Adipose Tissue and Atherosclerosis
Exploring the Connection
Giamila Fantuzzi, Theodore Mazzone

Abstract—The prevalence of obesity, especially among the young, is dramatically increasing in the United States. Obesity is associated with accelerated atherosclerosis and increased rates of cardiovascular death. There are many plausible mechanisms by which an increase in adipose tissue could adversely affect the vessel wall. These include the changes in blood pressure, glucose level, lipid/lipoprotein metabolism, and systemic inflammation. In addition, factors secreted by adipose tissue may directly influence vessel wall homeostasis by influencing the function of endothelial cells, arterial smooth muscle cells, and macrophages in the vessel wall. There is general agreement that central, as opposed to peripheral, adipose tissue confers the most cardio-metabolic risk. Although the basis of this differential risk has not been established, the pattern of gene expression and secretory products in visceral fat would be predicted to be more atherogenic compared with that in subcutaneous peripheral fat. Numerous studies have shown the beneficial effects of weight loss on markers of cardiovascular risk but fewer have demonstrated improvement in direct measures of large vessel disease. The unfolding role of adipose tissue as an important metabolic and secretory organ provides new opportunities for developing more effective approaches for preventing obesity and its atherosclerotic complications.

Key Words: obesity ■ atherosclerosis ■ adipocytokines ■ lipoprotein metabolism ■ visceral fat

The prevalence of obesity is dramatically increasing in the United States.1–3 Of special concern is the sharp increase in obesity among children and adolescents. In 2003 to 2004, 17.1% of US children were obese (as defined by being greater than the 95th percentile of sex-specific body mass index (BMI) for age growth charts); significantly increased compared with 1999 to 2000. Approximately 32.2% of US adults are obese as defined by a BMI ≥ 30 kg/m². Extreme obesity (defined as a BMI ≥ 40 kg/m²) affects 2.8% of men and 6.9% of women in the United States. Many studies have demonstrated that obesity increases mortality from all causes, including cardiovascular death. This review focuses on the contribution of excess adipose tissue to the major underlying cause of cardiovascular death, large vessel atherosclerosis. Studies measuring the effect of obesity on direct measures of large vessel atherosclerosis in humans are considered, along with evidence regarding potential mechanisms by which excess adipose tissue could adversely affect the vessel wall.

Obesity and Atherosclerosis
Numerous studies have demonstrated the effect of excess adipose tissue for increasing cardiovascular death for adolescents and adults up to 75 years of age.4–7 A number of more recent studies have specifically reported on the effect of excess adipose tissue on direct measures of macrovascular disease. Using the measurement of coronary artery calcium as a marker for coronary atherosclerosis, Cassidy et al studied 443 asymptomatic white individuals who had quantitation of coronary artery calcium an average of 8 years apart.8 After fitting multivariable linear regression models adjusting for the baseline risk factors, several indices of obesity predicted the progression of coronary artherosclerosis in a group otherwise defined as low risk for cardiovascular disease. In a study of 495 diabetic subjects undergoing a single measurement of coronary artery calcium, a multivariate analysis that corrected for multiple cardiovascular risk factors showed that waist-to-hip ratio was a significant predictor of coronary artery calcium.9 In another multicenter study in type 2 diabetes, visceral fat measured by CT scan predicted coronary artery calcium.10 With respect to obesity and atherosclerosis in younger individuals, the Pathobiological Determinants of Atherosclerosis in Youths Study collected arteries and tissue from 3000 persons, aged 15 to 34 years, dying of external causes.11 BMI was associated with both fatty streaks and raised lesions in the right coronary artery and stenosis in the left anterior descending artery. The link between obesity and macrovascular disease, demonstrated by imaging approaches, expands the opportunities for investigating potential mechanisms by which excess adipose tissue adversely impacts the vessel wall and for evaluating how adipose tissue distribution or reduction (weight loss) impact atherosclerosis.
Excess Adipose Tissue and the Vessel Wall: Mechanisms of Injury

There are numerous mechanisms by which obesity can adversely affect the vasculature and thereby increase cardiovascular mortality (Figure). Obesity has a number of consequences known to accelerate atherosclerosis, including hypertension, diabetes, and dyslipidemia. Systemic inflammation and the production of adipokines by adipose tissue have been considered as important mechanisms for the adverse effects of adiposity on the vessel wall. Adipose tissue–derived factors influence the composition and level of circulating lipoproteins and the levels of systemic inflammatory and clotting system components. Adipose tissue–derived factors also can directly regulate gene expression and function of endothelial, arterial smooth muscle, and macrophage cells in the vessel wall. FFA indicates free fatty acids; TNF, tumor necrosis factor; PAI, plasminogen activator inhibitor.

