Adipokines: molecular links between obesity and atherosclerosis

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Departments of 1Medicine, 2Biochemistry and Molecular Biology, and 3Pharmacology, Julia McFarlane Diabetes Research Center, University of Calgary, Calgary; 4Division of Cardiac Surgery, St. Michael’s Hospital, and 5Division of General Internal Medicine, University of Toronto, Toronto, Ontario, Canada

Lau, David C. W., Bikramjit Dhillon, Hongyun Yan, Paul E. Szmitko, and Subodh Verma. Adipokines: molecular links between obesity and atherosclerosis. Am J Physiol Heart Circ Physiol 288: H2031–H2041, 2005; doi:10.1152/ajpheart.01058.2004.—Atherosclerotic disease remains the leading cause of death in industrialized nations despite major advances in its diagnosis, treatment, and prevention. The increasing epidemic of obesity, insulin resistance, and diabetes will likely add to this burden. Increasingly, it is becoming apparent that adipose tissue is an active endocrine and paracrine organ that releases several bioactive mediators that influence not only body weight homeostasis but also inflammation, coagulation, fibrinolysis, insulin resistance, diabetes, and atherosclerosis. The cellular mechanisms linking obesity and atherosclerosis are complex and have not been fully elucidated. This review summarizes the experimental and clinical evidence on how excess body fat influences cardiovascular health through multiple yet converging pathways. The role of adipose tissue in the development of obesity-linked insulin resistance, metabolic syndrome, and diabetes will be reviewed, including an examination of the molecular links between obesity and atherosclerosis, namely, the effects of fat-derived adipokines. Finally, we will discuss how these new insights may provide us with innovative therapeutic strategies to improve cardiovascular health.

metabolic syndrome; adipose tissue; endothelium

ATHEROSCLEROTIC CARDIOVASCULAR DISEASE remains the leading cause of death in industrialized nations despite major advances in its diagnosis, treatment, and prevention (8). While there has been a trend over the last half century showing a general decline in the age-adjusted death rates of heart disease and stroke, the increasing epidemic of obesity (119a,105), followed closely by insulin resistance and diabetes (72), will likely slow the decline and reverse this trend. In addition to being an independent cardiovascular disease risk factor (20), obesity also increases the incidence of other risk factors, notably, diabetes, dyslipidemia, hypertension, and the prothrombotic state. The clustering of cardiovascular disease risk factors seen in many adults, which leads to premature illness and death, led Reaven (88) to postulate insulin resistance as the underlying cause of syndrome X, better known as the metabolic syndrome of insulin resistance. It has been estimated that metabolic syndrome affects one in four adults, making it the leading public health issue associated with increased cardiovascular disease risk (28). The recommendation by the National Cholesterol Education Program Adult Treatment Panel III (23) and, more recently, by the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (15) to identify and treat adults with metabolic syndrome further emphasizes the need for aggressive treatment to reduce associated cardiovascular disease risks. Achieving a healthy body weight through lifestyle intervention is universally endorsed as the first step in improving cardiovascular health, underscoring the prominent role of obesity as an etiological factor in the development of metabolic syndrome and cardiovascular disease.

Obesity is characterized by excessive body fat to the extent it causes health problems. Adipose tissue is an active endocrine and paracrine organ that releases a large number of cytokines and bioactive mediators that influence not only body weight homeostasis but also inflammation, coagulation, fibrinolysis, insulin resistance, diabetes, atherosclerosis, and some forms of cancer (51, 55, 71). The cellular mechanisms linking obesity and atherosclerosis are complex and have not been fully elucidated. This review summarizes the experimental and clinical evidence on how excess body fat influences cardiovascular health through multiple yet converging pathways. The molecular links between obesity and atherosclerosis are explored through the effects of fat-derived adipokines on endothelial function and vascular health. Because insulin resistance and diabetes are associated with endothelial dysfunction and atherogenesis, data on the role of adipose tissue in the development of obesity-linked insulin resistance, metabolic syndrome, and diabetes will be briefly reviewed to provide a broader view of the link between excessive adiposity and atherosclerosis. Finally, we will discuss how these new insights may provide us with innovative therapeutic strategies to improve cardiovascular health.

