Adiponectin is the most abundant circulating peptide hormone secreted by adipocytes and operates in conjunction with its two membrane receptors ADIPOR1 and ADIPOR2 in multiple systems to induce improvement of skeletal muscle and hepatic sensitivity to insulin. More recently T-cadherin has recently been recognized as a novel adiponectin receptor on vascular endothelial cells and smooth muscle. However, despite being secreted by adipocytes, circulating levels of adiponectin decline with obesity. This reduction is potentially in response to other adipocyte-derived factors such as cytokines, which are known to rise with obesity and can suppress adiponectin secretion. Or alternatively obesity-related changes in adipocyte morphology and size may drive this reduction with concomitant increases in leptin secretion. Consistent with the known associations with obesity and diabetes multiple observations now support adiponectin as a potent antidiabetic hormone. First, its administration to diabetic mice lowers blood glucose (1) and conversely adiponectin knockout mice exhibit widespread metabolic dysregulation, insulin resistance, and hyperglycemia (2). Second, its levels correlate positively and strongly with insulin sensitivity and are consistently lower in individuals with type 2 diabetes (3). Third, adiponectin levels correlate as anticipated with the lipid pattern associated with diabetes and insulin resistance, namely inversely with triglyceride but strongly and positively with high-density lipoprotein-cholesterol levels. Fourth, in prospective studies in a range of diverse populations, high adiponectin levels consistently predict lower risk for type 2 diabetes, independent of a range of confounders (3–5), although this protective effect may be stronger in obese individuals (3). Finally, the insulin-sensitizing thiazolidenedione drugs (peroxisomal proliferator-activated receptor-γ activators) strongly raise adiponectin levels in correlation with their glucose-lowering effects (6), with adiponectin acting to enhance fatty acid oxidation, particularly in liver. Collectively these observations would suggest that adiponectin per se is predominantly beneficial, and consequently, this had led to its proposal as a therapeutic target for obesity-related conditions.

Given the general thrust of evidence linking adiponectin to lower diabetes risk, one might anticipate higher adiponectin to also have vascular protective effects. Indeed if we further note that beyond its beneficial metabolic action, adiponectin exerts protective effects on the endothelium via induction of nitric oxide (7) and suppression of inflammatory signaling by inhibitory-κB kinase (8), then adiponectin must surely protect against cardiovascular disease. Certainly in apolipoprotein E-deficient mice, administration of exogenous adiponectin protects against development of atherosclerosis (9), but what about humans? Unfortunately, that is where the story becomes perplexing because although an initial case-control study reported high adiponectin to be independently linked to lower myocardial infarction (MI) risk (10), subsequent studies did not concur. For example, a recent metaanalysis of seven prospective studies encompassing 1313 coronary heart disease (CHD) cases (11) demonstrated negligible, if any, association of a single measurement of adiponectin with a combined end point of nonfatal MI and CHD death. More remarkably, in groups at elevated risk, including those with chronic heart failure (12), patients with angiographic coronary artery disease irrespective of coronary artery disease stability (13) or those with chronic kidney disease (14), high levels of plasma adiponectin have been shown to predict high, not low, mortality. Subsequent studies in elderly men and women with and without existing vascular disease (15, 16) have also reported a positive association of adiponectin with risk for all-cause and cardiovascular mortality.

In this issue of the Journal, Kizer and colleagues provide further support for this observation by demonstrating higher adiponectin levels predict increased risk of first-ever CHD in older adults (inclusive of both men and women), an observation that was more robust when they restricted their end point to nonfatal MI and fatal CHD. This new study, albeit a nested case-control...
studying design, included a large number of incident vascular events and good attention to potential confounders. Thus, there is now strong and consistent evidence that whereas higher circulating levels of adiponectin signal lower diabetes risk, they simultaneously signal higher all-cause and cardiovascular disease (CVD) mortality.

How can these apparent paradoxical observations be reconciled? In addition, what further investigations will help unravel the underlying mechanisms and take this field forward to begin to understand the relevance of adiponectin to potential interventions? With respect to the initial question, a number of theories have been proposed including the possibility that renal dysfunction and thereby impaired adiponectin clearance could potentially explain the association of higher adiponectin to high CVD and all-cause mortality. However, prior studies (16) and the current report by Kizer et al. have now considered and partially dismissed renal dysfunction as a confounder. Peripheral adiponectin resistance has also been put forward to explain higher levels in groups at elevated risk, but the evidence for this possibility is scant. Alternatively, unintentional weight loss/sarcopenia in the elderly has been linked both to higher mortality and higher adiponectin levels; however, again consistent with work from our own group (16), Kizer et al. included weight change in their analyses and also demonstrated that this association was independent of weight loss, although admittedly both studies relied in part on self-reported weight change.