Adipose tissue products work directly at the vessel wall and through the liver to modulate the atherogenic environment of the vessel wall. In obesity, the production of metabolites, cytokines, and hormones by adipose tissue is altered. In the case of visceral adipose tissue, these factors will have favored access to the liver through the portal circulation. At the liver, adipose tissue–derived factors influence the composition and level of circulating lipoproteins and the levels of systemic inflammatory and clotting system components. Adipose tissue–derived factors can also directly regulate gene expression and function of endothelial, arterial smooth muscle, and macrophage cells in the vessel wall. FFA indicates free fatty acids; TNF, tumor necrosis factor; PAI, plasminogen activator inhibitor.

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There are multiple mechanisms by which obesity can influence systemic lipid and lipoprotein metabolism. Increased release of fatty acids from adipose tissue in obesity with increased flux to the liver can increase very-low-density lipoprotein, apolipoprotein B (apoB), and triglyceride secretion. Other factors secreted by adipose tissue may cause adverse effects on circulating lipids. For example, in a study of white men with BMI values ranging from 22 to 35 kg/m², adiponectin was the most significant predictor of plasma very-low-density lipoprotein apoB concentration. Tumor necrosis factor expression is increased in adipose tissue from obese subjects and could have multiple effects on lipid metabolism via both paracrine effects on adipocytes, as well as on effects in the liver. Adipose tissue can also influence systemic lipoprotein metabolism and function by secreting apolipoproteins. ApoE is highly expressed in adipose tissue and its expression increased by treatment with peroxisome proliferator-activated receptor- agonists. ApoE is a key apolipoprotein involved in the systemic and cellular lipoprotein metabolism, and apoE secreted by extrahepatic tissue can have a profound effect on systemic lipoprotein metabolism. Endogenous expression of apoE in adipocytes has also been shown to play an important role in adipocyte triglyceride turnover and adipocytokine expression. Serum amyloid A is both an inflammatory cytokine and an apolipoprotein produced by multiple cell types, including adipocytes. Its level of expression is highly correlated with BMI, and weight loss produces significant decreases in serum amyloid A levels, as does treatment with peroxisome proliferator-activated receptor- agonists. In inflammatory conditions, serum amyloid A becomes an important surface constituent of HDL and thereby has a number of important effects on the metabolism and function
of HDL. Two other apolipoproteins are also produced in adipocytes, apoC1 and apoD, but their impact on systemic lipoprotein metabolism or cellular lipid flux is less well defined.

Increased free fatty acid release from adipose tissue in obesity may also accelerate atherosclerosis by mechanisms not directly related to lipids. Evidence for this is provided by the results of a prospective study of 3315 subjects followed for 5.3 years. Free fatty acid levels in these subjects independently predicted all-cause and cardiovascular mortality after adjustment for age, sex, BMI, triglycerides, HDL, LDL, homeostasis model assessment of insulin resistance, hypertension, smoking, C-reactive protein (CRP), homocysteine, creatinine, statin use, and β-blocker. Excess free fatty acid delivery to peripheral tissues may worsen insulin resistance and may play a role in activating inflammatory processes, possibly through activation of Toll-like receptor 4. Free fatty acids have also been shown to induce endothelial cell apoptosis and to impair endothelium-dependent vasodilatation.

A number of cytokines and adipokines secreted by adipose tissue may also influence vessel wall directly. Resistin is highly expressed in the fat tissue of rodents, and its level is elevated in models of obesity and insulin resistance. Some, but not all, studies have shown that resistin levels are also increased in human obesity and diabetes. In humans, resistin is expressed primarily in inflammatory cells, where its expression is increased by treatment with endotoxin and proinflammatory cytokines. Recently, the level of resistin in humans has been shown to positively correlate with increasing coronary atherosclerosis measured by coronary artery calcium after adjustment for established cardiac risk factors. On the other hand, recent data from Kunnari et al showed no relationship between resistin levels and another marker of atherosclerosis/coronary vascular risk, carotid intima/media thickness. High levels of resistin may negatively influence the atherosclerotic process through several mechanisms. Resistin directly activates the endothelium through upregulation of adhesion molecules, an effect that is antagonized by adiponectin (see below). Resistin also induces production of the proinflammatory cytokines tumor necrosis factor-α and interleukin (IL)-12 by macrophages through activation of nuclear factor κB.

