on medications; HDL cholesterol increased, LDL cholesterol and triglycerides decreased. In this study, however, the changes in serum lipids were similar for a given amount of weight loss whether weight loss was achieved on placebo or on sibutramine. Since sibutramine causes a greater weight loss than placebo, better lipid profiles were seen (48).

The effects of orlistat in obese patients with abnormal lipid profiles (LDL > 130 mg/dL, LDL/HDL > 3.5 or HDL < 35 mg/dL) have been evaluated in seven randomized controlled trials; 1-year treatment with orlistat showed a greater reduction in LDL cholesterol (−7.83% vs. +1.14%) and LDL/HDL ratio (−0.64 vs. −0.46) when compared to placebo, while HDL cholesterol increased in both groups (+18.8% vs. +20.1%) (60). Another short-term (12 weeks) study in obese patients without hyperlipidemia showed a small but significant decrease in serum total, LDL, and LDL/HDL ratio without significant changes in triglycerides or HDL cholesterol (61).

3. **Surgery.** Gleysteen et al. reported normalization of plasma triglycerides, an increase in plasma HDL cholesterol levels, and a reduction of total cholesterol/HDL ratio in 42 morbidly obese patients by 6 months after Roux-en-Y gastric bypass, with some further improvement occurring with additional weight loss at one year (mean weight loss of 61% of excess weight) (62,63). They also noted a sustained improvement in lipid profiles at 5–7 years postoperatively despite some weight regain. These data were similar to those reported by Brolin (64), Wolf (65), and Cowen (66): significant reduction in total triglycerides, total cholesterol, and increased HDL cholesterol levels within 6–12 months after gastric surgery.
### Table 29.2  
Age-adjusted relative risk for diabetes mellitus during 14 years of follow-up and weight change between age 18 years and 1976

<table>
<thead>
<tr>
<th>Weight change (amount)</th>
<th>Cases, n&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Person-years of follow-up</th>
<th>Age-adjusted relative risk</th>
<th>Relative risk adjusted for age and body mass index at age 18 years (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss (≥ 20.0 kg)</td>
<td>5</td>
<td>5921</td>
<td>1.9</td>
<td>0.13 (0.1 to 0.3)</td>
</tr>
<tr>
<td>Loss (11.0 to 19.9 kg)</td>
<td>17</td>
<td>22493</td>
<td>1.8</td>
<td>0.23 (0.1 to 0.4)</td>
</tr>
<tr>
<td>Loss (5.0 to 10.9 kg)</td>
<td>43</td>
<td>73645</td>
<td>1.4</td>
<td>0.54 (0.4 to 0.8)</td>
</tr>
<tr>
<td>Loss (4.9 to a gain of 4.9 kg)</td>
<td>197</td>
<td>464001</td>
<td>1.0</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td>Gain (5.0 to 7.9 kg)</td>
<td>130</td>
<td>192123</td>
<td>1.5</td>
<td>1.9 (1.5 to 2.3)</td>
</tr>
<tr>
<td>Gain (8.0 to 10.9 kg)</td>
<td>143</td>
<td>132630</td>
<td>2.2</td>
<td>2.7 (2.1 to 3.3)</td>
</tr>
<tr>
<td>Gain (11.0 to 19.9 kg)</td>
<td>545</td>
<td>211126</td>
<td>5.2</td>
<td>5.5 (4.7 to 6.3)</td>
</tr>
<tr>
<td>Gain (≥ 20.0 kg)</td>
<td>724</td>
<td>93840</td>
<td>15.1</td>
<td>12.3 (10.9 to 13.8)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Data missing on weight change from age 18 years to 1976 for 400 cases during 295,552 person-years of follow-up.

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### Table 29.3  
(BMI) at age 21 and risk of diabetes among a cohort of 27,338 US men age 40–75 years in 1986 and followed for 5 years

<table>
<thead>
<tr>
<th>BMI Range (kg/m&lt;sup&gt;2&lt;/sup&gt;)</th>
<th>Person-RR</th>
<th>Age-adjusted RR</th>
<th>Multivariate RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 21.0</td>
<td>29085</td>
<td>69</td>
<td>1.0</td>
</tr>
<tr>
<td>21.0–22.9</td>
<td>36891</td>
<td>50</td>
<td>0.6 (0.4–0.9)</td>
</tr>
<tr>
<td>23.0–24.9</td>
<td>33649</td>
<td>55</td>
<td>0.8 (0.6–1.2)</td>
</tr>
<tr>
<td>25.0–26.9</td>
<td>17775</td>
<td>44</td>
<td>1.2 (0.8–1.8)</td>
</tr>
<tr>
<td>27.0+</td>
<td>8357</td>
<td>48</td>
<td>2.9 (2.0–4.2)</td>
</tr>
</tbody>
</table>

Analysis includes 27,338 participants (266 cases) with complete information on BMI at age 21. Multivariate relative risk (RR) model for BMI at age 21 controls for age in 5-year intervals, family history, smoking status (never smoked, formerly smoked, or currently smoking <15, 15–24, or ≥25 cigarettes/day), and seven categories of weight change since age 21. Multivariate RR model for weight gain since age 21 controls for age, family history, smoking status (never smoked, formerly smoked, or currently smoking <15, 15–24, or ≥25 cigarettes/day), and quintiles of BMI at age 21.

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### Type 2 Diabetes Mellitus

A number of epidemiological studies have reported the increased risk of type 2 diabetes as body weight increases. The data from the Nurses’ Health Study showed that the risk of diabetes increased with BMI as low as 22. Women with BMI in the average range (24.0–24.9) had a five-fold elevated risk compared to women with a BMI less than 22. At BMI of 31 or greater, the risk of type 2 diabetes increased to at least 40-fold. This relationship between BMI and diabetes was noted in both black and white women and in women as old as 69 years (67). In addition, this study also demonstrated that change in body weight was a strong predictor of risk for diabetes. When compared with women with stable weight (those who gained or lost less than 5 kg), women who gained 20 kg or more after age 18 had a 12-fold increased risk for type 2 diabetes; in contrast, for women who lost more than 20 kg during adulthood, the risk of diabetes reduced by 87% (64) (Table 29.2).

A similar relationship between body weight or weight change and the risk of type 2 diabetes was found in men in the Professionals Health Study, a study of 51,529 male health professionals aged 40–75 years in the United States. The relative risk of diabetes in men with a BMI of 35 kg/m<sup>2</sup> was 42 times higher than in men with a BMI <23 kg/m<sup>2</sup> while the corresponding number in men who gained 15 kg or more after age 21 was 34 times that of men who were within 2 kg of their weight at age 21 (Table 29.3) (68).