OBESITY AND CARDIOVASCULAR HEALTH

The Framingham Heart Study was one of the first epidemiological studies to demonstrate that obesity is causally related to cardiovascular disease (CVD) (43). Other prospective studies suggest that obesity is a well-established and important

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The Pathobiological Determinants of Atherosclerosis in Youth study (68) has provided compelling and direct evidence linking obesity with accelerated atherosclerosis in both adolescents and young men. Obesity affects cardiovascular health and the process of atherosclerosis through diverse pathways. Obesity induces insulin resistance, a condition characterized by the impaired action of insulin in insulin-sensitive target tissues such as muscle, the liver, adipose tissue, and endothelium. Adaptive hyperinsulinemia is a compensatory state that fore-stalls the development of hyperglycemia and subsequent diabetes. There are strong prospective data from the Nurses’ Health Study that, even before the diagnosis of Type 2 diabetes, obesity and weight gain are associated with increased risk of coronary heart disease (CHD) (14). This finding, together with the significantly elevated CVD risk before the clinical diagnosis of Type 2 diabetes (42), point to the importance of elucidating the mechanisms whereby excess body fat predisposes individuals to CVD risks in the prediabetic insulin resistant state, which is now widely referred to as the metabolic syndrome of insulin resistance, or simply metabolic syndrome.

Adipose tissue is a rich source of proinflammatory mediators that may directly contribute to vascular injury, insulin resistance, and atherogenesis. These proinflammatory adipokines, or adipokines, include TNF-α, IL-6, leptin, plasminogen activator inhibitor-1 (PAI-1), angiotensinogen, resistin, and, more recently, C-reactive protein (CRP) (see Fig. 1). On the other hand, NO (123) and adiponectin confer protection against inflammation and obesity-linked insulin resistance (53) (see Fig. 1). It is likely that many more undiscovered fat cell-derived mediators will be causally linked to cardiovascular health, insulin resistance, and diabetes.

Circulating adipokine levels are elevated in obese and insulin-resistant states in animals and humans, and intra-abdominal fat appears to produce several of the adipokines in greater amounts than other fat depots (115). Weight loss is associated with a decrease in the serum levels of most of these adipokines, with the exception of adiponectin, which is increased (115, 121). A large number of adipokines also affect insulin action, glucose, and fat metabolism and consequently insulin resistance, which ultimately leads to Type 2 diabetes. Hence, they exert direct as well as indirect influences on the process of atherosclerosis.

Atherosclerosis is an inflammatory process that initially begins with endothelial dysfunction (61, 92, 109). Endothelial dysfunction, a systemic disorder and an early pivotal event in the pathogenesis of atherosclerosis, is characterized by an

Fig. 1. Anti- and proinflammatory adipokines. Adipose tissue serves as a rich source of proinflammatory mediators such as TNF-α, IL-6, leptin, plasminogen activator inhibitor (PAI)-1, angiotensinogen, resistin, and C-reactive protein (CRP), which promote endothelial dysfunction, insulin resistance, and, ultimately, atherosclerosis. Other adipocyte products such as nitric oxide (NO) and adiponectin confer protection, but these appear to decrease in amount with increasing levels of obesity. These proinflammatory mediators, released by adipocytes, exert effects on the vasculature promoting the various stages of atherogenesis, namely, endothelial dysfunction, plaque initiation, plaque progression, and plaque rupture. ET-1, endothelin; AT₁a, angiotensin II; oxLDL, oxidized low-density lipoproteins; MCP-1, monocyte chemoattractant protein 1; SMC, smooth muscle cell; MMP, matrix metalloproteinase; EC, endothelial cell.
imbalance between endothelium-dependent vasodilatation and vasoconstriction as well as antithrombotic and prothrombotic factors. NO maintains the vasodilatory property of endothelium and opposes the effects of such vasoconstrictors like endothelin (ET)-1 and angiotensin II (ANG II) (109). It inhibits leukocyte and platelet activation and aggregation and, together with prostacyclins, helps to maintain the endothelium as a smooth nonthrombotic barrier. In response to inflammatory triggers, an increase in endothelial adhesion and permeability leads to leukocyte entry and expression in the endothelium of adhesion molecules, namely, vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1) (109). The expression of P- and E-selectins, which are involved in leukocyte recruitment and rolling, monocyte chemotactic protein-1 (MCP-1), which promotes leukocyte transmigration, and integrins, which mediate subsequent adherence to the intima, are also increased (61). Recently, adipocytes have been demonstrated to produce MCP-1 directly (17). The phagocytosis of oxidized low-density lipoprotein (LDL) particles by monocytes leads to the formation of foam cells and the development of fatty streaks and plaques as well as smooth muscle cell proliferation. Thus endothelial dysfunction is a prominent feature at various stages of atherogenesis, from the development of early subclinical atherosclerotic fatty streaks to atheromatous plaques, to plaque vulnerability and rupture, vasospasm, thrombus formation, and eventually vessel occlusion and infarction, and should be considered a marker of atherosclerosis.

Evidence is mounting to suggest that adipokines may directly influence endothelial function through their proinflammatory properties. While the majority of the data are based on in vitro studies, they shed light on the molecular links between obesity, insulin resistance, and endothelial dysfunction. The secretory products of adipose tissue contribute to the elevated risks of CVD, and these effects appear to be independent of their effects on insulin resistance and diabetes. The effects of various adipokines on vascular homeostasis and insulin resistance are summarized in Table 1.

