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ASSOCIATION BETWEEN RISK OF CARDIOVASCULAR DISEASE WITH ADIPONECTIN LEVELS: A SYSTEMATIC REVIEW AND META-ANALYSIS

Biochemistry

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ABSTRACT

Background: Adiponectin is the most abundant circulating protein secreted by adipocytes. There is uncertainty about the association between adiponectin levels and risk of coronary heart disease (CHD). We conducted this meta-analysis to summarize the effect of adiponectin on the risk of CHD.

Methods: An extensive search was performed to identify all prospective studies on the association of adiponectin levels and risk of CHD. The fixed- or random-effects model was selected to pool the relative risk (RR) and 95% confidence interval (CI).

Results: Twelve prospective studies comprising 8 nested case-control studies and 4 cohort studies were included in the meta- analysis. The pooled RR for CHD was 0.83 (95% CI, 0.69–0.98, (P =0.031). No publication bias was found in our study (P= 0.911).

Conclusions: This meta-analysis showed that higher levels of adiponectin were associated with a low risk of CHD. The protective effect was consistently existed in men and women and in the middle-aged populations.

KEYWORDS

Adiponectin, CHD, Meta-Analysis

Introduction- Coronary artery disease (CAD) is a modern epidemic, closely competing infectious diseases in the Indian subcontinent. Indians are likely to account for at least 33.5% of total coronary heart disease (CHD) related deaths by 2015 and this figure will jump to 60% by 2020[1]. Adiponectin is a collagen-like plasma protein produced specifically by adipose tissue and is abundantly present in the circulation. Plasma concentrations of adiponectin are reduced in the setting of obesity, in patients with non-insulin dependent diabetes mellitus ,and in patients with coronary artery disease (CAD) [2]. One of the important biomarker which is currently used to study CAD, obesity, type 2 DM and metabolic syndrome is adiponectin. Serum adiponectin levels have been shown to be reduced in the presence of obesity, insulin resistance (IR), and cardiovascular disease [2]. Adiponectin is the most abundant circulating protein produced and secreted by adipocytes with circulating levels ranging from 0.5 to 30 mg/ml [3]. Previous studies have found that adiponectin played an important role in the development of atherosclerosis and inflammation. Since then, there were also other studies about the adiponectin and risk of CHD, and the results still have been conflicting [4]. Thus, we did this meta-analysis to reassess the effect of adiponectin on the incident risk of CHD.

Materials & Methods- A systematic search of the PubMed, EMBASE, ISI Web of Knowledge, and Cochrane Library databases up until 10th November 2017 was conducted to retrieve prospective studies matched to search terms like adiponectin,or "ACRP30" or "GBP28" or "APM1" or "ADIPOQ" and "coronary heart disease" or "coronary artery disease" or "myocardial infarction" or "angina" or "ischemic heart disease". Additional articles were extracted from the reference lists of the retrieved articles, reviews, and meta-analysis on the topic.

Inclusion criteria- (1) original studies; (2) prospective design; (3) studies with adiponectin levels measured in blood collected at baseline; (4) follow-up of at least 1 year; (5) CHD as outcome, including fatal events and nonfatal events.

A pre- tested semi—structured questionnaire was used to extract the following information from the published article for each included article: first author's name, publication year, sample size, study design, mean (SD) for Adiponectin levels, reported relative risks (RRs) or hazard ratios (HRs) of coronary heart disease and the corresponding 95%CIs. After search 1920 potentially relevant articles identified in database search (pubmed- 430, embase- 570, google scholar- 460, ISI web- 300, Cochrane- 160). Out of these 780 were duplicates, so only 1140 potentially relevant articles in which 1120 citations were excluded for following reasons: - non- human study, cross-sectional study, genetic study, review and editorial. So, only 20 potentially appropriate study left in which 8 studies did not meet the inclusion criteria, so only 12 articles were studied [3,4,5-14]. The multivariable-adjusted ORs or HRs were extracted from the selected publications. As the incidence of CHD was sufficiently low for the rare disease assumption to apply, ORs could be assumed to be accurate estimates of RRs. We therefore ignored the distinction between the various measures and referred to all these estimates (eg, OR and HR) as RRs. The pooled RR (95% CI) was estimated using fixed- or random-effect model, weighted for the inverse of the variance. The heterogeneity among studies was evaluated using Q test and the I^2 statistic, which represented the percentage of total variation across studies that was attributable to heterogeneity rather than to chance.