### Obesity and Type 2 Diabetes Mellitus: Pathophysiology

Obesity and type 2 diabetes both independently and synergistically result in insulin resistance with hyperinsulinemia, a state which is believed to play a primary role in the development of type 2 diabetes.
Although alterations in muscle fuel metabolism are central in insulin resistance related to obesity, all other major glucose-regulatory tissues including liver and adipocytes are affected. It is believed that obesity-induced insulin resistance is mediated in part by high levels of free fatty acid (FFA) and tumor necrosis factor \(\alpha\) (TNF\(\alpha\)) released by excess adipocytes (Figure 29.3). The elevation of FFA levels can inhibit muscle glucose utilization, increase hepatic glucose output, and stimulate insulin secretion from pancreatic \(\beta\) cells (69–72), causing hyperinsulinemia and, in genetically susceptible persons, overt hyperglycemia. Since insulin resistance is an adaptation of the obese state, any interventions that produce weight loss will improve insulin sensitivity. A reduction of fat mass that occurs with weight loss results in a reduction of lipid oxidation and an enhancement of glucose metabolism (73). Insulin secretion and plasma insulin concentrations have been shown to decrease significantly after weight loss. Furthermore, caloric restriction itself can deplete hepatic glycogen stores, thereby decreasing hepatic glucose output and improving fasting hyperglycemia. The effect of caloric restriction, however, will be maintained only if negative caloric balance leads to weight loss. Exercise, both aerobic and resistance, can also improve skeletal muscle glucose uptake and disposal (74).

**Effects of Different Modes of Weight Loss on Type 2 diabetes Mellitus**

1. **Lifestyle modification.** Weight loss produced by diet and/or exercise has been proven to improve insulin sensitivity and reduce blood glucose levels in both obese diabetic and non-diabetic individuals. Frequently, hyperglycemia lessens upon initiating a hypocaloric diet, suggesting that the restriction in caloric intake has a beneficial effect independent of weight loss. In one study of a VLCD in obese patients with type 2 diabetes, 87% of the reduction in plasma glucose levels was observed within the first 10 days of caloric restriction, while 60% of weight loss occurred between days 10 and 40 (75). In another study, 93 obese type 2 diabetic patients were assigned to receive either 1674 kJ/day (400 kcal) or 4185 kJ/day (1000 kcal) (76). At comparable degrees of weight loss (11% of initial body weight), subjects in the 1674 kJ/day (400 kcal) group had lower fasting glucose levels (7.61 vs. 10.13 mmol/L) and greater insulin sensitivity. When subjects who consumed 1674 kJ (400 kcal) changed to 4185 kJ (1000 kcal) 15 weeks later, glycemic control and insulin sensitivity worsened despite continued weight loss; whereas the group that consumed 4185 kJ (1000 kcal) from the beginning of the study had further improvement of glycemic control with further weight loss (76) (Figure 29.4). In obese patients with type 2 diabetes, even moderate weight loss can significantly improve glycemic control, as shown by a reduction in glycated hemoglobin (HbA1C) levels, and in some patients, an ability to discontinue insulin or oral therapy. Such improvements can last many years based on the level of weight maintenance. In one randomized controlled study of diet and exercise in overweight African Americans aged 55–79 years with type 2 diabetes, when compared to the control group, the intervention group lost 2.4 kg (3%) at 6 months and reduced HbA1C by 2.4% (77). In another study in newly diagnosed diabetes, patients who attended regular group education given by diabetes specialist...
nurses and dietitians lost 5 kg more weight than those who had no structured education, and had a lower HbA1C by 2% at 6 months (78). At 1 year (no further visits between 6 months and 1 year), the difference in weight loss was less (2.5 kg) and diabetic control was similar in both groups. For long-term effect of weight loss, Mancini et al. (79) have shown that patients who maintained losses of at least 5% of initial weight at 3 years had lasting improvement of glycemic control, whereas control worsened in those who had losses of less than 5%.

Although diet and exercise are mainstays of treatment in patients with type 2 diabetes, not all patients respond equally. The results of a 48-month retrospective study on 135 patients who were on diet therapy indicated that only 41% of patients who lost at least 9.1 kg had plasma glucose concentration below 10 mmol/L (80). Some of these individuals, however, decreased their plasma glucose levels after losing only 2.3 kg. It was noted that the improvement in glycemic control occurred early in the course of weight loss and patients who remained hyperglycemic after losses of 2.3 to 9.1 kg were unlikely to improve with additional weight reduction. These results might be explained by a relatively higher insulin resistance in patients who responded to diet therapy and a severe insulin deficiency in patients who did not do so. Other studies have shown that the initial fasting plasma glucose is a strong predictor for a successful response to diet therapy. In the UK Prospective Diabetic Study (UKPDS), the amount of weight loss required to achieve a normal fasting plasma glucose below 6 mmol/L was 10 kg (16% of initial body weight) if patients had initial fasting blood glucose of 6 to 8 mmol/L (108–144 mg/dL) versus 26 kg (41%) if initial blood glucose was greater than 14 mmol/L (252 mg/dL) (Figure 29.5) (81).

Heilbronn et al. (82) have studied the effects of different diet composition on weight loss and blood glucose control. They found that regardless of carbohydrate and fat content in the diet, a similar amount of calorie restriction resulted in an equal degree of weight loss and reductions in fasting plasma glucose, insulin, and HbA1C. However, a high carbohydrate diet (10% fat, 4% saturated) and high monounsaturated (MUFA) (32% fat, 7% saturated) diets reduced LDL cholesterol by 10% and 17% respectively, while a high saturated fat diet (32% fat, 17% saturated) did not. HDL cholesterol was transiently reduced only on the high carbohydrate diet. It was recommended by the American Diabetes Association (ADA) that overweight type 2 diabetes patients restrict their caloric intake (250–500 kcal less than average daily intake as calculated from a food history) along with total fat, especially saturated fat, and increase their physical activity (83).
In overweight individuals without overt hyperglycemia, several randomized trials of lifestyle changes or behavioral therapy found improvement of fasting plasma glucose and insulin levels with weight loss (84,85). The incidence of frank diabetes in persons with impaired glucose tolerance was also reduced.

2. Weight loss medications. Weight loss produced by weight loss medications has been shown to be no better than weight loss produced by lifestyle modification for lowering plasma glucose level in obese individuals with or without type 2 diabetes. Weight loss medications, however, may benefit those who have limited success with diet and exercise alone. One study of obese diabetes patients that used short-term treatment with dexfenfluramine in addition to conventional oral hypoglycemic drugs found a significant reduction in weight, BMI, and HbA1C at 3 months compared with the placebo (86). In another trial, 3 months treatment with dexfenfluramine was compared to behavioral therapy. Although, a greater weight loss was observed with medication at 3 months, there were no statistically significant differences in the improvement of HbA1C levels between the groups. At 1 year both groups regained some weight, resulting in similar total weight losses and HbA1C levels (87). A recent trial of fenfluramine and phentermine (88) showed that obese diabetic patients who were on active medication had significant reductions in body weight, BMI, and HbA1C between 2 and 6 months compared with patients on behavioral modification alone. At 6 months subjects taking active drug lost 9.6 kg and reduced HbA1C by 1.6%, while the corresponding figures for subjects taking placebo were 2.7 kg and 0.3% respectively. At 12 months, however, neither amount of weight loss nor reduction in HbA1C were significantly different between the two groups (Figure 29.6). It should be noted that only 16 of 44 subjects reached 12 months of treatment, when the study was terminated because of the withdrawal of fenfluramine.

A trial of sibutramine in 100 established type 2 diabetes with a mean baseline BMI of 31 kg/m² and mean HbA1C of 9.5% showed that subjects on medication and diet lost more weight at 2–12 weeks than subjects on diet alone (mean weight loss 2.4 kg vs. 0.1 kg). Although more patients treated with medication had a greater than 1% reduction in HbA1C at 12 weeks (15 out of 45 patients vs. 2 out of 41 patients), the mean drop in HbA1C was not significantly different from the control group (0.4% vs. 0%) (89). Available data for orlistat in combination with diet therapy for the treatment of obese type 2 diabetes showed a fall in HbA1C and fasting plasma glucose (1).