Leptin is a product of adipocytes, and its level in humans is decreased in obese and diabetic subjects. Levels of adiponectin increase with weight loss or with pharmacological treatment of insulin resistance. Adiponectin plays a role in regulating systemic substrate metabolism, and several recent publications have suggested a role for adiponectin in modulating vessel wall health. Adiponectin circulates in 3 different oligomers, and each of these may have a different biologic function. HDL cholesterol and high-molecular-weight adiponectin level are positively correlated, and both total serum adiponectin and high-molecular-weight adiponectin levels correlate negatively with triglyceride, homeostasis model assessment of insulin resistance, and circulating inflammatory markers. Serum high-molecular-weight adiponectin level is significantly lower in men with coronary artery disease, independent of other cardiac risk factors. Rewers and colleagues studied the progression of coronary artery calcification over 2.6 years in a group of patients with type 1 diabetes and nondiabetic subjects aged 19 to 59 years. Adiponectin levels were inversely correlated to progression of coronary artery calcium in both diabetic and nondiabetic subjects. Adiponectin levels after treatment with insulin sensitizers have also been shown to be the best predictor of an improvement in carotid arterial wall stiffness in a group of subjects with type 2 diabetes.

Mutations of the adiponectin gene are strongly associated with impaired glucose tolerance, diabetes mellitus, and coronary artery disease in humans. In adiponectin knockout mice, a high-fat and high-sucrose diet leads to marked elevation of plasma glucose and insulin levels, insulin resistance, and an increase in intimal smooth muscle cell proliferation after injury in the aorta; however, these alterations have not been observed in all of the adiponectin knockout strains that have been developed to date.

Treatment of apoE-deficient mice with an adi-
Adiponectin adenovirus has been shown to reduce plaque formation in the aortic sinus by 30%. As might be expected based on the above observations, adiponectin promotes an antiatherogenic and antiinflammatory program of gene expression and function in vessel wall cells. Adiponectin downregulates expression of adhesion molecules on endothelial cells through inhibition of nuclear factor κB activation and thereby reverses the effects of resistin. Adiponectin also reduces endothelial oxidative stress and proliferation while stimulating nitric oxide synthase activity. However, both induction and suppression of chemokine production by endothelial cells have been reported in response to adiponectin. In vascular smooth muscle cells, adiponectin reduces proliferation in a receptor-independent fashion by binding to, and inhibiting, the activity of growth factors, such as heparin-binding epidermal growth factor, basic fibroblast growth factor, and platelet-derived growth factor-BB. In macrophages, adiponectin reduces lipid accumulation and downregulates expression of scavenger receptors. Similar to what was reported in endothelial cells, controversy remains regarding the role of adiponectin for macrophage cytokine production.

Obesity leads to increased expression of additional inflammatory mediators in adipose tissue, including MCP-1. Adipocytokine expression of MCP-1 increases in obesity, and increased circulating MCP-1 levels have been shown to increase the number of circulating CD11B-positive monocytes in mice. CD11B is a component of MAC-1 and is involved in binding of monocyte/macrophages to the vascular wall. The expression of adipose tissue IL-6 is increased in human obesity, and up to one-third of plasma IL-6 is believed to be derived from adipose sites. In humans, IL-6 produces elevation of plasma free fatty acids and increased levels of hepatic CRP expression. CRP may also be produced in adipose tissue, and recent data suggest that CRP may be directly involved in atherogenesis at the vessel wall.

Angiotsinogen, angiotensin-converting enzyme, and plasminogen activator inhibitor-1 are also produced by adipose tissue, where their level of expression is increased in obesity. Angiotensin II produces vasoconstrictive effects and inhibiting, the activity of growth factors, such as heparin-binding epidermal growth factor, basic fibroblast growth factor, and platelet-derived growth factor-BB. In macrophages, adiponectin reduces lipid accumulation and downregulates expression of scavenger receptors. Similar to what was reported in endothelial cells, controversy remains regarding the role of adiponectin for macrophage cytokine production.

