Another Paradox Regarding Adiponectin Revisited

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Key words: Adiponectin, Gene polymorphism, CDH13, Genome-wide association study, Metabolic syndrome

Adiponectin, an insulin-sensitizing and anti-inflammatory adipokine specifically secreted from fat cells\(^1\), has been known to show several paradoxical facets (Fig. 1). The plasma levels of this adipose-derived cytokine have been shown to paradoxically decrease as the body fat (particularly visceral fat) mass increases and accumulates \textit{in vivo}. Moreover, higher plasma adiponectin levels have been reported to be associated with adverse clinical outcomes such as increased all-cause mortality in the general population\(^3\) (particularly in elderly subjects), which appears to be paradoxical when considering its favorable biological and metabolic effects.

Recently, another paradox regarding adiponectin has been observed from the results of genome-wide association studies (GWAS). A meta-analysis of GWAS of adiponectin levels has identified several single-nucleotide polymorphisms (SNPs) in the gene for T-cadherin (\textit{CDH13}) that showed the strongest association signal for plasma adiponectin concentrations at the genome-wide level\(^4\). Considering the fact that the \textit{CDH13} gene encodes an adiponectin receptor abundant in the vasculature and cardiomyocytes\(^5\), such genetic association observed between the \textit{CDH13} gene variants and plasma adiponectin concentrations at the genome-wide level\(^4\). Considering the fact that the \textit{CDH13} gene encodes an adiponectin receptor abundant in the vasculature and cardiomyocytes\(^5\), such genetic association observed between the \textit{CDH13} gene variants and plasma adiponectin levels appears to be very likely and appropriate. However, these \textit{CDH13} gene variants that are strongly associated with increased plasma adiponectin levels have been repeatedly reported to be associated not with better, but worse, deteriorated metabolic phenotypes that may result in the clustering of coronary risk factors and development of metabolic syndrome (Mets), potentially independent of adiponectin levels\(^6\)\(^8\). More recently, Teng \textit{et al.} used a mediation analysis to further elucidate this statistical association between \textit{CDH13} gene variants and metabolic phenotypes\(^9\). Among 530 Taiwanese participants that were examined, the abovementioned study confirmed the strong association between the \textit{CDH13} gene variants and adiponectin levels and showed that the major alleles of such gene variants associated with increased adiponectin levels (i.e., the adiponectin-inducing alleles) were associated with adverse metabolic phenotypes, particularly after adjusting for adiponectin levels; this appears to be substantially consistent with the previous reports\(^6\)\(^8\). The results of the mediation analysis have suggested that adiponectin may function as a suppressor of the association between the \textit{CDH13} genotype/haplotypes and various metabolic phenotypes or metabolic syndrome, although the underlying biological mechanism remains unclear\(^9\).

On page 309 of this issue of Journal of Atherosclerosis and Thrombosis, Kitamoto \textit{et al.} reports an additional independent study that evaluated the genetic association between the \textit{CDH13} gene variants and various metabolic phenotypes in 945 Japanese subjects with special attention to visceral fat accumulation precisely measured using computed tomography (CT) as visceral fat area (VFA). The authors have used a structural equation modeling (SEM) analysis to explore insight into the factorial correlation underlying the paradoxical association\(^10\). They have found that the major alleles of the three \textit{CDH13} SNPs (rs3865188, rs4783244, and rs12051272) were strongly associated with higher adiponectin levels even after adjustment for VFA and were significantly associated with features characteristic of metabolic syndrome such as higher levels of fasting plasma insulin, homeostasis model assessment-insulin resistance (HOMA-IR) scores, and plasma triglycerides and

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Received: November 6, 2015
Accepted for publication: November 9, 2015
lower levels of high-density lipoprotein (HDL)-cholesterol, which was quite consistent with the previous observations\textsuperscript{6-9).} The unfavorable effect of these adiponectin-inducing alleles on metabolic traits was associated with neither higher adiponectin nor lower VFA levels. The path diagram derived from the SEM analysis suggested that \textit{CDH13} SNPs exacerbated metabolic syndrome independent of their effects on increasing adiponectin levels. Based upon these observations and circumstantial evidence, Kitamoto \textit{et al.} hypothesized the presence of \textit{adiponectin resistance} that may be caused by lower expression of \textit{CDH13} because of these SNPs or their tightly-linked SNPs located within the regulatory region of \textit{CDH13} and that may result in compensatory increase in adiponectin levels as a response to metabolic injury\textsuperscript{10).} In contrast, another possible explanation has been proposed by Teng \textit{et al}.\textsuperscript{9)} who discussed the possibility that increased expression of \textit{CDH13} may interfere with the metabolically more important receptors for adiponectin (AdipoR1 and AdipoR2)\textsuperscript{11)} that may result in the decrease in adiponectin sensitivity coupled with compensatory increase in adiponectin levels.

Collectively, these recent observations\textsuperscript{6-10) have clearly established the paradoxical association between the adiponectin-inducing alleles of \textit{CDH13} and the clustering of the principal components of Mets independent of plasma adiponectin levels. Although several hypothetical and speculative explanations for the paradoxical association have been provided with statistical approaches\textsuperscript{9, 10)}, further experimental studies accompanying biological evidence are required to elucidate the molecular basis of the unsolved paradox.

\textbf{Conflicts of Interest}

None.

\textbf{References}


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