**CRP: A NOVEL, PROATHEROGENIC INFLAMMATORY ADIPOKINE**

CRP is an acute-phase reactant synthesized mainly in the liver and is regulated by circulating levels of IL-6, although IL-1 and TNF-α can also induce hepatic CRP mRNA expression (127). Emerging evidence suggests that elevated plasma levels of CRP have become one of the strongest independent predictors of CHD (89), being correlated with CHD in several large cross-sectional and prospective population studies, including the US Physicians Health Study, the monitoring of trends and determinants in cardiovascular disease (MONICA)- Augsburg Cohort Study, the Multiple Risk Factor Intervention Trial (MRFIT) study, and the Women’s Health Study (89, 114). Circulating plasma CRP levels are elevated in obese subjects, and the levels are also directly correlated with the amount of body fat, as assessed anthropometrically by body mass index, visceral obesity (assessed by high waist circumference), those with the metabolic syndrome of insulin resistance (90, 114), and Type 2 diabetes (86). Among children aged 6–18 yr from the Third National Health and Nutrition Examination Survey, the circulating CRP level is correlated to body mass index after adjustment for age, sex, race, or ethnicity (27). Weight loss by hypocaloric diets or surgical intervention reduced CRP levels in healthy middle-aged (22, 35) and postmenopausal obese women (22, 103) and obese men (52). More recently, two large cross-sectional, prospective studies have reported that CRP and IL-6 levels predict the development of diabetes in both obese men and women, implicating CRP as a possible link in the causal relationship between obesity and diabetes (26, 31, 86).

CRP is not merely an inflammatory marker but directly participates in the process of atherogenesis by modulating endothelial function (83, 85, 110). CRP, at concentrations known to predict cardiovascular events, induces the expression of VCAM-1, ICAM-1, selectins, and MCP-1 in cultured endothelial cells via increased secretion of ET-1, a potent endogenous vasoconstrictor, and IL-6 (83, 110). CRP attenuates basal and stimulated endothelial NO production by downregulating endothelial NO synthase mRNA and protein expression (112). The diminished NO activity may in turn inhibit angiogenesis, an important compensatory response in chronic ischemia. Furthermore, in vascular smooth muscle cells, CRP upregulates angiotensin type 1 receptor (AT1-R) mRNA and protein levels and increased AT1-R expression on the cell surface (117). The AT1-R is a key atherosclerotic switch that facilitates ANG II-induced reactive oxygen species production, vascular smooth muscle cell migration and proliferation, and vascular remodeling (73). Interestingly, the effect of CRP on endothelial dysfunction is potentiated by hyperglycemia, and these effects are attenuated by rosiglitazone, an insulin-sensitizing thiazolidinedione (TZD) antidiabetic drug (113).

CRP may also play a coordinating role by amplifying the proinflammatory activity of other adipokines. For example, it increases the expression and activity of PAI-1 in endothelial cells (19). PAI-1, a prothrombotic acute phase protein that suppresses fibrinolysis by inhibiting plasminogen activation (49), has been implicated as an active contributor to atherogenesis by promoting thrombus formation. Plasma PAI-1 levels are positively correlated with cardiovascular risk and mortality and, recently, the development of diabetes (49). Although platelets and endothelial cells are the major source of PAI-1 in humans, adipose tissue also produces PAI-1 and contributes to the higher plasma PAI-1 levels seen in the obese state (64). Indeed, it has been estimated that the biosynthetic capacity for adipose tissue-derived PAI-1 in obese states may match or exceed that of other tissues (64). The plasma levels of PAI-1 are elevated in obese rodents and humans and decreased with weight loss, diet, and bariatric surgery (64). In both rodents and humans, higher PAI-1 levels are expressed in omental than subcutaneous fat depots. PAI-1 levels in adipose tissue are upregulated by TNF-α, transforming growth factor (TGF)-β, ANG II, FFAs, hyperinsulinemia, and hypertriglyceridemia, all of which are produced in excess in obesity and insulin resistance states (47, 49, 64).

The close correlation between the degree of obesity and CRP levels in cross-sectional and prospective epidemiological studies has led us to hypothesize that adipose tissue is a potential source of CRP. We first reported CRP expression by real-time PCR and confirmed by DNA sequencing that CRP was expressed in rat and mouse as well as human adipose tissue in both mature and developing fat cells (54). A twofold increase in CRP expression was detected in adipose tissue derived from...
Adipokines and Atherosclerosis

Table 1. Effects of adipokines on vascular homeostasis and the metabolic syndrome of insulin resistance

