Links Between Adipose Tissue and Thrombosis in the Mouse

Peter F. Bodary

Abstract—Obesity has become a global epidemic and carries a considerable negative impact in regard to quality of life and life expectancy. A primary problem is that obese individuals are at increased risk of suffering from cardiovascular disease complications such as myocardial infarction and stroke. Because fat accumulation is a consistent aspect of obesity, mechanisms that may link adipose tissue to cardiovascular disease complications should be considered. Proteins expressed from adipose tissue, known as adipokines, are hypothesized to have important effects on the progression and incidence of cardiovascular disease complications. This review examines the evidence that adipokines play a direct role in vascular thrombosis, an important event in cardiovascular disease complications. (Arterioscler Thromb Vasc Biol. 2007;27:2284-2291.)

Key Words: hemostasis ■ coagulation ■ obesity ■ diabetes

Atherosclerotic complications such as myocardial infarction and stroke are among the leading causes of death among US adults.1 An important event in atherosclerotic disease complications is the thrombotic response to plaque disruption which causes thrombus formation within the diseased vessel and potentially leads to occlusive thrombosis.2 As a result, the prothrombotic milieu within diseased vessels likely plays an important role in cardiovascular disease (CVD) complications and influences the clinical severity of plaque disruption.2 Mouse models have been developed to understand the complex interplay of factors involved in the thrombotic response to injury.3 Because obesity is associated with both an increased cardiovascular disease mortality4 and an alteration in circulating thrombogenic blood factors,5 these mouse models of thrombosis have been used to explore factors that may link obesity and thrombosis. This review summarizes the evidence for select adipokines that potentially contribute to the development of arterial thrombi.

Changes in the Circulating Milieu of Obese Individuals

A number of circulating factors are produced by adipose tissue and altered in the plasma of obese individuals.6 Interestingly, there is a major inflammatory component present in the adipose tissue in the obese state that may have a direct effect on insulin resistance.7 This obesity-induced inflamed state may also have systemic effects on the development of atherosclerosis and has been the focus of recent reviews.8,9 In addition, this systemic inflammation may promote the hemostatic abnormalities that have been associated with increased fat mass.10 Although adipose tissue in lean individuals does not appear to have a substantial inflamma-
recently linked to the accumulation of adipose tissue are leptin and adiponectin. Circulating leptin concentration has a strong direct link to obesity, with the highest concentrations found in lean individuals and the lowest levels in the obese state. However, the absence of fat in lipodystrophy results in a deficiency in both proteins, indicating that the circulating concentration of these factors is produced primarily or completely by adipocytes. Among the factors produced by the SVC fraction and associated with fat accumulation are tumor necrosis factor-alpha (TNF-α) and plasminogen activator inhibitor, type 1 (PAI-1). These factors are less directly linked to the obese state as they have widespread expression from multiple cell types (see Table 1). Nevertheless, each of these factors appears to be altered in the obese state and may also relate to an enhanced thrombotic state in obese individuals. This review will focus on these 4 circulating adipokines for which a thrombotic phenotype is evident: PAI-1, leptin, adiponectin, and TNF-α.

**PAI, Type-1**

PAI, type-1 (PAI-1) is the primary inhibitor of tissue plasminogen activator (tPA) within the circulation and therefore plays an important role in fibrinolysis and hemostasis. PAI-1 is produced by multiple cell types including hepatocytes, adipocytes, and endothelial cells, making it complicated to quantitate the source of the elevated PAI-1 in the obese state. Nevertheless, elevations of plasma PAI-1 in the obese state are correlated with increased PAI-1 mRNA and protein from adipose tissue in both humans and mice. For example, the extremely obese leptin-deficient (“ob/ob”) mice have significantly higher adipose mRNA and circulating protein for PAI-1 than lean controls. Similarly, studies in human subjects have revealed a relationship between adipose stores, adipocyte expression, and circulating protein. Furthermore, several studies have found a significant correlation between PAI-1 and obesity-associated circulating factors, including elevations of TNF-α, insulin, and VLDL/triglyceride. The relationship between PAI-1 and triglyceride is hypothesized to be exaggerated by a common polymorphism in the PAI-1 gene (−675 / 4G4G) which appears to result in increased PAI-1 production in response to circulating triglyceride.

