Editorial

Adiponectin and myocardial infarction: a paradox or a paradigm?

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This editorial refers to 'Adiponectin is an independent predictor of all-cause mortality, cardiac mortality, and myocardial infarction in patients presenting with chest pain'[†] by E. Cavusoglu *et al.*, on page 2300

Once considered a disease of the affluent, obesity now prevails in the poorer developing nations as well.[1] Although it is widely acknowledged that obesity, together with its allied metabolic disorders, is closely associated with the pathogenesis of cardiovascular diseases (CVDs),[1,2] the precise molecular links between obesity and CVD remain speculative. It is evident that adipose tissue, traditionally viewed as a passive energy reservoir, plays a role in homeostasis and metabolism. Adipose tissue has autocrine, paracrine, and endocrine functions and synthesizes and releases a wide array of cytokine-like products collectively termed adipokines. Adipokines include pro- and anti-inflammatory molecules, complement factors, growth factors, and signalling proteins[2] that modulate inflammatory, metabolic, and cardiovascular events.[2]

Adiponectin is an adipocyte-specific protein that circulates in concentrations greater than any other hormone in the body. In contrast to many of the other adipokines, adiponectin appears to offer cardiovascular and metabolic protection via insulin sensitizing, anti-inflammatory, lipid metabolism, anti-atherogenesis, and anti-angiogenic effects, which, in part, are mediated through adiponectin receptors.[3] Adiponectin accumulates in the sub-endothelium of injured human arteries where it inhibits monocyte adhesion to endothelial cells and ultimately inhibits the migration and proliferation of vascular smooth muscle that contribute to the atherosclerotic process.[4]

Adiponectin levels are lower in females when compared with males, obese subjects vs. lean subjects, and type 2 diabetics vs. non-diabetics. There is a strong negative correlation between plasma adiponectin levels and visceral fat, as well as body mass index (BMI) in both humans and animals. Low levels of adiponectin are positively associated with an increased incidence and risk of obesity, diabetes mellitus, insulin resistance, low HDL, high triglycerides, and ultimately the development of vascular diseases.[5]

Cavusoglu *et al.*[6] reported on a 2-year study that included 325 high-risk males with cardiac-related chest pain and underwent coronary angiography. Elevated circulating adiponectin levels at presentation were found to be independent markers of both myocardial infarction (MI) and all-cause mortality at 2 years, challenging the accumulated cellular, animal, and human epidemiological data that support adiponectin's role as a protective cardiovascular molecule. Adding to this paradox was the finding that the same inverse relationship previously reported with type 2 diabetes mellitus-related hypertension, HbA1c levels, insulin, BMI, and triglycerides[5,7] was seen despite adiponectin levels paralleling cardiovascular morbidity. Only C-reactive protein (CRP),[2] a recognized inflammatory factor, and adiponectin persistently and independently transpired as risk factors for MI and mortality, regardless of further statistical adjustments.

A similar correlation of adiponectin levels with cardiovascular mortality was also evident in patients with congestive heart failure.[8] In this study, patients with adiponectin levels in the upper two tertiles had triple the mortality risk when compared with those patients within the lowest tertile. The mortality rate was also inversely related to BMI, most probably reflecting the known association of cardiac 'wasting' with increased mortality, suggesting that the paradoxical increase of adiponectin levels in those with the highest mortality may have been secondary to weight loss, a known stimulator of adiponectin.

Animal data support adiponectin as a cardiovascular protective molecule. In a mouse model of acute MI, adiponectin null mice responded with larger infarct sizes, greater myocardial cell apoptosis, and increased tumour necrosis factor α expression when compared with wild-type controls.[9] Rescue attempts with adiponectin delivered by adenovirus, and recombinant adiponectin infusion prior to or during the ischaemia-reperfusion procedure, ameliorated all the associated damaging effects,[9] suggesting that exogenous adiponectin protects the heart against ischaemic insults. Although adiponectin levels may decline acutely in the setting of an MI,[10] this may, in part, reflect sequestering of adiponectin at the site of vascular injury, a hypothesis that remains to be tested.

In a nested case-controlled study of the Health Professionals Follow-up Study (HPFS)[7] of 18 225 male health care providers, there are convincing clinical data for a positive correlation between high baseline plasma adiponectin and diminished MI risk over a 6-year follow-up in subjects with no prior cardiovascular disease. This correlation persists even after adjustments for matched variables, family history of MI, BMI, alcohol consumption, physical activity, and a history of diabetes and hypertension (RR 0.41, 95% CI 0.24–0.70, P for trend <0.001). Furthermore, adjustments for HbA1c and CRP had little impact, although adjustments for HDL and LDL moderately attenuated this relationship. The diabetic sub-group of HPFS had a similar relationship of adiponectin levels to cardiovascular risk, and this association was in part mediated by higher levels of HDL.[11] The plasma adiponectin levels reported by Cavusoglu et al. were within the boundaries of the lowest two HPFS quintiles, which were defined as the sub-populations with the worst MI odds ratio (OR). This indicates that the results may represent a statistical aberration or that there are other factors at play that have not been formally accounted for in the multivariate adjustment.