3. Surgery. It has been shown that gastric bypass operation can control type 2 diabetes in a majority of patients. In one large series from North Carolina (90,91), 608 morbidly obese patients underwent Roux-en-Y gastric bypass from 1980 to 1994; of these, 165 patients had type 2 diabetes and 165 had impaired glucose tolerance (IGT) prior to surgery. Adequate follow-up data was available for 90% of patients (146 of 165 with diabetes and 152 of 165 with IGT). Among patients who presented with diabetes, 121 of 146 patients (82.9%) maintained normal fasting blood glucose and HbA1C levels at the end of study, whereas 25 patients remained diabetic. Among patients who had IGT, only two progressed to overt disease. Normalization of blood glucose was observed as fast as a few days postoperatively before weight loss occurred, which is probably due to limitation of caloric intake, and by the end of first week, there were no longer requirements for insulin or oral hypoglycemic drugs in the majority of the patients. It was noted that diabetes patients who are older (48 vs. 40 years) or had diabetes of longer duration (4.6 vs. 1.6 years) were less likely to correct their hyperglycemia. In this series, mean BMI dropped from 50 kg/m² preoperatively to 31.5 kg/m² at 1 year after surgery and maintained at 34–35 kg/m² at 10 to 14 years.

Insulin Sensitizer in the Treatment of Type 2 Diabetes

Although dietary modification with subsequent weight loss can improve glycemic control, glycemic goals are usually not achieved by dietary restriction alone, and pharmacotherapy become necessary. Because obesity and insulin resistance are common in patients with type 2 diabetes, these patients often require high doses of insulin to control their hyperglycemia. However, insulin therapy is accompanied by weight gain, which would compromise the expected improvement of blood glucose levels. In such cases, addition of drugs that have different
mechanism of actions such as sulfonylurea or biguanide can be complementary. Unlike a sulfonylurea, which stimulates insulin secretion from the pancreas, a biguanide works by decreasing hepatic glucose output and improving peripheral insulin sensitivity (92,93). Metformin, a commonly used biguanide, has been shown to improve glycemic control in patients with type 2 diabetes when used either alone or in combination with sulfonylurea or insulin. In addition, an improvement in hypertriglyceridemia and weight loss has been reported in many patients with metformin use (92–96). In the United Kingdom Prospective Diabetes Study (UKPDS) (95), patients with suboptimal glycemic control on maximal sulfonylurea therapy decreased their fasting blood glucose levels by mean of 0.47 mmol/L over 3 years after the addition of metformin, in contrast to an increase of 0.44 mmol/L in subjects continuing on sulfonylurea alone. Both groups also lost a small amount of weight. In one recent study, the addition of metformin in patients taking insulin resulted in HbA1C levels that were 10% lower than that achieved on insulin therapy alone and without significant weight gain (96). Because of its lipid-lowering and weight-loss-promoting effects, metformin is now recommended by many physicians as a first drug choice in obese type 2 diabetic patients (92,93).

**Cardiovascular Disease**

Obesity is a significant factor related to the development of cardiovascular disease. As mentioned previously, obesity is strongly associated with hypertension, diabetes mellitus and dyslipidemia, classic...

**Figure 29.6** Mean ± SEM changes in weight from baseline and weight loss as a percentage of initial weight in placebo (○) and drug treatment group (●). Subjects in the fenfluramine/phentermine drug treatment group demonstrated rapid weight loss, which continued for the first 4–6 months and then reached a plateau. The control group showed a similar but quantitatively smaller, pattern of weight loss. * P ≤ 0.01 vs. placebo group. Reproduced from Redmon et al. (88) by permission of the American Diabetes Association. (b) Mean ± SEM change in fasting plasma glucose and HbA1C from baseline in placebo (○) and drug treatment group (●). Both fasting and HbA1C declined rapidly in the drug treatment group. HbA1C was significantly lower with drug treatment at all time points through 6 months. * P ≤ 0.01 vs. Placebo group. Reproduced from Redmon et al. (88) by permission of the American Diabetes Association
cardiovascular risk factors. In addition, obstructive sleep apnoea and hemorheological abnormalities such as elevated plasma plasminogen activator inhibitor 1 (PAI-1) levels and high blood viscosity in obese persons may contribute to the pathogenesis of coronary atherosclerosis. High levels of PAI-1, produced by visceral fat, impair fibrinolytic activity and increase the extent of thrombosis (97,98). Obesity, especially abdominal obesity, is also associated with increased morbidity and mortality from cardiovascular disease (99).

Recent clinical studies have suggested an association between BMI and coronary events such as non-fatal myocardial infarction, angina pectoris, and death from coronary heart disease. In the Nurses’ Health Study, after controlling for age, smoking, menopausal status, hormonal therapy, and family history, the risk of developing coronary heart disease (CHD) was increased 1.8-fold with a BMI of 25–29 and 3.3-fold with a BMI above 29, compared with a BMI of less than 21 (100,101). A weight gain of 20 kg or more during adulthood also increases mortality from CHD 7.4-fold when compared with women whose weight remained stable after 18 years of age (102) (Figure 29.7). Similar findings have been reported in men and many other populations. In British men, an increase of 1 BMI unit from BMI above 22 kg/m² is associated with a 10% increase in the incidence of CHD (103). Additional data suggest that the abdominal obesity may be a better predictor of cardiovascular disease than obesity per se (53).

Other cardiovascular diseases have been shown to be related to obesity including myocardial hypertrophy, cardiomyopathy, and congestive heart failure (104). These abnormalities are probably due to an elevation in cardiac workload to supply active metabolism of excess adipose tissue.

**Effect of Weight Loss on Cardiovascular Disease**

While the beneficial effects of weight loss on cardiovascular risk factors are well established, there is little information addressing the effect of weight loss on the progression of coronary artery disease. From available data, it appears that weight loss can help to reduce cardiovascular events and cardiovascular mortality (105). In the Lifestyle Heart Trial (106), patients with coronary artery disease were prescribed a lifestyle program including a low fat vegetarian diet, exercise, stress management training, stopping smoking, and group support. After one year, the treatment group had a mean weight loss of 10 kg, a significant reduction in total cholesterol and LDL-C, as well as a regression in coronary
lesions assessed by computed tomography and quantitative angiography. In contrast, the control group showed no change in weight or lipid profiles, and a progression of the stenotic lesions (106). Although one cannot conclude that weight loss per se causes regression in coronary artery lesions, the study proves that lifestyle modifications can have an impact on CHD.

Weight loss also results in the reduction of PAI-1 levels. One study of 52 healthy, premenopausal women found a 54% decrease in PAI-1 antigen and 74% decrease in PAI activity after weight loss by hypocaloric diet (107). These changes in PAI-1 levels were associated with changes in both BMI and body fat. The decreased PAI-1 levels remained low in subjects who maintained their reduced weight, but increased in those who regained weight.

In addition to the effects on cardiovascular risks, weight loss produced by either diet or gastric surgery has been shown to improve cardiovascular structure and functions. After successful weight loss, heart weight decreases as well as intraventricular septal and wall thickness. Although, cardiac function may not revert to normal, some improvement has been observed (104,108).