**Mouse Studies of Thrombosis and PAI-1**

The first phenotyping of mice with transgenic overexpression of PAI-1 demonstrated enhanced venous occlusions in the tail and hind limbs, but no evidence of arterial occlusions. However, phenotyping of PAI-1–deficient mice suggested a significant protection from vascular thrombosis using models of photochemical and ferric chloride-induced injury. In addition, in mice expressing a stable form of human PAI-1, 90% of the transgenic mice developed spontaneous coronary arterial thrombi whereas none of the nontransgenic mice had evidence of coronary thrombi. These studies support both an injury-induced and spontaneous prothrombotic role of PAI-1 in arterial thrombosis in mice.

Consistent with observations in humans, PAI-1 concentration in mice rises with increasing adiposity and is associated with adipose gene expression of PAI-1. However, there have not been studies to date that specifically explore the source or the relative importance of the increase in PAI-1 to arterial thrombosis in the obese state. However, 2 studies using a restraint stress model to initiate tissue fibrin formation have provided insights into PAI-1 expression from adipose tissue. These studies demonstrated that adipose tissue was a relevant source of restraint stress-induced elevations in PAI-1 and that obese animals were prone to renal fibrin deposition following restraint stress. In vivo thrombosis studies are needed to determine whether the elevated PAI-1 circulating in the obese state directly promotes arterial thrombosis.

PAI-1 appears to have varied effects on cardiovascular pathology. Nevertheless, PAI-1 inhibitors have been developed with the expectation of therapeutic benefit for cardiovascular disease. However, this remains a controversial area of study because PAI-1 has so many physiological effects beyond intravascular thrombosis. Of special note for this review, there is controversy regarding the importance of PAI-1 in weight gain and metabolism with several groups suggesting that PAI-1 deficiency is protective of diet-induced and genetic obesity. However, in contrast, other groups suggest no effect or greater weight gain in PAI-1–deficient mice as well as reduced weight gain in a transgenic PAI-1 overexpressing mouse. Nevertheless, if PAI-1 inhibitors are effective in reducing CVD complications, then obese individuals may be prime targets for this intervention because of their elevated circulating PAI-1.

**Leptin**

Leptin is an adipokine produced primarily by the adipocyte that has important effects on metabolism and feeding behavior. This is especially true in mice and people that completely lack the protein or the receptor. However, in addition to effects on metabolism and eating behav-
ior, leptin appears to have effects on immune function, fertility, and growth. Generally speaking, it appears that leptin represents a signal to the brain of energy reserves, thereby influencing feeding behavior and energy utilization. However, because there appears to be a disconnect in obese individuals (and diet-induced mice) between circulating leptin, satiety, and metabolism, an apparent “resistance” to the anorexic effects of leptin has been hypothesized and vastly studied. Current hypotheses include an upregulation of the inhibitory suppressor of cytokine signaling-3 (SOCS3) molecule which has been shown to suppress the anorexic effects of the signal transducer and activator of transcription-3 (STAT3) pathway of the leptin receptor. However, despite the apparent resistance to the anorexic effects of leptin after diet-induced obesity, the effects of leptin on renal sympathetic activation and blood pressure appear to be maintained. This “selective leptin resistance” hypothesis supports a role of leptin in the increased sympathetic activity and hypertension found in obese individuals as well as a potential proatherogenic effect of leptin. In support of these concepts, leptin has been suggested to be an independent predictor of coronary events in 2 separate observational studies. Nevertheless, there is still much work needed to completely understand the many functions of leptin in health and disease.

Mouse Studies of Thrombosis and Leptin
Studies of thrombosis related to leptin were first examined using the extremely obese “ob/ob” mice. Thrombotic phenotyping of these mice revealed a “protected” phenotype despite their extreme obesity accompanied by elevated FFAs, hyperinsulinemia, hyperglycemia, elevated PAI-1, etc. Konstantinides et al and Bodary et al provided complementary data (in different thrombosis models) that both leptin-deficient and leptin receptor–deficient mice were protected from thrombosis. Konstantinides et al further demonstrated that the delivery of exogenous leptin had a dose-dependent effect on arterial thrombus formation and that leptin enhanced agonist-induced platelet aggregation in wild-type and leptin-deficient mice but not leptin receptor–deficient mice. Bodary et al provided data from bone marrow transplant studies to suggest that removal of the leptin receptor from bone marrow–derived cells resulted in protection from photochemical-induced arterial thrombosis. Collectively, these studies demonstrated that leptin deficiency affords an antithrombotic effect despite the presence of extreme obesity and metabolic perturbations. Subsequent studies by Konstantinides et al provided evidence that inhibition of endogenous leptin (via neutralizing antibody) provided protection from both arterial and venous thrombosis. In addition, atherosclerotic (apoE-deficient) mice that were provided chronic delivery (4 weeks of daily injections) of exogenous leptin demonstrated an enhanced thrombotic response despite reductions in epididymal adipose stores and reduced circulating insulin, providing further evidence of the marked effects of leptin on thrombosis.

