Adiponectin
Just Along for the Ride?

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Adiponectin is the most adipocyte-specific of all secretory factors described to date. Despite its exclusive expression at the level of the fat cell, adiponectin concentrations in plasma are generally inversely proportional to fat mass.1,2 More detailed studies reveal that it is not fat mass, but rather fat quality that is the driving force for adiponectin expression. Comparing metabolically healthy and metabolically unhealthy obese individuals, the metabolically healthy individuals display higher levels of adiponectin despite identical body mass indices.3,4 This reflects the close relationship between adiponectin and insulin sensitivity. Mouse models that maintain high adiponectin levels similar to lean mice, despite gaining weight,5,6 retain full metabolic flexibility. Positive changes in adiponectin levels are also a reflection of therapeutic improvements in systemic insulin sensitivity, such as on exposure to a PPARγ (peroxisome proliferator-activated receptor gamma) agonists.7 We and many others concluded, therefore, that adiponectin levels are excellent integrators of adipose tissue health and systemic metabolic flexibility,8 including as a direct driving force for positive effects exerted on cardiovascular disease states.9

The authors present a conservative analysis—consisting of single nucleotide polymorphisms (SNPs) just within the gene encoding adiponectin (ADIPOQ) itself—and a liberal analysis—consisting of other SNPs across the genome highly associated with adiponectin levels. Given that many of the SNPs in the liberal analysis are also associated with significant differences in other well-established risk factors for coronary heart disease (CHD), it seems potentially misleading to use them in the analysis in the first place because they likely reflect SNPs with broader effects on metabolism or anthropometrics. We agree with the authors that this analysis is dangerously vulnerable to horizontal pleiotropy.

The authors found that each adiponectin-increasing allele was associated with a significant decrease in CHD risk. Although this suggests that adiponectin is actually cardiometabolically protective, the authors go on to adjust for the glycemic and lipid covariates they had access to and noted no independent effect of adiponectin in protecting against CHD. One wonders whether such adjustments are necessary and indeed correct to do from a biological standpoint, given that adiponectin’s biological action is played by improving insulin sensitivity while decreasing hepatic glucose output and triglyceride accumulation. This also begs the question of how well the Mendelian randomization worked to achieve an even balance of cardiovascular risk factors across allelic groups if additional adjustment was performed.

The issue of whether the randomization was successful in achieving a balance of demographic (age, race, sex) and clinical characteristics (diabetes mellitus, smoking, hypertension, hyperlipidemia, prior CHD) germane to a CHD-outcome analysis is critical in this case, and we are not given the data to make this conclusion. Otherwise, it is not clear that any conclusions can be drawn at all. For example, adiponectin concentrations are highly related to age, race, and sex, 3 of the most important nonmodifiable CHD risk factors. It is possible, for example, that the adiponectin-increasing alleles were associated with differences in male:female ratios or different ages at CHD presentation, which would underscore a potentially protective effect that the summary data presented in the present analysis cannot discern. Further, although >90% of the study population was white, potential confounding from population stratification is still possible, and it is unclear whether any adjustment for race was performed.

As mentioned by the authors, the inability to test for the effect of prior CHD is problematic because of the well-described adiponectin paradox, whereby increasing serum adiponectin concentrations are associated with increased cardiovascular mortality among patients with existing CHD or heart failure. This poses a problem insofar as the effect of

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Borges et al10 now undertook a Mendelian randomization study using data from several different genome-wide association studies consortia. The authors used the ADIPOGen consortium to pinpoint genetic variants that were then used as variables to gauge the effects of adiponectin on cardiovascular disease outcome. They used a conservative approach (restricting themselves to variants within the adiponectin gene proper), as well as a broader approach in which they took into account variants in any locus affecting adiponectin levels. Based on their analysis, the authors come to the bold conclusion that there was no genetic evidence indicating a causal role of adiponectin as a mediator of cardioprotective effects.

So, does this really mean that adiponectin, despite the wealth of clinical data and direct functional basic science data, is nothing but a bystander? Not quite. Several major issues with the present analysis suggest that the conclusions drawn are rather premature.

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adiponectin on CHD outcome may be influenced by duration or severity of pre-existing CHD in an opposite way to incident cases. Ma and colleagues recently presented strong evidence for adiponectin resistance under those conditions, providing a molecular mechanism for the events taking place during heart failure.  

One important assumption of the Mendelian randomization is that the risk allele(s) can explain a reasonable amount of the variation in the intermediate factor—that is, these SNPs significantly influence the levels of adiponectin. Several ADIPOQ polymorphisms have been variably reported to influence serum adiponectin concentrations, but it is not obvious from the present analysis to what degree these polymorphisms influence adiponectin levels in circulation to a biologically meaningful degree. With the large cohorts under investigation here, even small, but perhaps clinically irrelevant, differences in adiponectin levels may be detected.

Finally, the details of adiponectin quantification are not provided. Because there is no standard assay for adiponectin (as compared with, eg, low-density lipoprotein and glucose), the values from individual cohorts generally cannot simply be joined. How statistically the authors dealt with this is not stipulated, and it is not clear whether this would have potentially influenced their findings.

We think, therefore, that the conclusions reported by Borges et al should be interpreted with great caution. The combined clinical correlational data along with strong preclinical evidence continue to support an involvement of adiponectin as a direct driving force to sustain (cardio)metabolic health.

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None.

References


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