Adiponectin: A Promising Marker for Cardiovascular Disease

Obesity is a major risk factor for coronary heart disease (CHD). Obese persons have an ~1.5- to 2.0-fold increased risk for CHD, and between 15% and 20% of all cases of CHD can be attributed to overweight and obesity (1). Although hypertension, dyslipidemia, insulin resistance, and type 2 diabetes are core components of the metabolic syndrome and are probably key elements in the causal pathway from obesity to CHD, the underlying mechanisms are only poorly understood. It is known that adipose tissue itself is capable of producing a variety of cytokines and hormones (called adipokines or adipocytokines) that may be relevant for CHD development. Among others, these include pro-inflammatory cytokines, such as tumor necrosis factor-α (TNF-α) and interleukin-6; hormones involved in blood pressure regulation, such as those of the renin-angiotensin system; factors that affect hemostasis and angiogenesis, such as plasminogen activator inhibitor-1 and vascular endothelial growth factor; and hormones involved in energy metabolism, such as leptin (2).

Adiponectin may be the most relevant and promising adipokine with respect to a better understanding of the link between obesity and CHD. Adiponectin (also called ARCP30, AdipoQ, apM1, and GBP28) is a 247-amino acid peptide hormone discovered in 1995 (3). It is induced early in the differentiation of fat cells (adipocytes), consists of an N-terminal collagenous and a C-terminal globular domain, and shares homology with subunits of complement factor C1q. Contrary to other adipose-derived hormones, adiponectin circulates at relatively high concentrations in the blood stream, accounting for 0.05% of total serum proteins, and is inversely associated with obesity, insulin resistance, type 2 diabetes, and cardiovascular disease (CVD) (3–10). Data from animal studies suggest that administration of adiponectin improves insulin sensitivity and may have antiatherogenic and antiinflammatory properties (3).

Although adiponectin circulates in different molecular forms in plasma, which may limit the interpretability of total plasma concentrations (4), several features make adiponectin an attractive marker for cardiovascular risk. For example, plasma concentrations show little circadian variability, do not depend on fasting status, and show only a limited within-person variation over time (11–13). In addition, because adiponectin circulates in relatively high concentrations in plasma, measurement of adiponectin needs only a limited amount of blood. Finally, and more important for treatment and prevention, plasma concentrations can be manipulated by medications, lifestyle, and diet. The thiazolidinediones, which are used clinically to treat patients with type 2 diabetes, up-regulate production and increase plasma concentrations of adiponectin (4) and, although potentially associated with a modest weight gain, lead to beneficial cardiovascular effects (14). Weight loss is probably the most effective way to increase plasma adiponectin and improve cardiovascular risk in obese individuals; however, the long-term success of weight loss achieved by caloric restriction or increased physical activity is questionable, and additional drug therapy or surgery may be necessary (3, 15). The data from a limited number of studies have indicated that dietary factors, including alcohol consumption, may also determine plasma adiponectin concentrations (16–18).

In this issue of the Journal, von Eynatten et al. (19) report on the relationship between plasma adiponectin concentrations and metabolic and inflammatory markers in a large sample of 1174 patients with angiographically documented CHD. They found no association of adiponectin with inflammatory markers, including C-reactive protein (CRP), interleukin-6, and leukocyte count, but a positive association with HDL-cholesterol (HDL-C) and inverse associations with triglyceride (TG) concentrations and the ratio of total cholesterol to HDL-C (although the latter inverse association is probably driven largely by the positive relationship of adiponectin with HDL-C). They also found a positive association with N-terminal pro-B-type natriuretic peptide (NT-proBNP). These associations were mostly independent of traditional CVD risk factors, including body mass index and fasting plasma glucose concentrations.

The study by von Eynatten et al. (19) extends our knowledge about the role of adiponectin in CVD to a clinically important population, that is, persons with existing CHD. Several limitations must be taken into account when interpreting the findings, however. First, the study used a cross-sectional design (measuring biomarkers in patients with existing CHD enrolled in a rehabilitation program); this design limits interpretability about temporal relationships. It is unclear whether the biomarkers reflect metabolic abnormalities that led to CHD or whether they are a consequence of CHD. Second, medical history and information about diet and lifestyle were assessed at the beginning of a rehabilitation program, whereas biomarkers were measured in blood samples obtained at the end of the 3-week program. One of the aims of cardiac rehabilitation is to change diet and lifestyle to improve cardiovascular risk. It is therefore very likely that the information obtained at the beginning of the rehabilitation program does not accurately reflect the “true” status quo at the time of the blood collection at the end of the 3-week program. This difference in timing could cause substantial random error and reduce the strength of the associations reported for adiponectin. In addition, changes in diet, lifestyle, and medications over the rehabilitation period could affect adiponectin, lipids, and inflammatory markers differentially or nondifferentially and bias the results in either direction. Third, the source population, patients with CHD enrolled in a reha-
bilitation program, could be heterogeneous with regard to disease process and socio-economic status, ranging from health-conscious individuals with moderate angina pectoris (~40% had no previous history of myocardial infarction) to socially disadvantaged persons with severe multiple-vessel disease. This again could lead to random error or bias if not accounted for in the analysis. Finally, most (76.9%) participants were on statin therapy, which likely lowers LDL-cholesterol (LDL-C; mean of 1013 mg/L in this population) and CRP but does not affect adiponectin and only slightly affects HDL-C concentrations. Thus, this additional random error may have substantially reduced the correlation of adiponectin with LDL-C and inflammatory markers. Nonetheless, the results are an important contribution to the literature because little is known about the association between adipokines and other markers of metabolic disease in patients with existing CVD.