Differences in Atherosclerotic Risk Based on Adipose Tissue Distribution

There is widespread support in the literature for the conclusion that central adiposity (fat in the trunk and/or abdomen) confers more cardiovascular risk than peripheral adiposity (ie, that present in the hips and thighs). Terry et al reported that waist-to-thigh girth ratio positively correlated with triglycerides and small dense LDL particles and negatively with HDL cholesterol. Thigh girth correlated positively with HDL and with LDL particle size in women. Okura et al examined 128 obese women (aged 34 to 62 years) during a 14-week weight loss intervention with diet and exercise. During weight loss, fat tissue change in the leg correlated with worsening of CHD risk factors, whereas fat tissue change in the trunk correlated with improvement in CHD risk factors. Klein et al examined the effect of removing subcutaneous fat on metabolic parameters in 15 obese women before, and 10 to 12 weeks after, abdominal liposuction. Liposuction reduced the volume of subcutaneous abdominal tissue by 44% in subjects with normal glucose tolerance, and 28% in those with diabetes. Subjects with normal glucose tolerance lost approximately 9 kg of fat (an 18% decrease in total fat), and those with type 2 diabetes lost 10 kg of fat (19% of total fat). The comparison of pre-liposuction and post-liposuction values showed that removal of subcutaneous fat did not significantly alter insulin sensitivity, or change the plasma concentrations of CRP, IL-6, tumor necrosis factor-α, or adiponectin. It also did not produce significant changes in blood pressure, plasma glucose, insulin, or lipid concentrations. On the other hand, a number of studies have shown that a reduction in visceral fat in animals and humans is associated with increased in insulin sensitivity, HDL cholesterol, and decreased in triglyceride and blood pressure. Thorne et al randomized 50 subjects with a BMI >35 kg/m² to adjustable gastric banding alone, or this plus surgical removal of the greater omentum. Metabolic parameters were compared before surgery and 2 years after surgery. There were no significant differences between control and omentectomized patients at baseline. At 2-year followup, there was a decrease in weight and improved metabolic profile in both groups. Omentectomized subjects lost more weight than control subjects, but the difference was not statistically significant. Subjects who underwent omentectomy, however, had a statistically significant improvement in oral glucose tolerance, insulin sensitivity, fasting plasma glucose, and insulin levels independent of the change in BMI. There were no differences in blood lipids between the 2 groups.

Several recent studies have reported on the influence of adipose tissue distribution on direct measures of macrovascular disease. In a cross-sectional analysis of 1356 women, 60 to 85 years of age, aortic calcification (as an index of atherosclerosis) was evaluated. Peripheral fat mass showed an independent and dominant antiatherogenic effect in elderly women. Ferreira et al investigated 336 subjects (175 women) who were apparently healthy and examined the relationship among truncal fat, peripheral fat, and estimates of the stiffness of large arteries. Central fat was positively associated with stiffness of the carotid and femoral arteries, whereas peripheral fat was inversely associated with stiffness of the brachial and carotid-femoral segment. In a study of more than 5000 middle-aged women aged 30 to 69 years, a subsample of 310 participants underwent measurement of carotid intima/media thickness. An increase in carotid intima/media thickness was observed in abdominally obese (elevated waist-to-hip ratio) women to lean women. Moricone et al studied 55 patients undergoing coronary angiography, and multivariate regression analyses showed that coronary artery disease was significantly correlated with visceral adipose tissue as measured by abdominal CT. No relationship was found between coronary artery disease and BMI.

Although the basis for the apparent difference in vascular risk conferred by different adipose tissue depots remains under active investigation, patterns of gene expression between peripheral subcutaneous and visceral fat are consistent with a more proatherogenic influence of the latter.
al recently performed a microarray analysis of genes differentially expressed in subcutaneous versus visceral adipose tissue of obese subjects and identified 347 genes that were differentially expressed in the 2 depots, of which 131 genes were expressed at higher levels in subcutaneous adipose tissue and 216 were more abundant in visceral fat. Compared with subcutaneous tissue, visceral adipose tissue produces higher levels of several factors that have been implicated in cardiovascular disease and metabolic disturbances, including IL-6, IL-8, MCP-1, vascular endothelial growth factor, and plasminogen activator inhibitor-1. Many of these factors are produced by the stromovascular fraction of adipose tissue, mostly by macrophages, which infiltrate adipose tissue in greater number in obese compared with lean subjects. Increased levels of the chemokine MCP-1 in visceral adipose tissue attract more monocytes/macrophages, thereby creating a self-sustaining inflammatory cycle. In addition to creating a more proinflammatory environment, products of visceral adipose tissue—cytokines, free fatty acids, and hormones—also gain a direct access to the liver through the portal circulation (Figure 1), likely magnifying the adverse consequences of excess visceral adipose tissue. Leptin, on the other hand, has been shown to be produced at higher levels in subcutaneous compared with visceral adipose tissue.