<table>
<thead>
<tr>
<th>Adipokines</th>
<th>Vascular Action</th>
<th>Insulin Action and Resistance</th>
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<tbody>
<tr>
<td>Adiponectin</td>
<td>↓ ICAM-1, VCAM-1, and E-selectin (53, 79)</td>
<td>Plasma levels inversely correlated with obesity and insulin resistance (80)</td>
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<td></td>
<td>↓ NF-κB (79)</td>
<td>↑ Insulin sensitivity (80)</td>
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<td></td>
<td>↓ Transformation of macrophages to foam cells (78)</td>
<td>↓ TNF-α-induced changes in adhesion molecule expression (79, 80)</td>
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<td></td>
<td>↓ VSMC proliferation and migration (53, 79)</td>
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<tr>
<td>Angiotensinogen</td>
<td>↓ NO availability (104)</td>
<td>↑ Development of hypertension (2)</td>
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<tr>
<td></td>
<td>↓ NF-κB (104)</td>
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<tr>
<td></td>
<td>↓ ICAM-1, VCAM-1, MCP-1, and M-CSF (104)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>↓ Angiogenesis</td>
<td></td>
</tr>
<tr>
<td>CRP</td>
<td>↓ NO by destabilizing eNOS mRNA and decreasing protein expression (112)</td>
<td>↑ PAI-1 expression and activity in endothelial cells (19)</td>
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<tr>
<td></td>
<td>↑ ET-1 and IL-6 release (112)</td>
<td>CRP levels correlate with metabolic syndrome and predicts future CHD (90)</td>
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<td></td>
<td>↑ VCAM-1, ICAM-1, selectins, and MCP-1 in EC (12)</td>
<td>Predicts the development of diabetes (86)</td>
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<td></td>
<td>↑ LDL uptake in EC</td>
<td>Hyperglycemia potentiates proatherogenic action of CRP (113)</td>
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<tr>
<td></td>
<td>↑ Angiogenesis</td>
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<td>↑ Apoptosis in EC</td>
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<td></td>
<td>↑ ROS</td>
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<td></td>
<td>↑ SMC proliferation and migration and restenosis (73)</td>
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<td>↑ AT1-R on VSMC (117)</td>
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<tr>
<td>IL-6</td>
<td>↑ ICAM-1, E-selectin, VCAM-1, and MCP-1</td>
<td>↑ Preadipocyte differentiation (1)</td>
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<td>↑ SMC proliferation and migration</td>
<td>↑ Insulin receptor signal transduction</td>
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<td>Leptin</td>
<td>↑ NO by increasing eNOS production (18, 50)</td>
<td>↑ Systemic insulin resistance (94)</td>
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<td></td>
<td>↑ ET-1 (87)</td>
<td>↑ Hepatic CRP production (70)</td>
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<td></td>
<td>↑ Proliferation and migration of EC (68) and VSMC (3)</td>
<td>↑ Glucose transport</td>
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<td>↑ ROS accumulation and oxidative stress (7)</td>
<td>Reverses insulin resistance in lipodystrophy (96)</td>
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<td>↑ VSMC apoptosis (3)</td>
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<td>↑ Angiogenesis</td>
<td>↑ Blood pressure (87)</td>
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<td>↑ Release of M-CSF (63)</td>
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<td>↑ Cholesterol accumulation under hyperglycemia (77)</td>
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<td>PAI-1</td>
<td>↑ Thrombus formation (49)</td>
<td>PAI-1 expression stimulated by TNF-α, ANG II, and FFAs (49)</td>
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<td>↑ Restenosis</td>
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<td>Resistin</td>
<td>↑ ET-1 release (111)</td>
<td>↑ Insulin resistance in muscle and liver (102)</td>
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<td></td>
<td>↑ Expression of adhesion molecules and chemokines (111)</td>
<td>↑ Glucose uptake and insulin action (102)</td>
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<td>↓ TRAF-3 (111)</td>
<td>TZD downregulates resistin expression (102)</td>
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<tr>
<td>TNF-α</td>
<td>↑ NO bioavailability (5)</td>
<td>↓ Adipose cell differentiation (56)</td>
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<tr>
<td></td>
<td>↓ Vasodilatation (5)</td>
<td>↓ Insulin signal transduction (40)</td>
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<td></td>
<td>↑ NFκB via ROS (5)</td>
<td>↑ Systemic insulin resistance (41)</td>
</tr>
<tr>
<td></td>
<td>↑ VCAM-1, ICAM-1, E-selectin, and MCP-1 in EC and VSMC (5)</td>
<td>↑ Lipolysis (24)</td>
</tr>
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<td></td>
<td>↑ Apoptosis in EC</td>
<td>↑ FFAs (24)</td>
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ICAM-1, intracellular adhesion molecule 1; VCAM-1, vascular cell adhesion molecule 1; NF-κB, nuclear factor-κB; TNF-α, tumor necrosis factor-α; NO, nitric oxide; MCP-1, monocyte chemotactic protein 1; M-CSF, monocyte colony-stimulating factor; eNOS, endothelial NO synthase; ET-1, endothelin 1; IL, interleukin; EC, endothelial cells; LDL, low-density lipoprotein; ROS, reactive oxygen species; SMC, smooth muscle cells; VSMC, vascular SMC; AT1-R, angiotensin type 1 receptor; PAI-1, plasminogen-activator inhibitor 1; CRP, C-reactive protein; CHD, coronary heart disease; ANG II, angiotensin II; FFAs, free fatty acids; TRAF-3; TZD, thiazolidinedione; ↑, increase; ↓, decrease.