Obstructive Sleep Apnea

Sleep-disordered breathing encompasses a number of clinical conditions in which a normal pattern of respiration in sleep was lost. Obstructive sleep apnea (OSA), the most common form of sleep-disordered breathing, is characterized by a repetitive cessation of airflow (apnea) during sleep caused by collapse of the upper airway. Frequent arousals and episodes of cyclic hypoxia and hypercapnia during sleep lead to excessive daytime sleepiness and other clinical sequelae including systemic hypertension, cardiac arrhythmias, myocardial ischemia, and obesity–hypoventilation syndrome (OHS), an extreme from of OSA associated with awake respiratory failure, pulmonary hypertension and a degree of heart failure (109–111).

There are several predisposing factors for sleep apnea, and obesity, especially central obesity, is one of the most important risk factors (112,113). An increase of one standard deviation in any standard measure of body habitus is related to a threefold increase in the occurrence of sleep apnea (112); 60 to 70% of sleep apnea sufferers are obese. One group of investigators has found that 50 to 200 (40%) obese men and 6 of 50 (3%) obese women (mean BMI 45.3 kg/m²) without sleep complaints had sleep apnea severe enough for therapeutic intervention by a polysomnogram, compared with none of 128 non-obese age-matched control (114). Other risk factors for sleep apnea are male sex, age 40–65 years, family history, cigarette smoking and alcohol. In general, women have to be more obese than men for sleep apnea to be clinically apparent and at a similar degree of obesity, men tend to have more severe apnea (115). The difference in the severity of sleep apnea could be related to a man’s propensity for central obesity and more upper airway fat deposition (116).

Obesity and Pathogenesis of Sleep Apnea

There are a number of potential mechanisms by which obesity may lead to sleep apnea. Excess adipose tissue in the neck may predispose the airway to narrowing and/or closure. Alteration in the upper airway size due to fat deposit around pharyngeal tissue has been demonstrated by magnetic resonance imaging (110). This volume of pharyngeal adipose tissue correlates well with the severity of sleep apnea documented by polysomnography. Clinically, a large neck circumference in both men and women who snore is a strong predictor for sleep apnea (117). Increased fat in the chest wall and abdomen can also reduce lung volume, alter respiratory pattern, and decrease compliance of the respiratory system. Total lung capacity and vital capacity are usually decreased, resulting in a reflex decreased in pharyngeal intraluminal dimension as well as increased in airway resistance. Furthermore, function of the muscle that maintains upper airway patency has been reported to be abnormal in obese patients with sleep apnea (109).

Physiology of Weight Loss

Weight loss improves both the function and structure of the upper airway. Both the propensity for pharyngeal collapsibility and pharyngeal adiposity decrease with successful weight loss (118,119). In addition, the loss of chest wall and abdominal fat results in an increase in lung volume and lung compliance, which in turn improves respiratory function. It has been observed that only a small amount
Table 29.4  Summary of studies examining the effects of weight loss in patients with sleep apnea

<table>
<thead>
<tr>
<th>Study</th>
<th>Mode of weight loss</th>
<th>Weight(^a)</th>
<th>Apnea index</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Before</td>
<td>After</td>
<td>Before</td>
</tr>
<tr>
<td>Smith et al. (1985)</td>
<td>Diet</td>
<td>106 ± 7</td>
<td>97 ± 6</td>
<td>55 ± 7.5</td>
</tr>
<tr>
<td>Suratt et al. (1992)</td>
<td>VLCDs</td>
<td>153 ± 37</td>
<td>132 ± 29</td>
<td>90 ± 32</td>
</tr>
<tr>
<td>Sugerman et al. (1992)</td>
<td>Gastric bypass</td>
<td>166 ± 35</td>
<td>114 ± 28</td>
<td>64 ± 39</td>
</tr>
<tr>
<td>Charuzi et al. (1992)</td>
<td>Gastric bypass</td>
<td>117 ± 36(^b)</td>
<td>44 ± 35(^b)</td>
<td>60 ± 35</td>
</tr>
</tbody>
</table>

\(^a\)Weight in kilograms except the last study, which reported percentage excess body weight.
\(^b\)Percent excess body weight.
of weight loss can result in an improvement or resolution of sleep apnea in obese patients. Similarly, the onset of clinically significant sleep apnea may be apparent after weight gain as small as 10 kg, particularly in patients with underlying anatomic abnormalities of the upper airway (116). Recent data have suggested a possible threshold effect that directly relates to the collapsibility of the airway; those with minimal airway collapsibility will achieve greater improvement for the same amount of weight loss (120).

**Effects of Different Modes of Weight Loss on Sleep Apnea**

1. **Lifestyle modification.** Positive effects of weight loss induced by diet therapy on sleep apnea have been consistently demonstrated. An early study in a small number of moderately obese middle-aged patients (mean BMI 37 kg/m\(^2\)) found a significant improvement of sleep apnea as documented by a marked reduction in the frequency of apnea as well as an increase in arterial oxyhemoglobin saturation during remaining apneic events after only 9% weight loss (121). An increase in daytime alertness was also noted by patients and their spouses. Similarly, a study in eight morbidly obese patients (mean BMI of 54 kg/m\(^2\)) showed a reduction in severity of sleep apnea after a successful weight loss produced by a 4-week course of VLCD; a decrease in the number of apnea + hypopneas per hour (respiratory disturbance index/ RDI) from 90 to 62 and in the number of desaturations/hour from 106 to 52. It was noted that the most obese subject with BMI 81, despite the most weight loss (47 kg), did not improve, nor did the subject who lost the least weight (7 kg). Although in both these studies weight loss improved sleep apnea in most patients, it did not eliminate it in any of them. In the new era of nasal continuous positive airway pressure (CPAP) as a primary treatment for sleep apnea, it is possible that the maintenance of weight loss will obviate the need for lifelong CPAP treatment. However, further sleep studies are needed to confirm this.

2. **Surgery.** The results of gastric surgery on sleep apnea have been promising. In the largest series, 126 morbidly obese patients with sleep apnea and/or obesity–hypoventilation syndrome under- went gastric bypass surgery between 1980 and 1990 (123). Fifty-seven of 110 patients with sleep apnea were evaluated at a mean of 4.5 years postoperatively, when they had lost a mean of 31% of their preoperative weight. Of these 57 patients, 66% were completely asymptomatic while 25% had mild persistent sleep apnea. Among 40 patients who had polysomnography before and after surgery, the sleep apnea index (number of apneas/hour of sleep) decreased from a mean of 64 to 26. In another study of 47 obese sleep apnea patients, polysomnography was performed before and at 1 and 7 years after gastric surgery (124). After 1 year, a dramatic reduction in weight and the apnea index were noted. Seventy-two percent of patients had the apnea index < 10, and 40% did not have any apnea. After 7 years, however, regaining of weight in some patients was associated with a recurrence of sleep apnea syndrome.

**Liver Disease**

**Liver Abnormalities in Obesity**

Morphological and functional changes in liver are not uncommon among obese individuals. Fatty change and inflammation of the liver are associated with obesity, and their severity is directly related to the degree of overweight. Almost 90% of morbidly obese patients have some degree of morphological abnormalities. In one study, 80% of morbidly obese patients were found to have a fatty change in the liver and in > 50% of these patients more than one-quarter of the liver was involved (125). An autopsy of 172 non-alcoholic obese patients found steatohepatitis (a concomitant of fatty liver and portal or parenchymal inflammation) in 18.5%, fibrosis in 13.8%, and cirrhosis in 1–3%, in contrast to 2.7% steatohepatitis in 121 non-obese subjects (126). Although non-alcoholic steatohepatitis (NASH) that occurs among obese subjects rarely progresses to hepatic fibrosis or cirrhosis, coexistent type 2 diabetes may increase this risk.

