Obesity, diabetes mellitus, and hypertension are common, interrelated medical problems in Westernized, industrialized societies. These interrelated medical conditions are associated with an increased risk of cardiovascular disease and are more prevalent in several minority groups, including African-American and Hispanic populations. The associated cardiovascular risks of these problems are more thoroughly addressed in another review in this supplement. Obesity markedly enhances the development of Type 2 diabetes. Moreover, it enhances the cardiovascular risk associated with other risk factors, such as hypertension and dyslipidemia. Weight reduction in association with an aerobic exercise program improves metabolic abnormalities and reduces blood pressure in individuals with diabetes and hypertension.

Obesity plays a pivotal role in the pathophysiology of metabolic and cardiovascular disease (1–13). These disorders include impaired glucose tolerance, Type 2 diabetes, hypertension, and dyslipidemia. Obesity, defined as excessive storage of energy in the form of fat, has adverse effects on other diseases, such as certain cancers, which contribute to increased morbidity and mortality in our increasingly overweight society. If obesity is defined as a body mass index of 20% above the desirable index (approximately a body mass index of 27 kg/m²), ~34 million adult Americans can be considered obese (12). Increasing related adiposity as a function of increasing age (14–16) also contributes to the increase in diabetes and hypertension with aging in Westernized, industrialized societies.

The cause of obesity is unknown, but abnormalities of leptin homeostasis have been proposed to increase the propensity to obesity (17). Leptin is a 16-kDa polypeptide hormone synthesized and released by the adipose tissue in proportion to the amount of triglyceride stores (17). Development of obesity in some rodent models is related to mutations in leptin or the leptin receptor. Furthermore, administration of leptin to obese rats lacking leptin normalizes body weight, metabolism, and the regulation of the hypothalamic-pituitary axis (17). However, most obese persons have no mutations in leptin or the leptin receptor. Indeed, they have increased leptin proportionate to their adiposity (17). Because the expected increase in leptin concentration would be expected to decrease appetite and increase thermogenesis, some obese persons may be resistant to their high endogenous leptin concentrations. Thus, the clinical utility of measuring serum leptin concentrations is unknown. Clinical trials are in progress to evaluate the effects of administration of exogenous leptin or leptin analogs in an attempt to overcome the leptin resistance.

The 1990 guidelines of recommended weights for adults published by the United States Department of Agriculture (18) suggest that a weight gain of no more than 7 kg between the ages of 20 and 35 years and older may be desirable. However, recent data from the Nurses Health Study (19) suggest that this concept is incorrect. This study began in 1977 and has examined in a longitudinal fashion the relationships between diet, exercise, use of hormones, and the development of a number of chronic illnesses among women. In this cohort, those who gained substantial weight after age 18 were at significantly increased risk of coronary heart disease (CHD) (20), Type 2 diabetes mellitus (20–22), and total mortality (21), compared with women who remained within 5 pounds of their weight at age 18. The risk of weight gain for development of Type 2 diabetes was especially impressive. Over a 14-year follow-up of 114 824 women, the risk for development of diabetes increased monotonically with a body mass index $>$22 kg/m². In contrast, women who lost $>$5 kg from early adult life had a significantly reduced risk for diabetes. These results are also consistent with results in smaller numbers of males and females in other studies showing a relation between weight gain and risk for diabetes in adolescents (22) and adults (22, 23). In the latter study, men and women between the ages of 40 and 60 years had a similar associated risk for develop-
ment of diabetes with increases in body weight after 18 years of age (23). On the basis of these and other recent observations, the more recent Department of Agriculture guidelines (24) place greater emphasis on avoiding weight gain and state, “Balance the food you eat with physical activity. Maintain or improve your weight”. “Healthy weight ranges” for men and women are published in reference 24.

Visceral adiposity appears to be an especially strong risk factor for hypertension, dyslipidemia, CHD, and insulin resistance of Type 2 diabetes (24–28). Visceral fat is fat present in the omental and paraintestinal regions. Insulin resistance in persons with visceral obesity may relate in part to the metabolic characteristics of visceral fat cells, which when compared with peripheral fat cells, are more resistant to the metabolic effects of insulin and more sensitive to lipolytic hormones (29, 30). Indeed, increased release of free fatty acids into the portal system provides increased substrate for hepatic triglyceride synthesis and may impair first-pass metabolism of insulin. The insulin-resistant dyslipidemic state of visceral obesity is not typically associated with marked increases in plasma cholesterol and LDL-cholesterol concentrations (27). Techniques such as gradient gel electrophoresis and the measurement of plasma apolipoprotein (Apo) B concentrations have shown that the dyslipidemia characterizing visceral obesity is that of increased Apo B concentrations as well as the proportion of small dense LDL particles (27). These patients also typically display low concentrations of HDL-cholesterol and increased triglyceride concentrations in plasma.

The risk of CHD associated with the metabolic abnormalities of visceral obesity were recently described in a report from the Quebec Cardiovascular Study, a prospective study in which >2000 middle-aged men were followed over a period of 5 years. Two characteristic abnormalities of visceral obesity, fasting hyperinsulinemia and increased Apo B, were strong independent risk factors for CHD (31, 32). Concentrations of small, dense LDL-cholesterol are also increased in persons with central obesity (31, 32). The presence of small, dense LDL particles is associated with an approximately threefold increase in CHD risk; this risk is further increased in the presence of increased Apo B concentrations (10, 33) (Table 1). Visceral adipose tissue has greater lipolytic activity than subcutaneous adipose tissue (34–38). The consequent release of free fatty acids into the portal blood supply may contribute to abnormalities of lipoprotein metabolism, including the presence of increased small, dense LDL-cholesterol particles, lower concentrations of HDL, and hyperinsulinemia/insulin resistance (33–39), all of which are associated with increased propensity to CHD.

