decrease food intake, increase energy expenditure, modulate glucose and fat metabolism, and alter neuroendocrine function. Leptin plasma levels increase exponentially with increased fat mass (fourfold higher in obese compared with lean individuals in one study), and this is thought to reflect resistance to leptin in obesity. Leptin therapy in lipodystrophic patients has been shown to lower blood glucose, improve insulin-stimulated hepatic and peripheral glucose metabolism, and reduce hepatic and muscle triglyceride content, suggesting that leptin acts as a signal that contributes to regulation of total body sensitivity to insulin. It has also been found that leptin is independently associated with cardiovascular mortality. Although both adiponectin and leptin are integrally related to insulin resistance, adiponectin is more strongly related to visceral abdominal fat stores, whereas leptin is more closely related to subcutaneous fat.

Adipose tissue serves as a major source of TNF-α and substantial amounts of IL-6. Levels of these two proinflammatory cytokines correlate with obesity and are strongly related to insulin resistance. Several studies have demonstrated a strong link between TNF-α and cardiovascular disease. Plasma levels of TNF-α are increased in individuals with premature cardiovascular disease independent of insulin sensitivity. Conversely, circulating levels of TNF-α decrease after weight reduction in parallel with improvements in endothelial function.

Resistin is an adipocyte-derived, cysteine-rich signaling protein that is expressed predominantly in white adipose tissue and is also detectable in serum. Resistin is thought to act at sites remote from adipose tissue, similar to other adipokines, and to contribute to insulin resistance in obesity. PAI-1 is another bioactive peptide produced by subcutaneous and visceral fat. Its circulating levels correlate better with visceral than with subcutaneous adiposity and are a strong predictor of CAD. High PAI-1 levels are associated with increased blood coagulability. Improvement in insulin sensitivity by either weight reduction or medication lowers circulating levels of PAI-1. This decrease in PAI-1 correlates with the amount of weight loss and the decline in serum triglycerides.

Visceral and subcutaneous fat differ in their production of specific adipokines, pointing to differences in endocrine function between these two adipose depots. Removal of a significant amount of only subcutaneous fat by liposuction in obese individuals with and without diabetes resulted in reduction in serum leptin but did not change the serum levels of other cytokines or any other metabolic parameters. It also did not improve insulin sensitivity or decrease the high serum insulin level observed initially in those individuals. In animal models, removal of subcutaneous fat resulted in an increase in mesenteric fat volume and increased production of TNF-α by visceral fat. Although surgical removal of visceral fat has not been attempted in humans, two studies of aging in rodent models showed that removal of visceral fat reduces the production of inflammatory adipokines and improves glucose tolerance and insulin sensitivity.

Risks Associated with Obesity

Overweight and obese individuals are at increased risk for the following health conditions:

- Cardiometabolic syndrome
- Type 2 diabetes (T2DM)
- Hypertension
- Dyslipidemia
- Coronary heart disease
- Congestive heart failure
- Atrial fibrillation
- Osteoarthritis
- Stroke
- Gall bladder disease
- Fatty liver and nonalcoholic steatohepatitis
- Sleep apnea
- Asthma
- Gastroesophageal reflux (GERD)
- Some cancers (endometrial, breast, and colon)
- Gynecologic disorders (abnormal menses, infertility, polycystic ovarian syndrome)

Weight loss of 7%-10% is associated with reduced risk for many if not all of these disorders. Recent studies have shown that significant weight reduction (15% to 25% of initial body weight) after gastric bypass surgery in class 2 and class 3 obese patients with T2DM results in transient remission of diabetes for 2 to 10 years. The relative importance of the weight loss itself and the hormonal changes associated with gastric bypass surgery to terms of diabetes remission is not yet understood.

DIAGNOSIS AND ASSESSMENT OF OBESITY

The form of obesity that characteristically occurs in men—android or abdominal obesity (apple-shaped body configuration)—is closely associated with metabolic complications such as insulin resistance, hypertension, dyslipidemia, and hyperuricemia. By contrast, the typical female or gynecoid obesity (pear-shaped body configuration), in which fat accumulates in the hips and gluteal and femoral regions, has milder metabolic complications. The waist-to-hip circumference ratio (WHR) has been used to distinguish these forms of obesity. A ratio greater than 1.0 in men or greater than 0.8 in women, indicative of visceral fat deposition and abdominal obesity, correlates with increased health risks.

Previously, the "gold standard" technique for measuring total body fat was hydrodensitometry (underwater weighing). This is based on the principle that fatty tissue is less dense than muscle. Currently, dual-energy x-ray absorptiometry (DEXA) scanning is used to accurately measure body composition, particularly fat mass and fat-free mass. It has an additional advantage of measuring regional fat distribution. DEXA is more accurate than anthropometric measures and is more cost-effective than computerized tomography (CT) or magnetic resonance imaging (MRI) scans. However, DEXA cannot distinguish between subcutaneous and visceral abdominal fat depots, nor between subcutaneous and intramuscular peripheral fat depots. Bioelectric impedance is a simpler and less expensive method for measuring total body fat, but it is greatly affected by the hydration state of the body and is less accurate overall than DEXA.

BMI is widely used as measure of obesity. It is calculated by dividing a person's body weight in kilograms by the square of the person's height in meters; alternatively, weight in pounds × 703 is divided by the square of the height in inches). A BMI between 19 and 27 has little association with cardiometabolic risk in whites. Adverse health consequences occur with a BMI