**Effects of Weight Loss on the Liver**

In 1970 Drenick reported a regression of fatty liver in a group of seven patients after VLCDs (127). Similarly, in 1991 Anderson *et al.* (128) observed a marked regression of fatty changes in 41 morbidly
obese subjects without diabetes or history of alcohol use after a median weight loss of 34 kg produced by VLCDs. The regression of fatty change was significantly related to the degree of weight loss. However, some patients developed new lesions after weight loss, 10 patients developed slight degrees of portal inflammation, and five patients developed slight portal fibrosis. Of those who developed portal fibrosis, a large amount of weight loss occurred at a rapid rate. It was estimated that the risk for developing portal fibrosis during VLCD was 28% in patients with a mean weight loss greater than 230 g/day, in contrast to a 0% risk with a mean weight loss below this rate.

Effects of weight loss produced by gastric restrictive surgery on liver morphology have also been investigated. A liver biopsy of 91 patients performed 2 to 62 months after gastric bypass surgery showed a dramatic improvement of steatosis (129). In another study, 69 morbidly obese patients who received gastroplasty had a liver biopsy before and 27 ± 15 months after surgery when they had lost a mean weight of 32 ± 19 kg. Although almost 90% of preoperative biopsies showed pathological changes, 45% of the postoperative liver biopsies were considered normal. The incidence and the severity of fatty change were also significantly reduced. However, inflammatory lobular hepatitis was observed more often in postgastroplasty liver biopsy specimens (130).

Osteoarthritis

Osteoarthritis is one of the most common complications of obesity. The common sites of osteoarthritis in obese patients are the knee, carpometacarpal joint of the hand, and the hip. While osteoarthritis of the knee is contributed by mechanical trauma associated with excess body weight, the arthritis of non-weight-bearing joints is probably due to some systemic factors secreted in obese persons causing abnormalities of bone and cartilage metabolism (3,131). In a survey of more than 7000 Finnish people, BMI was closely related to the prevalence of osteoarthritis (132). The odds ratio for a BMI of 35, compared to a BMI of 25, was 2.8. In middle-aged women, it was estimated that for every kilogram increase in body weight, the risk of osteoarthritis of the knee and carpometacarpal joint of hand increases by 9 to 13% (133). In addition, weight loss is associated with a reduced risk of osteoarthritis. In the Framingham Study (134), a decrease in BMI of 2 units or more (weight loss approximately 5.1 kg) over a 10-year period decreased the odds for developing osteoarthritis of the knee by more than 50% whereas weight gain was associated with a slightly increased risk. The benefit of weight loss was also demonstrated in high-risk patients whose baseline BMI was > 25 kg/m² (134).

A prospective randomized controlled trial examined the effect of medication-induced weight loss on osteoarthritis. The group taking a course of phentermine had a mean weight loss of 12.6% over 6 months, in comparison to 9.2% in a control group. There was a significant clinical improvement in associated with weight loss, especially in patients with knee disease (135). One study from Japan (136) reported a better correlation between the percentage of fat loss and the symptomatic relief of knee osteoarthritis than percentage of weight loss per se. Similarly, a study of patients undergoing gastric bypass surgery showed a significant reduction in the prevalence of joint symptoms with a 45 kg weight loss at 1 year after surgery, although not all joint pains in this group were attributed to osteoarthritis (137).

Because osteoarthritis is very common among the elderly and accounts for much disability in lower extremities, prevention is very important, and one modifiable risk factor is overweight or obesity. It has been estimated that if men whose BMI was > 30 lost weight to BMI 26–29.9 and men whose BMI was 26–29.9 lost weight to BMI < 26, the rate of symptomatic knee osteoarthritis would decrease by 21.4%. In women, a similar degree of weight loss would decrease this rate by up to 33% (138).

Disorders of Female Reproductive Systems

Obesity, especially abdominal obesity, is a predisposing factor for polycystic ovary syndrome (PCOS). Up to 50% of patients with PCOS have BMIs > 25 kg/m² (139). Patients usually present with chronic anovulation along with signs and symptoms of hyperandrogenemia such as hirsutism, acne, and/or androgen-dependent alopecia. Biochemically, testosterone levels may be slightly elev-
ated as well as the ratio of luteinizing hormone and follicle-stimulating hormone (140). PCOS is associated with metabolic disturbance, i.e. hyperinsulinemia and insulin resistance, which may lead to coronary artery disease (139,140).

Besides an improvement in peripheral insulin sensitivity and a decrease in circulating insulin levels, weight loss can reduce serum testosterone levels and improve reproductive function in women with PCOS. Kiddy et al. (141) have examined the effect of weight loss on PCOS. Twenty-six obese women with PCOS (mean weight of 92 kg) were placed on a 1000 kcal low fat diet for 6–7 months; 13 patients who lost > 5% of their original weight had a decrease in free testosterone levels, and a decrease in insulin levels both fasting and in response to glucose load. Nine patients had return of normal menstrual cycle and four achieved pregnancy. Of those 13 patients who were unable to lose weight, only one had improved menstrual cycle.

### Psychosocial Disorders

In Western society where people have negative attitudes toward the fatness, obese people usually suffer discrimination. This stigma is seen in many places including schools, the workplace, and health care. Obese people are less likely to be married or have high household income (3,142).

Depression and binge eating disorder are more common among obese subjects seeking weight loss programs than among the general population (142,143). Binger eating disorder (BED) is characterized by recurrent episodes of binge eating, eating a larger amount of food than most people would eat in a discrete time period (e.g. within 2 hours) with a sense of lack of control during the episodes (144). Generally, binge eaters do not engage in inappropriate compensatory behavior such as purging, dieting or laxative use like patients with bulimia nervosa. Compared to obese patients without BED, obese binge eaters tend to be heavier, are more likely to have a psychological illness (especially depression), or emotional distress.

Weight loss has been shown to improve mood, body image, self-esteem and interpersonal functioning. Obese patients who receive group support and behavioral therapy frequently report some improvements in mood after only a few treatment sessions even before 5% of their initial weight loss (142,143). They feel better as a result of their ability to take control of their eating, exercise habits, and their weight. Many patients enjoy a sense of well-being as their medical condition improves. Also an improvement or resolution of obesity-related comorbid conditions improves patients’ mood. In obese binge eaters, symptoms of depression or emotional suffering can be ameliorated with successful weight reduction (10).

### Other Benefits

While obese patients are more likely to require general surgical procedures, they are at a higher risk for perioperative complications; a 5–10% weight reduction and concomitant diuresis before surgery has been shown to shorten length of hospital stay and to reduce the incidence of postoperative complications (11).