Is there a paradigm that unifies a biologically plausible hypothesis to account for adiponectin as a surrogate biological 'marker' for a good cardiovascular prognosis in low-risk patients, yet still be compatible with its association with a poorer prognosis in high-risk patients? The answer is affirmative if adiponectin is viewed first and foremost as a vascular protective 'mediator'. High levels of adiponectin were inversely proportional to adverse cardiovascular events in HPFS, a low-risk population, supporting a salutory role in mediating vascular protection. In high-risk populations, such as those in the study by Cavusoglu et al., the cardiovascular protective role of adiponectin should hypothetically be no different. The higher levels of adiponectin may be in response to the inflammatory milieu that triggers an increased expression, synthesis, and release, which is a physiological attempt to limit further endothelial damage. Despite all the counter-regulatory mechanisms that are mobilized in the high-risk patients, including up-regulation of plasma adiponectin levels, it is intuitive that the reparative processes of the body may be overwhelmed, translating into higher cardiovascular morbidity.

Circulating adiponectin predominantly exists as three primary oligomeric complexes—trimeric, hexameric, and high molecular weight (HMW) adiponectin. Although there is no consensus concerning the biological significance of the various adiponectin isoforms, the ratio of HMW to total adiponectin may correlate better with clinical benefit than total adiponectin alone,, at least with respect to insulin sensitivity.[12] Cavusoglu et al. did not examine the individual adiponectin entities, nor did HPFS for that matter either, leaving it open to speculation that the patients with the worse OR for MI may have had the lowest percentages of the biologically active HMW adiponectin or, alternatively, a higher ratio of 'inert' adiponectin complexes, despite high levels of total plasma adiponectin. Future studies may help to better define the levels of the individual adiponectin isoforms and their respective impact on endothelial function that includes the production of nitric oxide.

Central obesity is a reflection of visceral obesity and the risk of cardiovascular disease.[1] Importantly, both cardiovascular and metabolic health, including elevation of adiponectin levels, are enhanced following removal of visceral, but not subcutaneous fat. Recently, the INTER-HEART investigators determined that despite gross variations in waist-to-hip ratios between races, this measurement is a strong indicator for MI risk globally[1] and may be more predictive of MI than BMI, but the relationship of adiponectin to waist-to-hip ratio is not known.

Adiponectin levels may be altered by drugs, increasing in response to the peroxisome proliferator-activated receptor γ (PPARγ) agonists thiazolidinediones (TZDs),[3] as well as by inhibitors of the renin–angiotensin system, perhaps by combating insulin resistance and hypertension, respectively.[13] TZDs stimulate a substantial production of adiponectin, and considering PPARγ is predominantly expressed in adipose tissue and adipose tissue appears essential for TZDs to improve insulin sensitivity, this suggests a central role for adiponectin in the improved insulin sensitivity seen with TZDs.[3] Antagonism of the cannabinoid receptor type 1 with rimonabant has been associated with a 57% ($P < 0.001$) increase in adiponectin in obese dyslipidaemic patients. The increase in adiponectin is, in part, related to weight loss in addition to a direct effect of rimonabant to promote adiponectin mRNA expression.[14]

Although one might conclude from the study of Cavusoglu et al. that adiponectin is a deleterious adipokine given its relationship with increased MI and mortality, it could be argued that if adiponectin isoforms were measured, or serial measurements made, or waist-hip ratio was reported, the results may have differed. Regardless, the paradox is perhaps best viewed from the perspective that the preponderance of accumulated data supports a cardiovascular protective role of adiponectin and that adiponectin levels are suppressed in chronic diseases such as obesity and diabetes mellitus, yet still have the ability to be up-regulated in response to acute cardiovascular injury.

In the future, congeners of adiponectin, or pharmaceutical agents that augment endogenous adiponectin levels, may ultimately play a role in the management of obesity. However, the most logical and cost-effective approach of dealing with this burgeoning problem is through the prevention of obesity in childhood, which is a true epidemic. Children are increasingly sedentary as physical activity disappears from both schools and day to day life, and as well ingest a diet of energy dense foods and beverages, of questionable nutritional value. According to a recent study from the Institute of Medicine, food marketing may contribute to this epidemic, as advertisers 'intentionally target children too young to distinguish advertising from truth and induce them to eat high-caloric, low-nutritional (but highly profitable) 'junk' foods'.[15] If the factors leading to childhood obesity are so readily apparent, so are the actions necessary to mitigate them.

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