The hyperinsulinemia associated with visceral obesity (40, 41) appears to predispose persons to increased CHD and stroke (41–49). Four large prospective studies have shown that hyperinsulinemia is a predictor of CHD (31, 42–45), with a few prospective reports not demon-

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<th>Table 1. Metabolic and cardiovascular risk factors associated with visceral obesity.</th>
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<td>Insulin resistance</td>
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<td>Hyperinsulinemia</td>
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<td>Low HDL-cholesterol</td>
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<td>High triglyceride concentrations</td>
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<td>Increased Apo B concentrations</td>
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<td>Small, dense LDL-cholesterol</td>
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<td>Increased fibrinogen concentrations</td>
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<td>Increased plasminogen activator</td>
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<td>Increased inhibitor C-reactive protein</td>
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<td>Increased left ventricular hypertrophy</td>
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<td>Premature atherosclerosis (CHD and stroke)</td>
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strating such a relationship (40, 41). The greatest association of hyperinsulinemia with CHD has been found in Finland, in a population with a very high frequency of CHD (41). A recent report (31) of a prospective investigation of 2103 men from Quebec clearly showed that high fasting insulin concentrations are an independent predictor of CHD. This important study used an insulin assay without cross-reactivity with proinsulin, thus avoiding that confounding influence (31). Several recent studies have shown a relationship between carotid wall atherosclerotic lesions, angina, and insulin concentrations/resistance (48–55). Thus, hyperinsulinemia does appear to be a predictor for the development of CHD and stroke.

Concentrations of plasminogen activator inhibitor (PAI) have been reported to be increased in obese persons, particularly those with visceral obesity (56). PAI-1 complexes with tissue-type plasminogen activator, eliminating its fibrinolytic activity (57–60). The increased concentrations of PAI-1 appear to be related to hyperinsulinemia-associated obesity, particularly central obesity (31, 40, 41, 55, 56). A relative imbalance of the fibrinolytic factors may be associated with CHD. Increased concentrations of PAI-1 have been associated with an increased risk of thrombosis in animal and clinical studies (57–60). In one clinical study, low tissue-type plasminogen activator activity and higher PAI-1 concentrations were observed in survivors of myocardial infarction compared with healthy age-matched controls (58). In another study, low tissue-type plasminogen activator activity and increased PAI-1 concentrations were the only hemostatic variables associated with recurrent myocardial infarction in a group of men with early coronary heart disease (59). Imbalance of the fibrinolytic proteins can also have pathogenic consequences within the vascular wall. In vascular tissue, plasmin activates matrix metalloproteinases, which are crucial in remodeling after vascular injury through degradation of collagen and other glycoproteins that accumulate in plaques. Several groups have reported increased PAI-1 in and around atherosclerotic plaques, which in turn would be expected to reduce vascular
plasmin activation and, subsequently, metalloproteinase activity. This reduction in plasmin activation is also associated with reduced activation of transforming growth factor-β, which is important in suppressing the proliferation and migration of smooth muscle cells that contribute to atherosclerotic lesions (60).

Other risk factors associated with obesity that may be reduced with weight reduction include increased blood pressure, fibrinogen, blood viscosity, and C-reactive proteins (61). Increases in the concentrations of these CHD risk factors appear to track with increased concentrations of insulin and triglycerides. All of these important risk factors have been demonstrated to be reduced by modest weight reduction (61–75). Particularly in males, this is likely related primarily to the fact that initial weight loss is associated with a predominant reduction in visceral fat, the adipose tissue most strongly linked to these metabolic and hemodynamic CHD risk factors (61).

Various methodologies have been utilized to ascertain visceral adiposity, including imaging techniques such as computerized tomography and magnetic resonance imaging (24–33). These techniques are expensive and unavailable to many primary care providers. Thus, recently there have been a number of investigations of the utility of using simple anthropometric indexes as predictions of visceral adipose mass. The waist-to-hips ratio is the anthropometric variable that has been most widely utilized. The waist-to-hips ratio is, however, influenced by a number of factors other than regional adipose tissue distribution, such as frame size and skeletal muscle mass (76). It has been reported (76) that waist circumference is a better determinant of the absolute amount of visceral fat than the waist-to-hips ratio. This investigation also noted that waist circumference values of ≥1 meter in persons below 40 years of age and ≥90 cm among those between 40 and 60 years of age were associated with the metabolic abnormalities of visceral obesity and thus increased CHD risk (76).

Currently, there are potentially novel approaches to the prevention and treatment of obesity. It has recently been observed that leptin administration to rodents selectively decreases visceral adiposity and enhances insulin action (77). These observations suggest that this may be one of the promising strategies for approaching visceral obesity and the associated CHD risk factors. Similar to the observations for Type 2 diabetes, increases in indexes of obesity also relate strongly to increases in blood pressure (40). Furthermore, visceral adiposity is more closely associated with increases in blood pressure than is peripheral fat distribution (11, 40, 67–70). This may be of special importance in certain subsegments of the US population, such as in African-American women (9–11, 67), where the prevalence of obesity is 40% (72). Declining levels of physical activity in our society likely contribute substantially to obesity, diabetes, and hypertension (9–13). This has considerable importance in formulation of future public health policy because overweight and physical inactivity are both preventable and reversible (11, 13, 73–75).

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