### HEALTH RISKS OF WEIGHT LOSS

Although there are substantial health benefits from weight loss, it is not without risks. Therefore the priority is for an incremental modest change in body weight for a period of time that has been established to be safe. In general, the reasonable initial goal of weight loss therapy is a reduction in body weight of 5 to 10% in 6 months with a rate that does not exceed 1–2 lb (0.45–91 kg) per week (1). Once this target is achieved, further weight loss may be considered. A combined therapy with a low calorie diet (800–1500 kcal/day), exercise, and behavior therapy can usually achieve this health risk reduction goal in a safe and effective fashion. In some patients for whom self-help and commercial programs are not successful in reaching this therapeutic goal, medical treatment may become necessary. In 10% of obese persons no comorbidity is identified; therefore medical treatment would not be indicated. These provider-conducted programs including VLCDs, weight loss medication, and gastric bypass surgery can be associated with some adverse side effects, but they are usually mild, well tolerated, and easily managed.
Table 29.5  Adverse side effects of very low calorie diet

<table>
<thead>
<tr>
<th>Side effects</th>
<th>Treatment/prevention</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Minor reactions</strong></td>
<td></td>
</tr>
<tr>
<td>Fatigue, weakness</td>
<td>Tend to be worse during the first 2 weeks and improve later</td>
</tr>
<tr>
<td>Dizziness</td>
<td>Increase fluid and sodium intake</td>
</tr>
<tr>
<td>Hunger</td>
<td>Tend to be worse during the first 2 weeks and improve later</td>
</tr>
<tr>
<td>Nausea</td>
<td>Tend to be worse during the first 2 weeks and improve later</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Antidiarrhea medication</td>
</tr>
<tr>
<td>Constipation</td>
<td>A bulk laxative and increase fluid intake</td>
</tr>
<tr>
<td>Hair loss</td>
<td></td>
</tr>
<tr>
<td>Cold intolerance</td>
<td>Dress warmly</td>
</tr>
<tr>
<td>Edema</td>
<td></td>
</tr>
<tr>
<td>Dry skin</td>
<td>Moisturizers</td>
</tr>
<tr>
<td><strong>Significant reactions</strong></td>
<td></td>
</tr>
<tr>
<td>Gallstones</td>
<td>Prophylactic use of ursodeoxycholic acid</td>
</tr>
<tr>
<td>Hyperuricemia and gout</td>
<td>Unrestricted carbohydrate intake</td>
</tr>
<tr>
<td>Cardiac complications</td>
<td>Baseline echocardiogram; monitor serum electrolyte levels</td>
</tr>
<tr>
<td>Fluid and electrolytes imbalance</td>
<td>Monitor serum electrolyte levels</td>
</tr>
</tbody>
</table>

**Adverse Effects of VLCD Therapy** (Table 29.5)

The VLCDs are diets that provide fewer than 800 kcal/day, but greater than 400 kcal/day with complete protein, electrolytes, vitamin and mineral supplements. These diets have been shown to produce more weight loss in the first 3 months than general low calorie diets and exercise programs. VLCDs are more likely to cause adverse side effects than diet that provide more than 800 kcal/day due to metabolic consequences of semistarvation (8,145). They are, however, generally safe when administered to carefully selected patients under proper medical supervision. In patients with severe cardiac, renal or liver dysfunction, VLCDs should be avoided (146).

**Minor Short-term Adverse Effects**

The majority of patients using VLCDs experience some adverse health effects, but these are usually mild and well tolerated. The common complications are hunger, weakness, fatigue, dizziness, dry skin, hair loss, cold intolerance, nausea, diarrhea or constipation (146,147). These are usually transient, tend to improve with the time on diet, and rarely require modification of the program. When needed, symptomatic treatment is frequently adequate; constipation can be treated with a bulk laxative and increased fluid intake while diarrhea is easily controlled with over-the-counter antidiarrhea medication.

**Significant Short-term Adverse Effects**

**Gallstone formation.** Obesity itself is an important risk factor for gallstone formation in both men and women. In the Nurses’ Health Study (148), women with a BMI > 45 kg/m² had a seven-fold increased risk compared with those with a BMI < 24 kg/m². The incidence of gallstones was > 1% per year in women whose BMI > 30 kg/m², and up to 2% per year in women with a BMI equal to or greater than 45 kg/m². The high incidence of gallstone formation in obese individuals is due to an elevation of biliary cholesterol excretion, the presence of nucleating factors, and gallbladder hypomotility (125).

Prior to the prophylactic use of ursodeoxycholic acid, there was evidence of an increased risk of gallstones with a hypocaloric diet (126). One large prospective study of 648 obese subjects without gallbladder disease demonstrated an 11% incidence of gallstones after 16 weeks of VLCDs (149). Similarly, Liddle et al. (14) reported that 25% of their patients developed gallstones detected on abdominal ultrasonography following 8 weeks of VLCDs (26 kg weight loss) and another 6% developed biliary sludge, while the control group remained free of disease. Importantly, 6% of these patients develop-
ed symptoms severe enough to require a cholecystectomy. In one study, patients who developed gallstones were significantly heavier (BMI 43 kg/m²), stayed in an active weight loss program longer and lost more weight, compared to those who did not develop disease (150). A meta-analysis by Weinsier et al. (151) indicated a linear relationship between rates of weight loss and incidence of gallstone formation. Among patients who lost more than 1.5 kg per week, the incidence of gallstone formation was at least 0.5% per week, and when weight loss was greater than 3 kg per week, the rate went up to 3% per week. Interestingly, gallstone formation related to VLCDs may occur during active treatment or after solid foods have been reintroduced and some may disappear without any treatment (14).

The composition of biliary sludge and gallstones associated with dieting and rapid weight loss is primarily of cholesterol (152). The combination of caloric restriction and low fat intake increases cholesterol saturation in the bile as well as decreasing gallbladder contractility. This may be in part explained by inadequate diet stimulated cholecystokinin (125,126).

A controlled trial of 22 obese patients defined the importance of fat intake in maintaining adequate gallbladder emptying (153). Eleven patients assigned to VLCDs high in fat content (12.2 g of fat/day) did not have gallstone on ultrasonogram at 6-month follow-up, in contrast to 6 of 11 (54.5%) in a group receiving low fat VLCDs (3 g of fat/day) despite the same amount of weight loss. Gallbladder emptying was also greater with the high fat meals (154). In addition, ursodeoxycholic acid (UDCA) has been used successfully to reduce the risk of gallstone formation during VLCDs (125). It works by reducing the bile saturation of cholesterol and inhibiting prostaglandin-mediated gallbladder secretion of glycoprotein, a promoter of gallstone nucleation.

Hyperuricemia and gout. Plasma uric acid levels may increase transiently at the onset of VLCDs, but the levels rarely exceed 590 μmol/L (10 mg/dL) (146) nor is treatment required. This elevation is caused in part by cell breakdown and in part by ketone competition for tubular reabsorption of urate at the kidney tubule (8). Although patients with a history of gout may develop an acute gouty attack while on VLCDs, the development of symptoms is uncommon in patients without prior disease (146,147,153). When the symptoms occur, unrestricted carbohydrate intake will often normalize the levels.