Results-

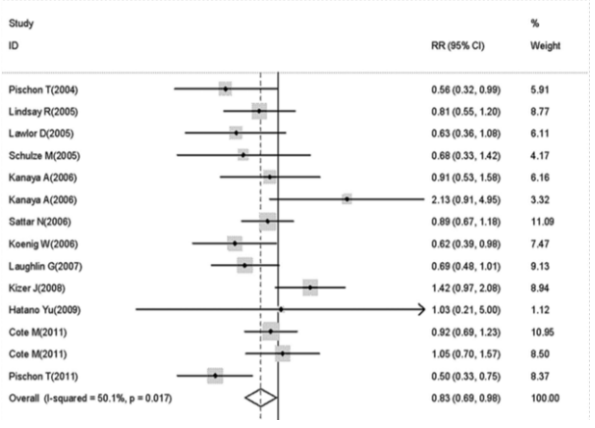
Table1- Characteristics of selected prospective studies

Study	Year	Age	Study design	CHD event	Non- CHD event
Pischon et al	2004	65.28.3	Nested case-control	266	532
Lindsay et al	2005	NR	Nested case-control	252	251
Lawlor et al	2005	70.25.4	Nested case-control	165	334
Sattar et al	2006	52.55.3	Nested case-control	589	1231
Kizer et al	2008	75.45.2	Nested case-control	604	782
Hatano et al	2009	64.98.4	Nested case-control	38	89
Cote et al	2011	65.47.6	Nested case-control	1035	1920
Pischon	2011	59.96.5	Nested case-control	455	911
Schulze et al	2005	63.1	Cohort	89	656
Kanaya et al	2006	73.52.8	Cohort	262	2211
Koenig et al	2006	54.15.8	Cohort	126	811
Laughlin et al	2007	72.49	Cohort	252	1100

Table 1 shows twelve prospective studies and included all these articles in the meta-analysis which met our inclusion criteria. A total of 14,960 study participants were enrolled and 4,132 cases of cardiovascular disease (CHD) were observed in the study. The present meta-analysis included eight nested case-control studies and four cohort studies, with a follow-up period ranging from 4 to 7years. Overall, the meta-analysis involved studies from 4 countries (7 studies from the United States, 3 from the United Kingdom, and 1 each from Japan and Germany). The median age for all the studies is 65.3 years.

Figure 1- Meta-analysis for the effect of adiponectin levels on CHD risk. Size of squares corresponds to the weight of each study in the meta-analysis, horizontal lines indicate 95% CIs, diamond indicates

summary risk estimate with its corresponding 95% CI. The pooled RR of incident CHD was 0.83 (95% CI, 0.69–0.98; P =0.031). Higher levels of adiponectin were independently associated with a decrease risk of CHD after adjustment for potential confounding variables. There was no evidence of publication bias by the funnel plot and Egger's test (P=0.911), but we found significant between- study heterogeneity in our analysis (I^2 =50.1%, P =0. 017). The sensitivity analysis revealed that there was not a single study influencing the result significantly.



Strengths and Limitations- Inclusion of all original articles were all are prospective studies which greatly reduced the likelihood of selection bias and reverse causation is the biggest strength of our study. However, there are certain limitations of our study these are:

First, the extracted RRs from most of the included studies were adjusted for a wide range of confounders.

Secondly, the eligible studies in our research were mainly from the United States and Europe, data of population from Asia (India) were limited.

Thirdly, the association estimated by total adiponectin is not very convincing.

Discussion- In the present study, we found a substantial negative association between baseline adiponectin levels and incidence of CHD. High adiponectin levels independently predicted lower CHD risk after adjustment for potential confounding variables. Experimental studies suggested that adiponectin had insulin-sensitizing and antiatherosclerotic properties that may lower the risk of CHD. Adiponectin stimulates glucose utilization and fatty acid oxidation by activating adenosine monophosphate– activated protein kinase thereby directly regulating glucose metabolism and insulin sensitivity in vitro and in vivo [15] .In vivo studies showed that adiponectin could reduce expression of adhesion molecules in endothelial cells and decrease cytokine production from macrophages by inhibiting nuclear factor kappa beta signaling through cyclic adenosine monophosphate– dependent pathway [16,17] .Epidemiology studies also found that adiponectin was associated with the risk of CHD. Some cross-sectional studies have demonstrated that hypoadiponectinemia was associated with the prevalence of CHD [16] .A meta-analysis for case-control studies of adiponectin levels and risk of cardiovascular disease in Chinese Han population suggested that serum total adiponectin levels were lower in patients with CHD. Prospective studies also found significant negative association between adiponectin and CHD. Health Professionals Follow-up Study found that high plasma adiponectin levels were associated with lower risk of myocardial infarction over a follow-up period of 6 years among men without previous cardiovascular disease [17].

Conclusion- Our findings demonstrate that higher adiponectin levels are associated with lower risk of CHD in prospective studies. This inverse relationship consistently exists in both men and women and the middle-aged populations. More substantial evidences need to be provided to confirm the usefulness of adiponectin concentration as a predictor of CHD, especially in Asian population and older people.

Conflict of interest- none declared

Source of funding- none

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