How do these observations fit in with the existing literature? In animal models, adiponectin leads to increased fatty acid oxidation and glucose uptake, reduced fatty acid synthesis, and decreased concentrations of molecules involved in gluconeogenesis (3). Downstream effects may include decreased TG content in the liver and skeletal muscle and suppression of hepatic glucose production. In vitro, adiponectin inhibits signaling of the endothelial nuclear transcription factor nuclear factor-kB, which mediates the effects of TNF-α and other pro-inflammatory cytokines (4). Adiponectin has also been shown to stimulate the production of nitric oxide in vascular endothelial cells and to inhibit the expression of adhesion molecules, inhibit class A scavenger receptor expression in macrophages, and inhibit proliferation and migration of human aortic smooth muscle cells (3, 4). These animal and in vitro studies suggest that adiponectin may affect glucose and lipid metabolism, inflammation, endothelial function, and thrombogenesis. In humans, CRP is the inflammatory marker most consistently related to CVD risk (20). Population-based studies found correlation coefficients of approximately −0.20 for the associations of adiponectin with CRP and of 0.45 and −0.40 for the correlations of adiponectin with HDL-C and TG concentrations, respectively (5,21). These correlations fueled the hypothesis that some of the effects of adiponectin on CVD may be mediated via lipid metabolism or inflammatory pathways. In fact, recent cross-sectional studies found low plasma adiponectin concentrations associated with higher hepatic lipase activity and lower lipoprotein lipase activity (22,23). In prospective studies, adjustment for HDL-C, TG, or CRP concentrations attenuated the inverse association between adiponectin concentrations and risk of CHD to some extent (5,6). Nevertheless, animal and human studies suggest that part of the potential protective effect provided by adiponectin against atherosclerosis may be independent of traditional cardiovascular risk factors, including plasma lipoprotein concentrations (5,24).

The study by von Eynatten et al. (19) suggests that, once CHD is established, adiponectin is no longer inversely related to systemic inflammation, whereas its positive association with HDL-C and negative relation to TG remain. Furthermore, the study suggests that among CHD patients without apparent signs of heart failure, adiponectin is positively related to plasma concentrations of NT-proBNP, a marker primarily for heart failure (25). Of interest, the authors of a recent study reported that plasma adiponectin concentrations are related to higher mortality among persons with chronic heart failure (26), presumably because a lower body mass index is a marker of wasting. Taken together, these findings suggest that among persons with advanced atherosclerosis, the purportedly beneficial effects of adiponectin may not be readily reflected by its concentration in plasma. This issue is further complicated by reports that the effects of adiponectin may depend on its quaternary structure (3). Downstream effects may include decreased TG content in the liver and skeletal muscle and suppression of hepatic glucose production. In vitro, adiponectin inhibits signaling of the endothelial nuclear transcription factor nuclear factor-kB, which mediates the effects of TNF-α and other pro-inflammatory cytokines (4). Adiponectin has also been shown to stimulate the production of nitric oxide in vascular endothelial cells and to inhibit the expression of adhesion molecules, inhibit class A scavenger receptor expression in macrophages, and inhibit proliferation and migration of human aortic smooth muscle cells (3, 4). These animal and in vitro studies suggest that adiponectin may affect glucose and lipid metabolism, inflammation, endothelial function, and thrombogenesis. In humans, CRP is the inflammatory marker most consistently related to CVD risk (20). Population-based studies found correlation coefficients of approximately −0.20 for the associations of adiponectin with CRP and of 0.45 and −0.40 for the correlations of adiponectin with HDL-C and TG concentrations, respectively (5,21). These correlations fueled the hypothesis that some of the effects of adiponectin on CVD may be mediated via lipid metabolism or inflammatory pathways. In fact, recent cross-sectional studies found low plasma adiponectin concentrations associated with higher hepatic lipase activity and lower lipoprotein lipase activity (22,23). In prospective studies, adjustment for HDL-C, TG, or CRP concentrations attenuated the inverse association between adiponectin concentrations and risk of CHD to some extent (5,6). Nevertheless, animal and human studies suggest that part of the potential protective effect provided by adiponectin against atherosclerosis may be independent of traditional cardiovascular risk factors, including plasma lipoprotein concentrations (5,24).

The study by von Eynatten et al. (19) suggests that,

References


Tobias Pischon1*
Eric B. Rimm2

1 Department of Epidemiology
German Institute of Human Nutrition
Potsdam-Rehbruecke, Germany

2 Departments of Nutrition and Epidemiology
Harvard School of Public Health
Boston, MA
and
Channing Laboratory
Department of Medicine
Brigham & Women’s Hospital
Harvard Medical School
Boston, MA

* Address correspondence to this author at: Department of Epidemiology, German Institute of Human Nutrition (DIfE), Potsdam-Rehbruecke, Arthur-Scheunert-Allee 114-116, 14558 Nuthetal, Germany. Fax 49-33200-88-721; e-mail pischon@mail.dife.de.

DOI: 10.1373/clinchem.2006.067819