Although the leptin receptor of the platelet is implicated as a primary player related to the prothrombotic effects of leptin, the possible contribution of other cell types expressing the leptin receptor has not been determined. For example, the leptin receptor is also evident on endothelial cells and has been implicated to have a role in endothelial function including the inhibition of vasodilatation and increased oxidative stress. These effects of leptin could also accelerate thrombus formation. In addition to potential endothelial-mediated leptin effects, there are also remarkable central-mediated effects of leptin on sympathetic tone and arterial blood pressure. The increased sympathetic activation resulting from acute or chronic exogenous leptin could directly influence the thrombotic phenotype. To date, there are no published studies that have directly examined the central-mediated effects of leptin on thrombosis.

Translational studies have been conducted to determine the role of leptin in human platelet physiology. Although some studies have suggested that leptin does not play a role in the platelets of obese and leptin deficient patients, others have observed significant effects. Although several studies have suggested a wide-ranging leptin-induced response in human platelets, this inconsistent effect may be the result of varying leptin resistance among patients. Many studies have demonstrated intracellular signaling effects of leptin in human platelets and megakaryocytes providing additional clues about the underlying mechanisms of leptin’s diverse effects. Further research is needed to determine the exact role of leptin in arterial thrombosis.

ACRP30/Adiponectin
Adiponectin is a unique protein that appears to be produced primarily by adipocytes, but its concentration decreases with increasing adipose stores. Adiponectin has received a lot of attention since its discovery as it appears to have both insulin sensitizing and antiatherosclerotic effects. In addition, it appears to be an important protein resulting from peroxisome proliferator-activated receptor (PPAR) gamma agonists which are gaining widespread use in diabetic patients. There have been at least 3 receptors suggested to mediate the hormonal effects of adiponectin: adipor1, adipor2, and T-cadherin. However, given the abundance of adiponectin in the circulation (> 5 μg/mL), there may also be important non–receptor-mediated physiological effects.

Mouse Studies of Thrombosis and ACRP30/Adiponectin
A recent study by Kato et al has provided evidence that adiponectin influences thrombus formation after laser-induced injury to the carotid artery. The adiponectin-deficient mice examined in this study exhibited a modest increase in thrombus formation in vivo and in collagen-coated plates. In addition, a proaggregatory platelet phenotype was present in the adiponectin deficient mice. The use of an adiponectin-expressing adenovirus to reestablish circulating adiponectin reversed the phenotype back to that of control mice. However, these phenotypes should be interpreted carefully as the adiponectin-deficient mice have metabolic abnormalities secondary to the effects of adiponectin on insulin sensitivity and the return of adiponectin would also reverse these metabolic abnormalities. Therefore, it is difficult to demonstrate a direct effect of adiponectin on thrombus formation and platelet aggregation with this model.
To further address this issue, Kato et al provided evidence that the acute in vitro application of recombinant adiponectin attenuated agonist-induced platelet aggregation. However, no in vivo studies were provided to demonstrate an attenuation of thrombus formation with recombinant adiponectin. Nevertheless, the authors also demonstrated that the adiponectin adenovirus attenuated the total thrombus volume formed in wild-type mice despite their high circulating adiponectin concentration (≈8 μg/mL) providing evidence that increasing adiponectin above the basal state in normal mice can provide protection from thrombus formation. Finally, Kato et al also provided evidence of a platelet adiponectin receptor which was hypothesized to be directly responsible for the antiaggregatory effects of adiponectin on platelets. Additional studies are needed to confirm and extend these findings which have implicated a primary role of adiponectin in thrombus formation.