Cardiovascular Benefits of Weight Loss
Observational studies have shown that mortality rates among obese persons who have lost weight are not lower compared with those who have not lost weight. The absence of a reduction in mortality in these studies has been attributed to underlying diseases that cause unintentional weight loss, or to the adverse effect of repeated weight cycling. There are no interventional studies demonstrating the benefit of weight loss on cardiovascular events. One problem with obtaining such data are the limited therapeutic success for producing significant long-term weight loss in obese individuals. Perhaps reflecting the limitations of current therapeutic interventions, a definition of successful weight loss maintenance has recently been proposed as a loss of at least 10% of body weight for at least 1 year. Clearly, loss of almost any amount of weight for only 1 year would have limitations for showing differences in cardiovascular outcomes. In a recent metaanalysis of trials testing the effect of weight loss medications, a net reduction from baseline weight of 2.9% was shown for orlistat and 4.6% for sibutramine at 1 year. Similar effects have been reported for rimonabant. Lifestyle interventions can produce an average net reduction of 5.8% over an average of 67 weeks. Only a few weight loss studies have followed subjects for longer than 1 year, and, among these, approximately 15% to 20% of individuals maintain a weight loss of at least 5 kg or more at 5 years. There have been multiple studies demonstrating improvement in metabolic or inflammatory markers with short-term weight loss, but there have been fewer reports of the effects of weight loss on direct measures of macrovascular disease. Dengel et al have recently studied 12 overweight individuals without known diabetes or vascular disease and measured parameters of vascular structure, function, and mechanical properties using ultrasound. An intravenous glucose-tolerance test, blood pressure, body composition, and lipids were also measured. During weight loss, there were significant reductions in BMI and percentage of body fat. There were the expected improvements in total cholesterol, LDL cholesterol, triglyceride, and insulin sensitivity. After 6 months, there were also significant improvements in brachial artery compliance and distensibility; however, endothelial function and arterial intima/media thickness did not change. Ziccardi et al reported that after 1 year of weight loss, the vascular response to L-arginine improved in obese women. Balkenstein et al reported that 3 months of negative caloric balance improved carotid distensibility in obese men. Overall, the results of studies evaluating the effect of weight loss on measures of macrovascular disease are mixed, and longer-term studies with sustained weight loss are needed.

As compared with medical therapy, surgical intervention can produce more substantial long-term weight loss. Sjostrom et al recently reported on a prospective controlled study involving obese subjects who underwent gastric surgery compared with a matched conventionally treated obese control group. After 10 years, weight had increased by 1.6% in the control group and decreased by 16.1% in the surgery group. Two- and 10-year rates of recovery from diabetes, hypertriglyceridemia, low HDL, hypertension, and hyperuricemia were more favorable in the surgery group. The surgical group also had lower 2- and 10-year incidence of diabetes, hypertriglyceridemia, and hyperuricemia. There were no differences in the incidence of hypercholesterolemia or hypertension between the groups. This study is important because it demonstrates that the improvements in the metabolic parameters that have been repeatedly demonstrated in short-term weight loss are durable for up to 10 years. However, there were no direct measures of macrovascular disease reported for this study.

Conclusion
The recent increase in the prevalence of obesity, especially among the young, has significant implications for rates of atherosclerosis and consequent cardiovascular disease in the coming decades. Several plausible mechanisms exist for a causative role for obesity in producing atherosclerosis. These include changes in blood pressure, lipids, glucose metabolism, and systemic inflammation. In addition, evidence is emerging that factors produced by adipose tissue in obesity can directly impact the atherogenic environment of the vessel wall by regulating gene expression and function in endothelial, arterial smooth muscle, and macrophage cells. There is also substantial support in the literature that adipose tissue distribution is important for atherosclerotic risk. Truncal fat confers more vascular and metabolic risk than peripheral fat, and this may be at least partly related to a less favorable pattern of adipokines and cytokines released by visceral fat and its favored access to the portal circulation.

Important questions for additional research remain for successfully meeting the challenge presented by the epidemic of obesity. The development and evaluation of additional tools for prevention and treatment of obesity and its vascular
complications are critical. The use of surrogate vascular end points can be useful not only for investigating the mechanistic relationship between excess adipose tissue and macrovascular atherosclerosis but also for evaluating the effect of weight loss sustained over a shorter period of time than that needed for measuring changes in cardiovascular events. Additional work is also needed to further explore adipocyte and adipose tissue biology. The recent recognition that adipose tissue is an active endocrine and metabolic organ, with a major role in regulating organismal substrate flux and metabolism and in influencing systemic inflammatory state provides new opportunities for investigations that could lead to more effective approaches for preventing and/or treating obesity and its vascular complications.

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References


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