Obese db/db mice and cp/cp rats compared with their lean controls, along with elevated circulating CRP plasma levels, lending further support to a possible role of fat-derived CRP in insulin resistance. Immunohistological staining for CRP in adipose tissue revealed positivity near the nuclei of mature fat cells (H. Yan, B. Dhillon, and D. C. W. Lau, unpublished observations). Because adipose tissue is a much larger organ than the liver, especially in the case of humans, it can be reasoned that the total amount of CRP produced in adipose tissue may be quite significant even though CRP expression in fat is weaker compared with that for the liver (B. Dhillon, H. Yan, and D. C. W. Lau, unpublished observations). A recent report (81) confirmed that CRP mRNA is expressed in human adipose tissue and that its expression levels are inversely correlated to adiponectin mRNA levels. In addition, CRP mRNA levels are higher in adipose tissue of adiponectin-deficient knockout mice compared with that of controls (81). The emerging data on adipose tissue as a source of plasma CRP, along with the increased adipose tissue-derived IL-6 release in obesity, have revised our understanding of the regulation of CRP production. Until recently, the liver was believed to be the major source of CRP, with its synthesis...
mainly under transcriptional control by IL-6 and, to a lesser extent, by other cytokines. However, now adipose tissue-derived IL-6 appears to be a major regulator of hepatic CRP production. In healthy subjects, about 30% of circulating IL-6 originates from adipose tissue (70). Thus the amount of adipose-derived IL-6 is likely much higher in obese subjects who have both an increased total body fat mass and adipokine overexpression (4). Furthermore, adipose tissue provides a second source of plasma CRP. It is unclear at present to what extent adipose tissue contributes to circulating CRP levels, but this is a topic currently under investigation. The proposed scheme by which adipose tissue is thought to play an increasing role in modulating plasma CRP levels is supported by a recent study (58) suggesting that obesity and abdominal tissue mass are best correlated with elevated CRP levels found in men with the atherogenic dyslipidemia of the metabolic syndrome of insulin resistance.

LEPTIN

Emerging data also link leptin to CVD. Leptin is a fat cell-specific hormone that functions as a signaling molecule on the brain to complete the negative feedback loop of the lipostatic theory of weight control (30). Recent data from our laboratory suggest that leptin exerts a paracrine effect on fat cells and that its expression and secretion by fat cells can be induced by IL-6 and inhibited by TNF-α, underscoring the potential role of interaction among adipokines on their release by fat cells (1, 54). Leptin, like CRP, upregulates ET-1 and endothelial NO synthase production in endothelial cells and promotes accumulation of reactive oxygen species (18, 50). It stimulates the proliferation and migration of endothelial cells (82) and vascular smooth muscle cells (3). MCP-1 expression in aortic endothelial cells is stimulated by leptin (120). Furthermore, leptin increases platelet aggregation and arterial thrombosis via a leptin receptor-dependent pathway (18, 50), has a direct action on endothelial cells by increasing the release of ET-1 in adipose tissue (70). MCP-1 expression is dramatically upregulated in the diabetic state (62). The increase in acute phase reactant protein A1 from high-density lipoprotein (HDL)-cholesterol, dyslipidemia associated with diabetes. SAA displaces apolipoprotein A1 from high-density lipoprotein (HDL)-cholesterol, increasing HDL binding to macrophages and thus decreasing cardioprotective HDL cholesterol (62).

SERUM AMYLOID A

Serum amyloid A (SAA) is an acute-phase reactant like CRP, which has been associated with systemic inflammation, linked to atherosclerosis and used as a predictor for coronary artery disease and cardiovascular outcome (46). SAA levels correlate significantly with insulin resistance and obesity in Type 2 DM patients (57). Adipose tissue has been shown to express SAA at low levels under normal conditions, but expression in adipose tissue is dramatically upregulated in the diabetic state (62). The increase in acute phase reactant proteins may affect lipid metabolism and thus contribute to the dyslipidemia associated with diabetes. SAA displaces apolipoprotein A1 from high-density lipoprotein (HDL)-cholesterol, increasing HDL binding to macrophages and thus decreasing cardioprotective HDL cholesterol (62).

