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Role of Adiponectin

Important or Null?

Mechanick and colleagues (1) described recent information about adipokine effects on the cardiovascular system. We already discussed that adiponectin plays an important role in metabolic and cardiovascular homeostasis, and circulating adiponectin levels might act as a biologic marker by having insulin-sensitizing, anti-inflammatory, and antioxidant effects (2,3). With regard to the potential association of adiponectin with clinical outcomes, longitudinal studies have indicated that hypoadiponectinemia is an important risk factor for atherosclerosis, and that hypoadiponectinemia is independent of traditional cardiovascular risk factors, including hypertension and diabetes.

In contrast, Borges et al. (4) investigated the causal effect of adiponectin on coronary heart disease (CHD) risk by performing a Mendelian randomization study using data from genome-wide association studies consortia. Findings from the liberal approach (including variants in any locus across the genome) indicated a protective effect of adiponectin that was attenuated to the null after adjustment for known CHD predictors. Therefore, this study does not seem to support a causal role of adiponectin levels in CHD etiology. It is used by the most updated technique. Furthermore, several recent papers have suggested that high adiponectin levels are linked to unfavorable patient outcomes, particularly in older adult populations (5). What is the clinical meaning of these studies? Unfortunately, this aspect has not yet been investigated much; therefore, further studies in this field should be investigated.

Recently, a high-throughput screening assay was developed to determine adiponectin secretion modulators in 3T3-L1 adipocytes. These compounds could be useful drug candidates for cardiometabolic disorders. Such tools might be applicable to screening for other adipokine modulators that could be useful for the treatment of other conditions.

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REPLY: Role of Adiponectin

Important or Null?

We thank Dr. Koh for these comments that point to examples of discrepant data pertaining to adiponectin's role in cardiometabolic disease. We also have a primary research interest in adiponectin and have shown that it can contribute to both vascular and metabolic disease components (1). Regarding vascular disease, it has a direct action on macrophages to inhibit lipid accumulation and foam cell formation when exposed to oxidized low-density lipoprotein (2,3). In adipose tissue, it acts as an autocrine and/or paracrine factor to increase insulin sensitivity, augment lipid storage capacity, and decrease the

inflammatory posture of adipocytes (3,4). Of course, adiponectin helps regulate metabolism in the context of a network of interactions together with many other hormones, genetic effects, and environmental influences.

The discrepancies highlighted by Dr. Koh reflect the failure to fully regard adiponectin within this complex matrix of interactions. His comment further illustrates the need to understand adiponectin from a network perspective. We note that other adipokines, such as chemerin and apelin, also have mixed contributions on atherogenesis and obesity, respectively. These observations, in which one target can have mixed effects, are not uncommon (5) and inspire the primary motivation for studying adipokines from a network perspective. Our network analysis can only capture known connections, and there are obviously many unknown interactions yet to be discovered.

In addition, any trajectory toward personalized effects of adiponectin will require computational analyses. Network analysis can potentially provide additional insights from genome-wide associated studies and high-throughput screening. For example, we can answer questions about strategies to prioritize novel drug targets to treat coronary artery disease. This ability to personalize treatment promises to reduce unfavorable outcomes and increase beneficial outcomes. We thank the reviewer for raising this issue, which we think helps substantiate the main thrust of our paper.

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