Editorial

Adiponectin: Vascular Protection From the Fat?

Peter F. Bodary, Daniel T. Eitzman

The obesity pandemic will likely have a significant impact on the global incidence of cardiovascular disease. Although the mechanisms linking obesity and cardiovascular disease are unclear, recent studies have implicated the adipocyte as a potentially important mediator of vascular complications. The adipocyte is no longer considered a passive storage depot for triglycerides and fatty acids, but rather an active metabolic organ capable of producing several factors, commonly referred to as adipocytokines or adipokines, that may have effects on many physiological and pathophysiological processes. With increasing fat mass, several adipose-related factors are upregulated that may affect local and distant inflammatory processes, including atherothrombosis. However, the most abundant known factor produced by the adipocyte, adiponectin, appears to be downregulated in most cases associated with increasing fat mass. Although most adipokines are thought to promote vascular disease, several studies over the past few years indicate adiponectin is actually protective against vascular disease. Adiponectin is actually protective against vascular disease (Figure).

In the previous issue of Arteriosclerosis, Thrombosis, and Vascular Biology, Kato et al12 demonstrate that adiponectin may have direct effects on vascular thrombosis. The authors demonstrate that mice deficient in adiponectin have increased thrombus volume after laser-induced carotid arterial injury, and they demonstrate that restoration of adiponectin levels to a normal range with an adenovirus expressing adiponectin rescues the thrombotic phenotype. They also show that overexpression of adiponectin (via adenovirus) has significant protective effects in this model of arterial thrombosis. Consistent with a direct adiponectin effect on thrombosis, the authors demonstrate the presence of an adiponectin receptor on platelets from wild-type mice. The authors also demonstrated that AdipoR1 and AdipoR2 are expressed from isolated human platelets and the human megakaryocytic cell line CMK. Platelets from adiponectin-deficient mice displayed an enhanced response to ADP and collagen that was attenuated by the addition of recombinant adiponectin, demonstrating an inhibitory effect of adiponectin on platelet aggregation. Similarly, the addition of recombinant human adiponectin to isolated human platelets resulted in a significant reduction in collagen-induced platelet aggregation, demonstrating that the antiplatelet effect of adiponectin is present in humans as well as mice. A limitation of the study is that many of the in vivo experiments examined the effects of chronically altered expression of adiponectin, which have been demonstrated to result in metabolic improvements via actions of adiponectin through liver and muscle adiponectin receptors. Thus, indirect versus direct effects of adiponectin on a vascular end point may be difficult to distinguish in these studies. Nevertheless, several important in vitro experiments in this article demonstrate that recombinant adiponectin can have direct effects on platelet function when added acutely.

This study indicates that pharmacological manipulation of adiponectin expression could lead to beneficial cardiovascular effects. A class of drugs, the thiazolidinediones (TZDs), are on the market that are capable of affecting the adipocyte transcription profile, including upregulation of adiponectin expression. Of interest, these effects occur in the setting of modest weight gain. In addition to improved glycemia, these drugs reduce inflammation as measured by C-reactive protein, an effect that may be influenced by adiponectin expression. Several groups have shown beneficial effects of the TZDs in animal models of vascular disease, including thrombosis. A recent human clinical trial suggests that TZDs may lead to a reduction in cardiovascular complications. The specific impact of increased adiponectin on these vascular end points remains to be determined.
Weight loss appears to be effective at increasing adiponectin levels\(^1\) and reducing cardiovascular risk factors associated with obesity, although sustained weight loss has proven difficult to achieve. Thus, there is an urgent need to develop therapeutic strategies to reduce the cardiovascular risk associated with obesity and diabetes. Because adiponectin is such an abundant protein, recombinant proteins or peptide agonists may not be a feasible means to enhance adiponectin activity. Pharmacological compounds that enhance adiponectin expression may be the best approach. If possible, we should use the fat mass to our advantage by converting it from a vasculopathic to a vasculoprotective organ. Therapeutic compounds designed to specifically target the rapidly expanding adipocyte transcription factory may allow us to achieve these goals.

**References**


3. Berg AH, Scherer PE. Adipocyte transcription factory may allow us to achieve these therapeutic strategies to reduce the cardiovascular risk associated with obesity and diabetes. Because adiponectin is such an abundant protein, recombinant proteins or peptide agonists may not be a feasible means to enhance adiponectin activity. Pharmacological compounds that enhance adiponectin expression may be the best approach. If possible, we should use the fat mass to our advantage by converting it from a vasculopathic to a vasculoprotective organ. Therapeutic compounds designed to specifically target the rapidly expanding adipocyte transcription factory may allow us to achieve these goals.

**Potential beneficial effects of adiponectin on metabolic and vascular disease processes.** Adiponectin is synthesized and secreted in relatively high concentrations from adipocytes. Adiponectin interacts with receptors (AdipoR1 and AdipoR2) present in liver and skeletal muscle to affect glucose regulation. Adiponectin may also have anti-inflammatory and antithrombotic effects that could protect against vascular complications. In the setting of increasing adiposity attributable to increased caloric intake or reduced energy expenditure, adiponectin expression is reduced, whereas other potential deleterious adipose tissue-derived factors are increased. This reduction in adiponectin, along with upregulation of other factors, may lead to increased inflammation and thrombotic tendency.
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