Editorial

Adiponectin, Adipokines, and the Need for Long-Term Human Studies With Comprehensive End Points

Philip W. Connelly, Anthony J. Hanley

Adiponectin is arguably the adipokine most specifically expressed in white adipose tissue. It was described in 1995 as Acrp30, AdipoQ, apM1, and GBP28. The x-ray crystallographic observation in 1998 that there was structural homology to complement C1q and tumor necrosis factor should have been a clue that this would be a complex beast.[1] Adding further to the complexity, adiponectin monomers are assembled into multimers that can be separated by size into 3 broad groups. The largest high-molecular weight adiponectin has been shown to be protease resistant, which became the basis for a selective immunoassay.[2] The complexity of adiponectin structure—with both covalent and noncovalent interactions stabilizing the multimers—adds further challenges to quantification for patient–based studies. Indeed, not all assays have been found to give agreement. In the absence of a gold standard, we require stability from suppliers of assays and carefully characterized cohorts to establish biovalidation.

See accompanying article on page 2259

Advances require that not all evidence be accrued in human or patient–based studies. Adiponectin has proven a challenge, as while it is found in species such as mice, there are major species-specific differences in tissue expression patterns[3] (Biogps GeneAtlas U133A, gcrm; GeneAtlas MOE430, gcrma). That is, mouse is not a small furry human—at least physiologically speaking. To further add to the complexity, adiponectin receptors (AdipoR1 and AdipoR2 as the most clearly validated) have markedly different distributions of tissue expression between species. Thus, validation of expression of mRNA and protein at the cell and tissue level is incomplete at present. Adiponectin is higher when central adipose tissue and overall energy stores are low. There is good evidence that adiponectin expression is increased by PGC1α (peroxisome proliferator-activated receptor gamma coactivator 1-alpha), PPARγ (peroxisome proliferator-activated receptor gamma), and brain natriuretic peptide (Figure). The support for regulation by catecholamines and the NAD(+) (nicotinamide adenine dinucleotide)/sirtuin pathway is evolving.[5] These factors limit the ability to move from the specifics of a model system observation to the general and highly complex state of human biology.

Nowhere is this conundrum more evident than in the studies of adiponectin in different patient populations and otherwise healthy population cohorts. The evidence from prospective cohort studies is clear that low adiponectin predisposes to incident type 2 diabetes mellitus.[7,8] It was tempting to extrapolate these observations to health benefits for higher concentrations of adiponectin. Yet that has not been borne out, particularly for cardiovascular end points[9] and in patient populations with underlying morbidity, including heart failure[10,11] or chronic kidney disease. As the study in this issue reinforces, a higher concentration of high-molecular weight adiponectin is predictive of increased cardiovascular mortality in subjects with type 2 diabetes mellitus.

The study by Liu et al[12] has significant strengths including utilizing data from a well-recognized and extensively studied cohort of male health professionals; achieving a large sample size of men with diabetes mellitus supported by a validated supplementary questionnaire to confirm the diagnosis of diabetes mellitus; adjustment in multivariate regression models for a large number of carefully measured known confounding factors, including education and socioeconomic status; a remarkable 22-year follow-up, with contact every 2 years to update lifestyle information, medical history, and disease diagnosis; and finally, a validated method to identify deaths, allowing the researchers to confirm vital status and cause of death in a large proportion of the cohort. The Health Professionals Follow-up Study diabetes cohort, consisting of 950 men, experienced 580 deaths, 220 of which were due to cardiovascular disease. The plasma concentrations of fatty acid–binding protein 4 and of high-molecular weight adiponectin were positively ($P \leq 0.001$) associated with cardiovascular disease death (hazard ratios, 1.78 and 2.07, respectively) in multivariate Cox regression models. Retinol-binding protein 4 concentrations did not reach statistical significance.

We have to consider that biomarkers were only measured at baseline, and the analysis is not able to disentangle the possibility that subjects with low adiponectin were recognized early by established risk factors and received specific diabetes mellitus treatment regimens that themselves would affect mortality and outcomes. However, what is clear is that not all patients with diabetes mellitus have low concentrations of adiponectin or its high-molecular weight form. Whereas we might have speculated that subjects at the top end for the distribution of adiponectin were out of the woods, that is clearly not the case.

Are there any clues as to what we can attribute this observation? Is this because of resistance to the action of

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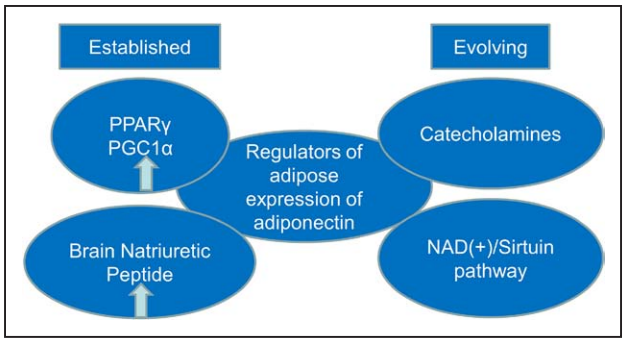

Figure. Regulation of adiponectin expression. Adiponectin expression has been established to increase in response to activators of PPARγ (peroxisome proliferator-activated receptor gamma) or PGC1α (peroxisome proliferator-activated receptor gamma coactivator 1-alpha).[1] More recently, brain natriuretic peptide receptor A has been described in adipocytes and can function to promote adiponectin production.[4] Newer studies have identified the NAD(+) (nicotinamide adenine dinucleotide)/sirtuin pathway[5] and catecholamines through the β-adrenergic receptor system[6] as likely factors that determine adiponectin concentrations.

adiponectin? or to a biomarker keeping bad company? or to a biological control circuit responding to adverse biology (ie, induction of adiponectin expression in response to brain natriuretic peptide[4,10–13] or catecholamine[6]), but not able to overcome the strengths of the inciting agent (Figure)?

One of the challenges for the design of future studies is that we are now in an era where obesity and type 2 diabetes mellitus have swept across the globe. Maintaining cohorts, and selection of outcome measures that can be applied to today's patient or asymptomatic individual, keeping in mind the critical importance of assay stability and validity, is a particular challenge given the resource implications.

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