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Review

Serum total adiponectin level and the risk of cardiovascular disease in general population: A meta-analysis of 17 prospective studies

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ABSTRACT

Objective: Many studies have assessed the association between serum adiponectin and the risk of cardiovascular disease (CVD), yet whether adiponectin is an independent risk factor for CVD remains controversial. We performed a meta-analysis of 17 prospective epidemiologic studies to evaluate this relationship in the general population.

Methods: PubMed and Embase databases were searched through June 2012 to identify studies meeting a priori inclusion criteria, in addition to conducting a secondary reference review. Two principle investigators respectively extracted the information with either fixed-effect model or random-effect model to calculate the relationship between adiponectin and the risk of CVD.

Results: We summarized 17 prospective studies with a total of 23,717 participants. Overall, higher serum adiponectin was related to an increased risk of ischemic stroke: pooled risk ratio (RR) of 1.34 [95% confidence intervals (CI): 1.06–1.69] with no heterogeneity ($Q = 1.23$; $P = 0.541$). Serum adiponectin was not related to coronary heart disease (CHD) or CVD: pooled RR of 0.96 (95% CI: 0.85–1.08) and 1.00 (95% CI: 0.89–1.13), respectively.

Conclusions: Increased serum adiponectin was related to an elevated risk of ischemic stroke, but there was no clear evidence indicating a positive relationship between adiponectin and the risk of CHD or CVD.

Contents

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1. Introduction

Adiponectin, also known as GBP-28, apM1, AdipoQ and Acrp30, is a protein in the human body encoded by the ADIPOQ gene [1]. It is involved in many pathways related to the development of atherosclerosis such as glucose and lipid metabolism, inflammation, endothelial function, and thrombogenesis [1,2], and it could be an independent risk factor of cardiovascular disease (CVD). Here, we define CVD as a composite of coronary heart disease (CHD) including coronary death, myocardial infarction, and ischemic stroke. A number of studies have reported that lower serum adiponectin is associated with increased incidence of CHD events [3,4], while others have not found an association [5–7]. One reason for these mixed results may be over adjustment for biological markers such as glucose, high density lipoprotein cholesterol (HDL-C), and C-reactive protein (CRP) [4]. Other reasons include effect modification by gender [8,9] and confounding by pre-existing disease [10]. For example, a meta-analysis of 7 cohort studies including 1313 CHD patients showed that there was no relationship between serum adiponectin and CHD events, but after excluding studies with participants with pre-existing diseases, a weak relationship between low serum adiponectin and decreased risk of CHD was observed [10]. Overall, the impact of adiponectin on CVD remains unclear [11]. It is important to improve the understanding of this issue for both public health and clinical practice who aim to reduce CVD occurrence [5,6]. We conducted a meta-analysis of epidemiological prospective studies in the general population in order to evaluate the relationship between adiponectin and the risk of CVD events.

2. Methods

2.1. Search strategy

According to Meta-analysis of Observational Studies in Epidemiology (MOOSE) [12], we performed a systematic search of Pubmed and Embase databases through June 2012 for relevant studies of the association between adiponectin and CVD. Search strategy for subject headings and key words as follows: 1) cardiovascular diseases, coronary disease, coronary thrombosis, myocardial ischemia, myocardial infarction, coronary stenosis, coronary re-stenosis, cerebrovascular disorders and stroke; 2) adiponectin and adipocytokines; 3) cohort study, prospective study and follow-up study. No restrictions were imposed. Following this search, a secondary reference review was conducted.

2.2. Selection criteria

The titles, abstracts and full-texts were reviewed respectively. The eligible studies matched the following criteria: 1) a prospective study in the general population; 2) serum adiponectin was analyzed in recruited participants; 3) the endpoint was major CVD attack or death including CHD and stroke; 4) the association of adiponectin with CVD events was evaluated by odds ratio (OR), risk ratio (RR), or hazard ratio (HR) with the corresponding confidence intervals (CI).

2.3. Data extraction

We collected the following information from each study: first author, year of publication, country of origin, research design, sample size, age range, gender, follow-up period, disease outcome, serum adiponectin, adjustment variables, RR (or OR, HR) of CVD with the corresponding 95% CI. Two independent investigators respectively calculated and tabulated the data with a standard extraction formula. The discrepancies were discussed by our research team and compared with the related references.

2.4. Quality assessment

A professional authority evaluated the quality of the method including report examination, internal and external validity, and the power with Downs and Black score [13]. Another specialist verified the evaluation accuracy done by the first authority.

2.5. Statistical analysis

The association across study was commonly measured with RR (or OR, HR) and all results were reported by RR for simplicity. In the present analysis, the lowest quartile was used as the referent group, as well as the final confounder set for all studies, except one study for which the highest quartile was used as the referent group, and we recalculated the RR and CI [14]. One study indicated that the association between adiponectin and CVD occurrence related to race, black and white, then the results were stratified [15]. The combined risk estimations were computed with either fixed-effect model or random-effect model if heterogeneity existed. The Cochrane Q statistics (significance level of $P < 0.10$) and the I^2 statistics were used to assess the heterogeneity of RR across studies. Since the characteristics in populations, research design and adjustment of confounding were not consistent from study-to-study, we further conducted meta-regression and sensitivity analysis to explore the possible explanation for heterogeneity, and the cumulative meta-analysis was performed to determine the track evidence over time.

For sensitivity analysis, the effect of a single study on overall risk factors was investigated by omitting one study in turn. Stratified analyzes was run by gender, research design, follow-up period, and assay method. The possibility of publication bias was assessed using a Begg and Egger test. We also performed the visual inspection of Begg funnel plots in which log RRs were plotted against their SEs [16]. All analyzes were conducted using STATA version 11.2 (Stata Corp LP, College Station, TX). A value of $P < 0.05$ was defined as statistically significant.

3. Results

3.1. Literature search

We initially retrieved 1796 abstracts from PubMed and Embase databases (1448 from PubMed and 578 from Embase). A majority of those references were excluded after reviewing the abstracts or titles and finding no research criteria matches. There were 2 studies

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