Cardiac complications. Cardiac dysrhythmias and sudden death were reported with the earlier use of VLCDs in the 1970s (154,155). This VLCD (called liquid protein diet) consisted of low quality protein from hydrolyzed gelatin and collagen was not routinely supplemented with vitamins and minerals. In some of these patients, dysrhythmias were refractory to antiarrhythmic drugs and patients subsequently died. It is believed that myocardial protein depletion and electrolyte abnormalities may be responsible for the development of these dysrhythmias, although the actual causes have never been proven (146). More recent use of VLCDs containing protein of high biological quality with appropriate electrolyte supplementation for 16 weeks or less have not been found to increase the risk of cardiac conduction disturbance (155–157). Moreover, the mortality rate has been reported to be lower in patients receiving VLCDs with high quality protein than in similarly obese persons not dieting. Nonetheless, every patient who considers VLCDs should have a baseline echocardiogram done. Any patients with unstable angina, recent myocardial infarction, malignant arrhythmia, or prolonged QTc syndrome should not be placed on VLCDs, and asymptomatic patients with QTc interval prolongation, i.e. greater than 0.44 ms, should be evaluated by a cardiologist before starting a diet (146). It is recommended that all patients on VLCDs are examined by a physician and have their serum electrolyte levels checked on a regular basis during both the active weight loss and refeeding states (155).

Fluid and electrolyte abnormalities. Weight loss results in substantial loss of water and electrolytes including sodium, potassium, magnesium, calcium, and phosphorus in the urine (8). These minerals must be replaced accordingly to maintain normal serum and tissue levels. Without proper replacement, deficiency states can occur leading to abnormal cardiac, respiratory, neuromuscular, and other organ functions.
Adverse Effects of Weight Loss

Medications

Medications for the treatment of obesity may include drugs that reduce energy intake, drugs that increase energy expenditure, and drugs that block nutrient absorption from the gastrointestinal tract (158). Although all of these medications can help obese patients lose weight, they also have some limitations. Fenfluramine and dexfenfluramine have been reported to be associated with pulmonary hypertension (159) and valvular heart disease (160), leading to the withdrawal of these drugs in 1997. The adverse side effects of the newer drugs are usually mild and self-limiting, and in carefully selected patients, pharmacotherapy should not be excluded.

Drugs that Reduce Food Intake (Anorectic Drugs)

By decreasing appetite, drugs in this group can reduce food intake, which leads to weight reduction.

Noradrenergic drugs. Noradrenergic drugs release norepinephrine (noradrenaline) or blocks its reuptake into neurons of the hypothalamus. Amphetamine, methamphetamine, and phenmetrazine are no longer recommended for treatment of obesity due to their strong central nervous system stimulation and high potential for abuse (161,162). Newer drugs such as diethylpropion, phentermine, phenylpropanolamine, and mazindol are less stimulant and less addictive, but retain anorectic properties. Some patients, however, may experience adverse side effects related to central nervous system stimulation including insomnia, irritability, agitation, nervousness, and anxiety, which may require discontinuation of the drugs. Other side effects are abdominal pain, nausea, diarrhea, and constipation. Severe hypertension, severe headache, atrioventricular blocks, and bowel infarction has been reported with phenylpropanolamine, but they rarely occur (163). Recently, pulmonary hypertension and valvular heart disease have been described especially, with combined use of phentermine and fenfluramine.

Serotonergic drugs. Fenfluramine and dexfenfluramine work at the neurons by stimulating serotonin release and at the receptors as serotonin agonists. In addition, dexfenfluramine can inhibit reuptake of serotonin into the neuron (158). Both medications were withdrawn from the world market in September 1997 after several reports of pulmonary hypertension (159) and cardiac valvular heart abnormalities causing significant insufficiency of the valve (160). The incidence of pulmonary hypertension is low with short-term use of anorexiant, but increases significantly with use of more than 3 months. The Center for Disease Control and Prevention recommends that all people who have taken fenfluramine or dexfenfluramine have a complete physical examination to determine any possible heart or lung disease (164). If cardiac abnormalities are suspected, an echocardiogram should be performed to identify possible valvular heart disease. This is especially important in patients before undergoing medical or dental procedures for which the American Heart Association recommend prophylactic antibiotic therapy to prevent bacterial endocarditis.

Drugs that affect both norepinephrine and serotonin. Sibutramine blocks the reuptake of both serotonin and norepinephrine, but has no effect on their release. Although there is no association between sibutramine and valvular heart disease, this drug may cause an increase in blood pressure and heart rate in some individuals (48,165). It should not be used in patients with hypertension, coronary artery disease, and those who take certain medications such as monoamine-oxidase inhibitors, tricyclic antidepressants, and decongestants (162). In addition, patients on sibutramine should have blood pressure checked regularly. Other minor side effects include insomnia, dry mouth, headache, irritability, anorexia, and constipation (165).

Drugs that Increase Energy Expenditure

Ephedrine stimulates norepinephrine secretion, which in turn increase thermogenesis. In high doses, it can increase heart rate, blood pressure, plasma glucose levels, and cause tremor (158). Currently, none of the drugs in this group is approved by the Food and Drug Administration (FDA) for weight reduction.
Drugs that Reduce Absorption of Nutrients from the Gastrointestinal Tract

Tetrahydrolipstatin (orlistat), a selective gastric and pancreatic lipase inhibitor, blocks systemic absorption of dietary fat. Its main adverse effects are gastrointestinal, such as soft or liquid stool, oily spotting, fatty and oily stool, flatus with discharge, fecal urgency, increased defecation, and fecal incontinence (60). The incidence of these side effects appear to be dose-related, and gastrointestinal tolerability is also inversely related to the amount of dietary fat intake. In addition, orlistat can reduce the absorption of some fat-soluble vitamins and β-carotene. Patients taking orlistat should be instructed to consume less than 30% of dietary fat and take a multivitamin supplement.

Complications of Gastric Restrictive Surgery (Table 29.6)

The original operation introduced in the mid 1950s was jejuno-ileal bypass, which was designed to create a controlled malabsorption. This operation is not currently used due to significant late sequelae including liver failure, protein malnutrition, vitamin and mineral deficiency, urinary calculi, and arthritis. Liver disease was reported in about 29% of patients and frank cirrhosis in up to 7%, leading to a 12% mortality rate at 15 years (120,160,161). In addition, 25% of patients developed severe diarrhea, dehydration, abdominal pain, and vomiting which required hospitalization within the first 2 years. Most of these problems were caused by either nutrient malabsorption or bacterial overgrowth in the bypass intestinal segment (166,167).

The current gastric restrictive procedures, gastroplasty, gastric bypass, and gastric banding, are associated with low postoperative complication rates. Mortality has been reported to be less than 1% (166). Perioperative complications include anastomotic leaks, peritonitis, wound infection, thromboembolic disease, pulmonary and cardiac events, or even death. Older and heavier patients are at higher risk for severe complications (50).

Late complications can also occur, particularly when patients are not compliant with vitamin and mineral supplements or do not consume a healthy diet. Once complications occur, they are often easy to manage. These complications include macronutrient and micronutrient deficiencies, dehydration, persistent nausea, dumping syndrome, and gallstones. As in VLCD treatment, surgical weight reduction also increases risks for nutrient deficiencies, especially with gastric bypass procedure due to gastroduodenal discontinuity. Low blood levels of iron and vitamin B₁₂ occur in up to 70% of patients, while low levels of folate occur in 30–45%. About 12–25% of patients develop actual clinical deficiency states (50), such as iron deficiency anemia, megaloblastic anemia, peripheral neuropathy, and encephalopathy. Although hematological syndrome is not uncommon, neurological syndrome is rare and tends to occur in patients with protracted vomiting and maladaptive eating behavior. With routine use of oral vitamin and mineral supplements, these micronutrient deficiencies and caloric malnutrition are seen less commonly. However, lifelong period assessment of complete blood count, iron, folate, vitamin B₁₂, calcium, and phosphorus levels is necessary (15).