RESISTIN

Resistin is a recently discovered fat-specific hormone that directly induces insulin resistance in muscle and the liver. Circulating resistin levels are increased in diet-induced and genetic forms of obesity in rodents (102). Neutralization of resistin by specific antibodies resulted in decreased blood glucose levels and improved insulin sensitivity (102), thereby providing a more direct link between fat mass and insulin resistance. We recently reported that resistin exerts direct vasoactive effects in cultured endothelial cells (111). Resistin treatment activated endothelial cells by promoting ET-1 release, in part by inducing ET-1 mRNA expression, suggesting it participates in the endothelial dysfunction observed in patients with insulin resistance. Resistin also significantly augmented the expression of the cell adhesion molecule VCAM-1 and the chemotactic cytokine MCP-1, key processes in
early atherosclerotic lesion formation. Furthermore, resistin-treated cells expressed lower levels of tumor necrosis factor receptor-associated factor (TRAF-3), a potent inhibitor of CD40 ligand-mediated endothelial cell activation. This observation suggests marked endothelial dysfunction may arise in the presence of elevated resistin levels by exaggerating CD40 ligand-mediated endothelial activation. Resistin has also been demonstrated recently to have a proinflammatory effect on smooth muscle cells. Resistin, in a dose-dependent manner, induced human aortic smooth muscle cell proliferation, suggesting it may play a role in the increased incidence of restenosis observed in diabetic patients (12).

ADIPONECTIN

Adiponectin, also known as adipQ and Acrp30, is a complement factor (C1q) abundantly expressed in adipocytes that increases fat oxidation and insulin sensitivity (122). Adiponectin gene expression in human visceral adipose tissue is negatively regulated by glucocorticoids and TNF-α and positively by insulin and IGF-1 (115). Adiponectin levels are decreased in obesity and are inversely correlated to insulin-resistant states and high-sensitivity CRP levels (37). Subjects with coronary heart disease have lower adiponectin levels compared with age- and body mass index-adjusted controls (80), suggesting that adiponectin, in contrast to other adipokines, confers a protective effect against atherosclerosis. In vitro data and an animal model of premature atherosclerosis, the Apo E-deficient mouse, support this tenet (76, 79). Weight loss in obese subjects and treatment of diabetes with a TZD insulin-sensitizing drug restores plasma adiponectin levels to those of controls (124, 125). Adiponectin exerts antiatherogenic properties by suppressing the endothelial inflammatory response, inhibiting vascular smooth muscle proliferation, and decreasing VCAM-1 mRNA expression, all of which are associated with endothelial injury and the subsequent development of atherosclerotic lesions (76, 79). Adiponectin has been shown to inhibit the TNF-α-induced changes in monocyte adhesion molecule expression and in the endothelial inflammatory response (79, 80). Adiponectin also suppresses the transformation of macrophages to foam cells (78). Finally, adiponectin-deficient mice are markedly insulin resistant and demonstrate a twofold greater neointimal proliferation than wild-type mice in response to injury (53).

ANGIOTENSINONEGEN

Angiotensinogen, a precursor to the major proatherogenic vasoconstrictor ANG II, is expressed and produced in adipocytes (2). ANG II directly stimulates ICAM-1, VCAM-1, MCP-1, and macrophage colony stimulating factor (M-CSF) expression in vascular cells by activating NF-κB-regulated genes (104). ANG II also promotes the formation of free oxygen radicals from NO, thereby decreasing the availability of NO and incurring damage to the vascular tissue (109). Augmented angiotensinogen production by adipose tissue in obesity has been linked to angiogenesis (22) and the development of hypertension (2), both of which are known to be associated with endothelial dysfunction.

Taken together, evidence is now mounting to suggest a more direct role for adipokines in endothelial and cardiovascular health and that these effects are independent of their influence on insulin resistance and diabetes. Hence, experimental studies are beginning to shed light on the cellular and molecular mechanisms directly linking excess body fat in obesity and overweight people to elevated CVD risks.

INSULIN RESISTANCE, THE METABOLIC SYNDROME, AND ENDOTHELIAL DYSFUNCTION

Insulin resistance correlates with the degree of obesity, notably abdominal obesity, and is a strong predictor for the development of Type 2 diabetes. The continuing dual epidemics of obesity and diabetes lend support to the notion that insulin resistance is the causal link between the two prevalent conditions (72). Insulin resistance is a central abnormality of the metabolic syndrome of insulin resistance, or syndrome X, originally hypothesized by Reaven (88) to describe a constellation of metabolic abnormalities, including hyperglycemia, hyperinsulinemia, hypertension, dyslipidemia with increased triglycerides, and decreased HDL. Metabolic syndrome is strongly associated with endothelial dysfunction and increased atherosclerosis risk (34, 109). Insulin resistance and adaptive hyperinsulinemia are thought to cause endothelial dysfunction and exert mitogenic influences on vascular smooth muscle cells, in contrast to insulin’s vasodilatory effect by promoting NO release under normal physiological conditions (67).