Treatment with the thiazolidinedione (TZD) drug class (which act as PPAR gamma agonists) results in a significant increase in plasma adiponectin concentration in obese and diabetic patients. Recent basic science studies suggest that the beneficial effects of TZDs are at least partially mediated through the increase in adiponectin caused by these drugs. Because of the increased risk of cardiovascular disease complications in diabetic patients, an antiadhesive drug that has direct antiatherosclerotic effects would be quite beneficial. Some recent studies have demonstrated that TZD treatment slows the progression of atherosclerosis (specifically the carotid artery intima-media thickness) in diabetic patients compared with the use of a sulfnylurea drug. However, the preliminary examination of randomized trials using another drug from the TZD class have revealed no benefit or even detrimental effects on cardiovascular disease end points including myocardial infarction. Because numerous tissues are responsive to PPAR gamma agonists with diverse effects on gene expression, there are likely many adiponectin-independent effects of TZDs on cardiovascular endpoints.

**TNF-α**

TNF-α is produced by inflammatory cells such as the macrophage, natural killer (NK) cells, and T-cells, and is an important inflammatory mediator. In addition, inflammation and thrombosis are considered interrelated in regard to feedback and cross-talk with each other. For example, TNF-α is thought to be partially responsible for elevations in PAI-1 within adipose tissue and to oppose the physiological effects of adiponectin. Furthermore, TNF-α is commonly believed to be an important player in such varied pathologic effects as insulin resistance and the production of tissue factor from circulating monocytes. In vitro studies suggest that TNF-α could lead to a prothrombotic milieu in vivo by causing an increase in tissue factor activity and reduction in thrombomodulin. Furthermore, recent studies have provided in vivo evidence that the absence of TNF attenuates the prooxidative milieu present in obese/diabetic mice and improves their endothelial function.

**Mouse Studies of Thrombosis and TNF-α**

Although no studies have been published demonstrating the direct effect of adipose-derived TNF-α on thrombosis, there have been interesting data demonstrating a direct effect of exogenous TNF-α on thrombosis. Despite many preconceived notions about the likely prothrombotic effects of TNF-α, Cambien et al have provided compelling data to suggest that TNF-α actually has antithrombotic effects in mice when delivered acutely. This study demonstrated a surprising transient antithrombotic effect of high levels of TNF-α likely mediated through the TNF-receptor of vascular smooth muscle cells. Acute high doses of TNF-α were adequate to result in procoagulant plasma and increased plasma microparticles, yet still provided an overall antithrombotic effect. The mediator of this acute TNF-α–induced protection was demonstrated to be an antiplatelet effect which was nitric oxide–dependent. The antithrombotic effects of TNF-α were lost in mice lacking TNF-receptors or inducible nitric oxide synthase (iNOS) providing evidence that iNOS is an important mediator of this transient effect. Although this study demonstrated that TNF-α has antithrombotic effects, the transient and pharmacological elevation of TNF-α in these studies may not replicate the chronic TNF-α elevation that is evident in the obese state.

There is little to no in vivo evidence available to support TNF-α as a prothrombotic or antithrombotic factor in human patients. However, as TNF-α has been mechanistically tied to arthritis, clinical trials of arthritis patients have examined the utility of TNF-α inhibition with infliximab, an anti–TNF-α antibody. In addition to an improvement in arthritis symptoms, this treatment also resulted in improvements in fibrinolytic balance (reduced PAI-1) providing indirect evidence of a reduced thrombotic profile after TNF-α inhibition. Another clinically-available TNF-inhibitor, enbrel/etanercept, has been prescribed to patients with rheumatoid arthritis. Subanalyses of the use of enbrel/etanercept in patients with the metabolic syndrome has demonstrated an increase in plasma adiponectin and reductions in fibrinogen and C-reactive protein. However, no effects on insulin sensitivity have been demonstrated. Additional studies are needed to determine whether the elevation of TNF-α in the obese state has a significant effect on arterial thrombosis.

**Other Adipokines**

In addition to the adipokines mentioned previously, a number of other factors may link adipose tissue to arterial thrombosis. For example, although this review has focused on factors in which evidence of a thrombotic phenotype exists, there are many additional adipokines that may have a direct or indirect influence on blood clot formation, including angiotensinogen, visfatin, resistin, acylation-stimulating protein, and retinol binding protein 4. However, there is not yet compelling experimental evidence that these factors are involved in thrombus formation. In addition, there are nonadipokine factors altered in the circulating milieu of obese individuals that may have an important influence on blood clot formation. For example, there is a great interest in the influence of elevated C-reactive protein (CRP) on cardiovascular disease mortality. Although mouse CRP does not appear to play the same inflammatory role as human CRP, studies in transgenic mice expressing human CRP have revealed a significant shortening in the time to occlusion after arterial injury.
Table 2. Studies of Select Adipokines in Experimental Thrombosis Studies