A more attractive option is the possibility of reverse causality, whereby silent or clinically apparent vascular disease leads to compensatory rises in adiponectin. Indeed, adiponectin synthesis has been proposed to be stimulated in response to vascular inflammation to counter the atherosclerotic process, although at least systemic markers of inflammation (e.g., C-reactive protein) appear to not explain the link between adiponectin and mortality (Kizer et al.) (16). Alternatively, a rise in brain natriuretic peptide levels may link silent ischemia or existing vascular disease to higher adiponectin levels because the circulating levels of these two parameters show remarkable positive correlations in patients with and without chronic heart failure (17). Whatever the mechanism(s), we (17) recently suggested that high levels of adiponectin in those with acute coronary syndrome or heart failure may be a reflection of a salvage mechanism to improve insulin resistance and fatty acid metabolism. In other words, elevations in adiponectin represent chronic or acute on chronic compensatory mechanisms to counteract metabolic and vascular stress. Notably, if correct and adiponectin levels did indeed rise as a result of being driven by chronic vascular disease, one may anticipate that the positive link between adiponectin and mortality risk would be stronger in those with prevalent vascular disease. A recent excellent study by Dekker et al. (18) hinted at this possibility, but other studies do not necessarily concur (16), and thus, this hypothesis requires additional study.

Finally, despite the current evidence, we cannot exclude the possibility (as unlikely as it may seem) that under certain circumstances, higher adiponectin levels may actually be damaging to the vasculature. In this respect, recent events should serve to remind us that modalities that improve diabetes control or protect against its development do not necessarily lessen CVD risk. Equally, it is increasingly appreciated that risk factors and risk factor patterns for incident diabetes and CVD are more different than similar (19).

So how do we take this field forward and better understand the role of adiponectin in health and disease? A number of simple suggestions merit consideration. Additional studies are needed to determine whether the link between adiponectin and higher CVD risk is stronger for fatal vs. nonfatal events, for which current evidence conflicts (18) (Kizer et al.). Future studies also need to more robustly examine whether the association of adiponectin with CVD and all-cause mortality interacts with age, gender, or a history of existing vascular disease. A better insight into adiponectin role may also come from studies that have serial measurements ideally over many years of blood samples (for adiponectin, leptin, brain natriuretic peptide, renal function, plus other relevant factors linked to changes in adiponectin levels), together with serial measures of cardiac function, peripheral vascular function, weight change, and ideally detailed body composition to address the concept of relative levels in a dynamic system. In this way, we could determine the baseline characteristics of individuals in whom adiponectin increases more over time and also better tease out accompanying changes in potential mediating factors. Interestingly, there will be some individuals who start high and stay high, and their characteristics could be helpfully contrasted to those who reach similar final levels but from a much lower starting point. Of course, additional studies should also address whether differing adiponectin fractions, with the high-molecular-weight fraction apparently the most insulin sensitizing, associate differently with metabolic and vascular outcomes, although current prospective evidence for the high-molecular-weight fraction suggests its associations with CHD outcomes at least may be broadly similar to those for total adiponectin (20).

In tandem with the above suggestions, the use of genetics to tease out adiponectin’s role in vascular disease may be of particular merit. This work would involve the emerging process of mendelian randomization in which reliable genetic polymorphisms that signal higher circulating parameter levels in a population are examined in relation to end points of interest. In this case, if the parameter is causally linked to the end point of interest, the genetic polymorphisms leading to the higher parameter levels should have comparable associations with end points. The central tenet of this approach is that genes are allocated randomly at conception, before disease occurrence and are therefore not confounded by other factors. In this way, an unbiased estimate of risk and causality is sought. This approach of mendelian randomization has been used to tease out whether C-reactive protein is causally linked to vascular event risk with current evidence against a directly causal association (21). However, to examine causative associations of adiponectin (or other candidates) with outcomes of interest, a cohesive strategy for collaboration among investigators with extensive DNA and serum biobanks from cohorts with large number of prevalent or incident events will be required to enable sufficient power and thus robust answers. Fortunately, it is now clear that such wide collaborations are feasible and
fruitful, and it would be reassuring if such studies reported that genetic polymorphisms specifically associated with higher adiponectin levels were not associated with higher vascular disease or mortality risk.

Finally, in view of its abundance and widespread receptor expression, adiponectin has potential roles in many other conditions, ranging from reproductive conditions, fatty liver disease, and central nervous system pathologies, to name but a few. Therefore, enhanced knowledge of adiponectin’s exact role in vascular disease, in particular understanding the true nature of its association with mortality risk, may well have ramifications for relevant work in other conditions and determining its value in risk assessment for differing conditions. Thus, although there are now well over 2000 papers with adiponectin in their title, we are perhaps only at the end of the beginning in our discovery of the true and complex physiological roles of this fascinating hormone.

Acknowledgments

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