In addition to hyperinsulinemia, several other factors in the metabolic syndrome have been implicated in endothelial dysfunction (Fig. 2). Impaired insulin action in adipose tissue causes elevated rates of lipolysis and augmented FFA release. The increased flux of FFAs not only impairs insulin secretion by pancreatic islet β-cells (107) and induces insulin resistance in muscle and the liver by interfering with glucose transport and insulin-mediated glucose uptake (59) but also exerts negative influences on vascular health. FFAs impair vasodilatation (101) and reduce NO bioavailability by attenuating endothelial function.
NO synthase activity and stimulating the production of reactive oxygen species by NADPH oxidase (45). FFAs are believed to play a major role in increased hepatic gluconeogenesis and overproduction of triglyceride-rich very-low-density lipoproteins, which in turn lead to higher levels of small, dense, atherogenic LDLs and decreased cardioprotective HDLs (59). The abnormal lipoprotein metabolism that results from the metabolic syndrome negatively influences endothelial function and the atherogenic process.

High glucose levels induce endothelial free radical production and activate NF-kB and protein kinase C as well as enhancing intracellular advanced glycation end-product formation (9). As a result, hyperglycemia enhances nonenzymatic oxidation of lipoproteins, which independently contribute to atherogenesis (9). Hyperglycemia also increases superoxide in endothelial cells and oxidative stress, both of which can result in endothelial injury (66). Hyperglycemia also augments the expression of adipokines, including PAI-1 (49), further fueling the vicious cycle of adipokine-related endothelial dysfunction (Figs. 1 and 2).

**ADIPOKINES ARE THE MOLECULAR LINK BETWEEN OBESITY AND METABOLIC SYNDROME**

Emerging data are lending support to the proposal that obesity, and notably abdominal obesity, increases CVD risk through its effects on insulin resistance and endothelial function (Fig. 3) (115). Adipokines appear to play a central role and conceivably may serve as the cellular link mediating both the metabolic syndrome of insulin resistance and the endothelial dysfunction present in the obese state. Adipokine levels appear to correlate closely with adiposity, with increasing levels in subjects with higher body mass index values. For example, plasma IL-6 levels, which are 30% higher in obese people, decline toward basal levels with weight loss (10, 70, 93). Many of the proinflammatory adipokines exert multiple actions in a variety of cellular processes leading to a complex array of abnormalities characteristic of metabolic syndrome. TNF-α, which is overexpressed in obese states, is a potent inhibitor of adipose cell differentiation and downregulates the expression and release of many proteins that are involved in fat and glucose metabolism (48). It induces insulin resistance by two mechanisms. First, TNF-α stimulates lipolysis through down-regulation of perilipin, which coats the lipid droplets, protecting them from the action of hormone-sensitive lipase (99). Second, it interferes with the insulin signaling cascade by promoting serine phosphorylation of insulin receptor substrate-1, which inhibits insulin receptor tyrosine kinase (40). In insulin-resistant obese mouse models, neutralization of TNF-α in the circulation can restore insulin-mediated glucose uptake (38). TNF-α or TNF-α receptor knockout mice showed improved insulin sensitivity in both diet-induced obesity and in the db/db model of obesity (108). Obese TNF-α-deficient mice had lower levels of circulating FFAs and were partially protected from the obesity-related reduction in the insulin receptor signaling in muscle and fat tissues (108). IL-6 has also been reported to impair IR signal transduction and insulin action in culture (1, 94). It may indirectly induce insulin resistance in vivo by stimulating lipolysis (74). Mice lacking the gene encoding IL-6 (IL-6−/− mice) developed mature-onset obesity that was partly reversed by IL-6 replacement (116). The obese IL-6−/− mice have elevated leptin levels and decreased responsiveness to leptin treatment (116).

Leptin exerts direct effects on several metabolic actions of insulin: stimulation of glucose transport, glycogen synthase, lipogenesis, inhibition of lipolysis, and protein kinase A activation as well as stimulation of protein synthesis in insulin-sensitive target cells (30). Insulin resistance of skeletal muscle and white adipose tissue, while not affected by acute leptin treatment, could also be corrected in the long term and account for some of leptin’s insulin-sensitizing effects (11). In a rodent model of congenital generalized lipodystrophy with marked insulin resistance and leptin deficiency, leptin administration reverses both insulin resistance and DM (96).