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Thrombosis Model</th>
<th>Results</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasminogen activator inhibitor (PAI-1)</td>
<td>Ferric chloride-induced injury to carotid artery</td>
<td>PAI-1 deficient mice had significantly less (~50%) thrombus evident 24 h after injury.</td>
<td>Effects only evident in total deficiency.</td>
</tr>
<tr>
<td>Farrehi et al, 1998</td>
<td>Photochemical-induced injury to carotid artery</td>
<td>Antithrombotic (time to occlusion) effect of PAI-1 deficiency and vitronectin deficiency.</td>
<td>Effects only evident in total deficiency.</td>
</tr>
<tr>
<td>Eitzman et al, 2000</td>
<td>Photochemical-induced injury to carotid artery</td>
<td>Less thrombus formation (based on transillumination of the vessel) in PAI-1 deficient mice. Reconstitution of PAI-1 deficient mice with wild-type platelets had minimal effect.</td>
<td>Effects only evident in total deficiency.</td>
</tr>
<tr>
<td>Kawasaki et al, 2000</td>
<td>Ferric chloride-induced injury to carotid artery</td>
<td>Less occlusive thrombi were formed in PAI-1 deficient mice and vitronectin deficiency resulted in less stable thrombi compared to wild-type mice.</td>
<td>Effects only evident in total deficiency.</td>
</tr>
<tr>
<td>Konstantinides et al, 2001</td>
<td>Ferric chloride-induced injury to carotid artery</td>
<td>Less occlusive thrombi were formed in PAI-1 deficient mice and vitronectin deficiency resulted in less stable thrombi compared to wild-type mice.</td>
<td>Effects only evident in total deficiency.</td>
</tr>
<tr>
<td>Konstantinides et al, 2001</td>
<td>(Spontaneous)</td>
<td>Mice with transgene expressing a stable human PAI-1 developed spontaneous thrombi in coronary arteries.</td>
<td>Does not provide evidence of the relevance of increased adipose-tissue PAI-1 expression.</td>
</tr>
<tr>
<td>Yamamoto et al, 2005</td>
<td>Restraint stress-induced microthrombi</td>
<td>Increased microthrombi present in obese mice associated with PAI-1 induction.</td>
<td>No direct evidence of PAI-1 playing a role in this obesity-induced effect.</td>
</tr>
<tr>
<td>Konstantinides et al, 2001</td>
<td>Ferric chloride-induced injury to carotid artery</td>
<td>Protection evident in leptin deficient and leptin receptor deficient mice with implication of platelet leptin receptor mediating the effect. Recombinant leptin promoted thrombosis in leptin deficient and wild-type mice but not leptin receptor deficient mice.</td>
<td>Platelet implicated by in vitro data but not proven with in vivo evidence.</td>
</tr>
<tr>
<td>Konstantinides et al, 2004</td>
<td>Ferric chloride-induced injury to carotid artery</td>
<td>Leptin neutralizing antibody protected mice from thrombosis to wild-type. Transplantation of leptin receptor deficient bone marrow results in protection from thrombosis compared to leptin receptor competent bone marrow.</td>
<td>Bone marrow transplant implicates platelet leptin receptor but does exclude other bone marrow derived elements.</td>
</tr>
<tr>
<td>Bodary et al, 2002</td>
<td>Photochemical-induced injury to the carotid artery</td>
<td>Leptin deficient and receptor deficient mice protected from thrombosis compared to wild-type. Transplantation of leptin receptor deficient bone marrow results in protection from thrombosis compared to leptin receptor competent bone marrow.</td>
<td>Not clear whether chronic inhibition may have negative effects on adiposity metabolism.</td>
</tr>
<tr>
<td>Konstantinides et al, 2004</td>
<td>Ferric chloride-induced injury to carotid artery</td>
<td>Leptin neutralizing antibody protected mice from occlusive thrombosis and models of venous thromboembolism. Evidence that inhibition of basal leptin is sufficient to provide protection from thrombosis.</td>
<td>Supraphysiologic concentrations of leptin used.</td>
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<tr>
<td>Bodary et al, 2005</td>
<td>Photochemical-induced injury to the carotid artery</td>
<td>Daily exogenous leptin provided to atherosclerotic-prone mice resulted in pro-thrombotic state despite improvements in adiposity and fasting insulin.</td>
<td>Implications of adiponectin.</td>
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<td>Adiponectin</td>
<td>Laser-induced injury of carotid artery</td>
<td>Adiponectin deficient mice had increased thrombus volume following injury which was rescued by an adenovirus expressing adiponectin. Evidence of adiponectin receptors (adipoR1 and R2) on platelets was a potential mediator of these effects.</td>
<td>Modest effect on thrombosis in mice deficient in protein.</td>
</tr>
<tr>
<td>Kato et al, 2006</td>
<td>Intravital microscopy; ferric chloride-induced injury of mesenteric arteries</td>
<td>Acute delivery of TNF-alpha had a surprising protective effect on thrombus formation mediated by iNOS and associated with an antiplatelet effect.</td>
<td>No direct evidence that platelet receptor mediates the antithrombotic effects of adiponectin.</td>
</tr>
<tr>
<td>TNF-alpha</td>
<td>Cambien et al, 2003</td>
<td></td>
<td>No evidence of the chronic effects of elevated TNF-alpha</td>
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</table>