Persistent vomiting and maladaptive eating behavior may occur in as many as 20–30% of patients (15). This is a complex problem usually related to inappropriate eating behavior and psychological instability, but structural failure from surgery may also be responsible. These patients should be managed by the multidisciplinary team assisting in eating behavior, lifestyle changes, and stress management.

Fluoroscopic or endoscopic examination of the surgical area is essential in patients with persistent vomiting or other digestive symptoms after gastric restrictive surgery. Occasionally, revision surgery may be required to treat structural abnormalities occurring during the late postoperative period (50).

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<th>Table 29.6 Complications of gastric restrictive surgery</th>
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<td><strong>Early complications</strong></td>
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<td>Wound infection</td>
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<td>Peritonitis</td>
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<td>Persistent vomiting and maladaptive eating behavior</td>
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<td>Gallstones</td>
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The incidence of gallstone formation also increases with rapid weight loss after gastric restrictive surgery. Shiffman et al. (168) found that 36% of their patients developed gallstones and another 13% developed gallbladder sludge 6 to 18 months after gastric bypass surgery (168). Of those who developed gallstones 40% became symptomatic, and 28% underwent elective cholecystectomy. As with gallstone associated with VLCDs, gallstones occurring after surgical weight reduction are composed primarily of cholesterol (152) and prophylactic use of UDCA (600 mg/day) has also been shown to be effective (169).

**Weight Loss and Mortality**

Several epidemiologic studies of weight loss and mortality have been published (1,7,170,171). Most, but not all, of these studies have suggested that weight loss is associated with increased mortality risk. For example, data from the NHANES I Epidemiologic Follow-up Study (170), a longitudinal study of 2140 men and 2550 women aged 45–74 years who participated in the NHANES I (1971–1975), show an increased risk of death with increasing weight loss among men and women whose baseline BMI was 26 to 29 kg/m^2^. Subjects who lost 15% or more of their maximum weight had more than twice the mortality risk of those who lost less than 5%, after adjustment for age, race, smoking, parity, preexisting illness, and maximum BMI. At a BMI of 29 or higher, mortality risk increased with the degree of weight loss in women, but weight loss of 5–15% appeared to decrease the risk in men (170).

These observational studies, however, have several methodological problems and some limitations. Hardly any studies have examined the cause of weight loss or differentiated between intentional and unintentional weight loss, and it is possible that weight loss, especially unintentional weight loss, is an indicator for subclinical disease.

Two studies of factors related to weight loss intention have been conducted in the general population (172,173). The results suggested that both intentional and unintentional weight losses occur at similar frequency in the US population. Older populations, however, have a higher incidence of unintentional weight loss and lower incidence of intentional weight loss, and unintentional weight loss often occurs in patients who have poor health status, who use medications for chronic diseases, and who smoke.

To date, very few studies have examined the association between intentional weight loss and mortality. In the Iowa Women’s Health Study (174), a prospective cohort study of health risk factors in postmenopausal women showed that one or more intentional weight loss episodes of 9.1 or more kilograms (20 lb) during adulthood was not associated with higher total or cardiovascular disease mortality risk, compared with never losing more than 9.1 kg. On the other hand, one or more unintentional weight loss episodes of at least 9.1 kg was associated with a 26–57% higher total mortality risk and a 51–114% higher cardiovascular mortality risk, compared with never losing more than 9.1 kg. The increased mortality risk with unintentional weight loss were seen mostly in women with prevalent disease, hypertension, or diabetes (174).

In premenopausal women, Williamson et al. (175) have reported a 12-year prospective observation study of intentional weight loss and mortality in 43,457 overweight, non-smoking, white women aged 40 to 64 years. In women with obesity-related comorbid conditions, intentional weight loss of any amount was associated with a 20% reduction in all cause mortality, compared to women who had stable weight (175); this is primarily due to a 40–50% reduction in mortality from obesity-related cancer and 30–40% reduction in mortality from diabetes. In women without comorbidities, intentional weight loss was generally not related to mortality. However, a loss of at least 9 kg (20 lb) in the previous year was associated with small to moderate increases in mortality. This suggested that the association between weight loss and mortality may be influenced by health status. One study of diet and exercise in diabetic patients (176) showed that a modest weight loss decreased the 5-year mortality in diabetic patients to lower than the mean for the general population (3.2% vs. 3.7%). In contrast, diabetic patients who did not lose weight had a mortality of 11.9% (176).

**GUIDELINES ON THE EVALUATION AND TREATMENT OF OBESITY** (1,177)

Treatment of overweight and obesity consists of two processes: assessment and management (1). As-
essment requires the determination of the degree of obesity and absolute risk status. Management involves not only weight loss and weight maintenance at a lower weight, but also the measures to control other risk factors. Persons at increased risk for obesity-related morbidity and mortality include those with BMI > 30 kg/m², those with upper body fat distribution (waist circumference > 40 inches (102 cm) in men, > 35 inches (89 cm) in women), and those who have obesity-related diseases or psychological disorders.

Depending on the severity of obesity and associated risk factors, management of obesity can be done at four different levels of care, from self-help, a certified commercial weight loss clinic, a primary care physician to a nutrition medicine clinic. Patients at high risk should be managed more aggressively by obesity specialists.

Step one: self-help. All overweight or obese individuals should incorporate healthy lifestyle changes including a reduction of caloric intake by 500–1000 kcal/day and an increase in physical activity. The minimal goal in this step is to stop weight gain and to achieve weight loss of 5–10% in 3 to 6 months.

Step two: a commercial weight loss clinic. Patients are screened by their primary physicians and referred to a certified commercial weight loss clinic to assist in achieving weight loss goals.

Step three: primary physician care. Patients are monitored and supervised by their primary physicians; intervention can be carried out by a commercial weight loss clinic or by patients themselves.

Step four: a nutrition medicine clinic. Patients are referred to an obesity treatment clinic for aggressive intervention which includes use of VLCDs, medication, or surgery. The goal of treatment is a 30–50% reduction of excess body fat and improvement of overall metabolic fitness.

In general, low calorie diet, exercise, and behavior therapy are safe and effective. Patients should be instructed to modify their diets to a lower calorie intake. Individually planned diets should help to create a deficit of 500–1000 kcal/day and aim to achieve weight loss of 1–2 lb (0.45–91 kg) per week. Alternatively, an energy controlled, nutrient dense meal replacement can be used, as it is viable, practical, safe and also effective (178). Medical treatment of obesity, when conducted by a physician specializing in obesity treatment, is associated with mild and tolerable side effects.

CONCLUSIONS

Overall, there is ample evidence that weight loss improves obesity-related comorbid conditions, including hypertension, hyperlipidemia, type 2 diabetes, cardiovascular disease, sleep apnea, and osteoarthritis. Although the data on the relationship of weight loss and cardiovascular or overall mortality are limited, available evidence also suggests a beneficial effect of intentional weight loss. Safe and effective diet, exercise and lifestyle modifications are available to most patients. Adverse effects of weight loss are not uncommon with medical treatment of obesity such as VLCDs, medications, or gastric bypass surgery. However, they can usually be prevented or effectively treated and do not contraindicate weight loss.

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HEALTH BENEFITS AND RISKS OF WEIGHT LOSS