**THERAPEUTIC IMPLICATIONS**

It follows from the above discussion that obesity mediates increased CVD risk through multiple pathways. Excess body fat not only leads to changes in fat tissue development and growth and the induction of insulin resistance but also leads to endothelial dysfunction via the proinflammatory and prothrombotic effects of adipokines. Treatment focused on reducing total fat mass as well as visceral fat should theoretically reverse
most, if not all, of the metabolic and vascular abnormalities. The magnitude of improvement appears to correlate with the amount of weight lost. Two landmark studies have provided irrefutable evidence that even modest weight loss of 5–7% through lifestyle modification is highly effective in delaying, if not preventing, diabetes in individuals with insulin resistance and impaired insulin action (48a, 106). The reduction in diabetes risk is directly proportional to the amount of weight loss in both studies. Lifestyle intervention appears to be twice as effective as medical therapy with metformin to decrease diabetes risk (48a). Weight loss also results in a decrease in the inflammatory proteins and improvement in insulin resistance, both of which have favourable effects on endothelial health (22, 35, 52, 103). In very obese subjects with metabolic syndrome, weight loss results in the attenuation of circulating CRP and IL-6 by as much as 80% and 23%, whereas no significant change in TNF-α levels was observed (52). Multivariate analysis showed a significant correlation of reduction in IL-6 with improvement in insulin sensitivity measured by the homeostatic model assessment but not for CRP despite a much greater reduction. CRP lowering, but not IL-6, however, is correlated with body fat loss (52), suggesting that changes in IL-6 and CRP respectively have differential effects on insulin resistance and, by extension, cardiovascular health. Furthermore, the data are in keeping with the proposed concept of adipose tissue as a key modulator of circulating CRP levels. These findings contrast with observations from a similar study (99) where plasma CRP levels were elevated in obese subjects with insulin resistance and the reduction in CRP with improvement in insulin resistance was independent of weight loss.

The evolving role of augmented adipokine production in obese and insulin-resistant states in cardiovascular disease risk opens new avenues for therapeutic interventions. Treatment of metabolic syndrome will need to embrace new strategies to reduce the burden of proinflammatory adipokines. Lifestyle intervention remains the cornerstone therapy, but considerations should also be given to a number of drugs that can decrease the inflammatory adipokines. These agents include TZDs, cholesterol-lowering statins, aspirin, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers.

TZDs are a new class of antidiabetic insulin-sensitizing agents that are potent agonists of the transcription factor peroxisome proliferator-activated receptor (PPAR)-γ. In addition to their predominant role in ameliorating insulin resistance, TZDs have been reported to decrease inflammatory proteins and their proinflammatory properties and may become useful adjuncts to reduce CVD risks in obesity-linked insulin resistance and diabetes. For example, TZDs downregulate TNF-α expression in adipose cells and attenuate the TNF-α-induced expression of VCAM-1 and ICAM-1 in endothelial cells (84).

Our finding in endothelial cells of rosiglitazone reversing the potentiation of the proatherogenic effects of CRP by hyperglycemia may have important implications on the role of TZDs in adipokines (111). The same study (111) also demonstrated that hyperglycemia may, in states of high CRP, serve to exaggerate the proatherogenic effects of CRP on endothelial cells and may potentially uncover a severe atherosclerotic phenotype. Hence, the use of PPAR-γ agonists may serve to attenuate the proatherogenic effects of CRP under basal and hyperglycemic states. PPAR-γ agonists also inhibit leptin-induced endothelial cell migration (32). Because PPAR-γ is expressed mainly by adipose tissue, it can be reasoned that the actions of PPAR-γ agonists are mediated mainly within fat cells. PPAR-γ agonists downregulate resistin expression and stimulate adiponectin expression in fat tissue (65, 125). Finally, PPAR-γ agonists upregulate adiponectin expression and protein levels in normal, obese, and diabetic subjects (125).

**CONCLUSIONS**

We have attempted in this review to briefly describe the cellular and molecular mechanisms whereby excessive body fat contributes to CVD. The evolving role of adipokines in endothelial dysfunction adds a new dimension to our understanding of the relationship between obesity, notably for those with increased abdominal fat, and CVD risks. Among the adipokines, CRP and IL-6 are the two most strongly associated with increased CVD risk and the prediction of future CVD or Type 2 diabetes. The wide-ranging direct effects of CRP on endothelial and smooth muscle cells argue favorably for CRP as a key cellular mediator linking obesity, the metabolic syndrome of insulin resistance, and Type 2 diabetes to increased atherogenesis. Emerging data suggest the beneficial effects of TZDs, and possibly statins and angiotensin-converting enzyme inhibitors, may in part be mediated via the reduction of the levels and the direct effects of the adipokines on atherogenesis. Further investigations into the molecular links between obesity and atherosclerosis will unravel innovative therapeutic strategies to improve cardiovascular health in people affected by obesity-linked insulin resistance, metabolic syndrome, and Type 2 diabetes.

**GRANTS**

This work was supported by grants from the Heart and Stroke Foundation (to D. C. W. Lau and S. Verma), Canadian Institutes of Health Research (CIHR), and the Canadian Diabetes Association (to S. Verma). B. Dhillon was the recipient of a CIHR Industry graduate studentship and a University of Calgary Scholarship.

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