Compared with nontransgenic controls. Additional studies are underway to explore the underlying mechanism of the prothrombotic effect of human CRP. An additional example is the potential effect of elevated free fatty acids in influencing thrombosis, possibly through an increase in Factor VII. Although this is an interesting and testable hypothesis, there have not been direct studies using knock-out or transgenic animals to test this concept. Additionally, the prothrombotic effects of a high fat diet on arterial thrombosis are likely multifactorial and difficult to pinpoint.

**Effects of Weight Loss**

Weight loss is generally recommended for overweight and obese individuals to reduce cardiovascular disease risk.
Furthermore, classic cardiovascular disease risk factors improve with relatively modest weight loss. For example, a meta-analysis of randomized clinical trials to examine the effect of weight reduction on blood pressure revealed that a net reduction of \( \approx 5 \) kg reduced blood pressure by \( \approx 4.5 \) mm Hg. Similarly, plasma adipokine concentrations also tend to have a significant improvement with weight loss. For example, studies have demonstrated significant reductions in PAI-1, leptin, and TNF-\( \alpha \) with weight loss. Similarly, adiponectin levels have been demonstrated to increase (ie, improve) with weight loss, though not all studies have observed this effect. Although the long-term success of weight loss programs for overweight/obese individuals has been quite poor, it is important to recognize that strategies that result in significant weight loss can result in significant improvements in circulating adipokine concentrations.

Summary
The strongest evidence of adipokine effects in vascular thrombosis arguably comes from PAI-1 and leptin. In the case of PAI-1, there is a considerable effort to develop specific inhibitors for PAI-1 function which could improve fibrinolysis by limiting the inhibition of intravascular plasminogen activators. These preclinical studies of PAI-1 inhibitors are predicting a benefit for obese patients in part because of recent evidence of reduced adipose tissue accumulation with PAI-1 inhibition in mice. However, because of the pleitropic effects of PAI-1, the specific and targeted inhibition of this molecule in vivo will likely be very challenging. In regard to leptin, murine models of thrombosis suggest that reducing leptin in obese populations may be beneficial. However, because of the many endocrine actions of leptin, it is not clear what other global effects may accompany leptin inhibition. Further dissection of the leptin/leptin receptor signaling pathways will likely uncover other functional strategies for suppressing the apparent negative effects of leptin on CVD complications without altering the salutary effects of leptin. In the case of TNF-\( \alpha \), there is interesting data that supports an antithrombotic effect of acute elevations. However, more evidence is needed to understand the potential thrombotic effects of chronic elevations in the obese state. Finally, adiponectin, the apparently favorable adipose-derived protein that is suppressed in the obese state, appears to have both antiinflammatory and antiatherosclerotic effects. Additional evidence is needed to confirm the apparent direct antithrombotic effect of adiponectin and to reveal the importance of the adiponectin receptors located on the platelet.

Basic science and translational evidence continues to accrue regarding the importance of adipokines on atherosclerotic vascular disease complications. It is intriguing to consider the role that adipokines may play, but there is considerably more work to be performed in both basic science and clinical arenas to understand and reduce the enhanced cardiovascular disease risk that is evident in the obese state. However, it remains apparent that weight loss results in improvements in both traditional CVD risk factors (eg, dyslipidemia, hypertension, etc.) and the adipokines outlined in this review.

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Disclosures
None.

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