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Circulating adiponectin and carotid intima-media thickness: A systematic review and meta-analysis

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ABSTRACT

Background. Adiponectin (APN) is an adipokine with insulin-sensitizing, anti-inflammatory, and vasculoprotective properties. Hypoadiponectinemia has been linked with disease states, such as obesity, type 2 diabetes, and cardiovascular disease. Carotid intima-media thickness (cIMT) is a strong and independent predictor of both coronary and cerebrovascular events, and has been used as a surrogate marker of subclinical atherosclerosis. The aim of this report is to systematically review the evidence on the relationship between APN and cIMT in a wide range of individuals.

Materials and methods. Medline, Embase, Biosis, Scopus, Web of Science, and Pubmed were searched for published studies and conference abstracts. The "sign test" and "vote count" methods were used to estimate the direction and significance of the relationship between APN and cIMT. The quality of the eligible studies was evaluated using an adapted version of the New Castle Ottawa quality assessment scale.

Results. Fifty-five articles fulfilled the inclusion criteria, comprised of only cross-sectional studies, including healthy subjects, general population, and individuals with metabolic, inflammatory, or other chronic diseases. Most associations between APN and cIMT followed a negative direction in the healthier and general populations, and also in cohorts with metabolic disorders and other chronic diseases, but not in those with inflammatory diseases (sign test). These associations were generally found to be weak or non-significant among all cohort groups studied (vote count).

Conclusion. Our results are suggestive but not conclusive for an inverse association between APN levels and cIMT in diseased and non-diseased populations.

Abbreviations: CVD, cardiovascular disease; cIMT, carotid intima-media thickness; APN, adiponectin; T2DM, type 2 diabetes mellitus; CV, cardiovascular.

Conflicts of interest. None.

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1. Introduction

Atherosclerosis is the main underlying cause of cardiovascular disease (CVD), leading to the occurrence of myocardial infarction and ischemic stroke. Large epidemiological studies, such as The Atherosclerosis Risk in Communities study and The Cardiovascular Healthy Study, have established carotid intima-media thickness (cIMT) to be a strong and independent predictor of cerebral ischemic and coronary events in individuals free of overt CVD [1,2]. In particular, increased cIMT has been demonstrated to predict the occurrence of ischemic stroke events, independent of the traditional risk factors represented in the Framingham Stroke Risk Score [3]. Thus, cIMT has become widely used as an imaging surrogate marker of subclinical atherosclerosis, as well as a surrogate end-point for clinical vascular outcomes [4].

Adiponectin (APN), the most abundant adipose tissue-secreted adipokine, circulates at high concentrations in healthy individuals. Experimental evidence has shown APN to possess insulin-sensitizing, anti-inflammatory, and anti-atherogenic properties [5,6]. In humans, low circulating levels of APN are associated with obesity, type 2 diabetes mellitus (T2DM), as well as with CVD [6–9]. However, in relation to cIMT, conflicting results have been reported, with studies demonstrating either a significant or non-significant association between hypoadiponectinemia and severity of cIMT [10,11]. These disagreements may in part be the result of heterogeneity in the studied populations. Therefore, the objective of our systematic review and restricted meta-analysis was to summarize and critique the existing evidence (observational studies) with regards to the association between circulating APN levels and cIMT (subclinical atherosclerosis) in a wide range of populations, including healthy subjects of varying ages, individuals from the general population, and subjects with metabolic, inflammatory, or other chronic diseases.

2. Materials and Methods

2.1. General Search Strategy

A general search strategy was developed by a librarian (BN) for Ovid Medline (1946 to Present) including Ovid Medline In-Process & Other Non Indexed Citations and Ovid OLDMedline, Ovid Embase Classic and Embase (1947 to Present), Ovid Biosis Previews (1969 to Present), Wiley Cochrane Library, Scopus, Web of Science and PubMed. Search strategies were peer-reviewed by a second librarian. The search strategy was designed to answer four specific research questions relating APN levels to (a) cIMT, (b) carotid atherosclerotic plaque presence, (c) ischemic stroke, and (d) mortality due to ischemic stroke. Herein, the results pertaining to the **first research question** are presented. Results were restricted to human and adult (>19 years old) studies. No language restrictions were applied. See Supplementary Material 1 for Ovid Medline search strategy details. The searches were run May 23rd, 2013. Conference abstracts were retrieved via Embase and congresses not covered by Embase between 2008 and 2012 were searched manually for "adiponectin" in June 2013. See Supplementary Material 1 for the list of manually searched congresses. Two trial registries were also searched (clinicaltrials.gov and the WHO International Clinical Trials Registry Platform) along with gray literature sources (Supplementary Material 1). On February 8th 2016 the full search strategy was re-run to retrieve new studies published since the initial search. Reference lists of eligible studies were also hand-searched, from which no additional studies were identified; thus validating our search strategy. In addition, investigators were contacted through email for missing baseline population data or clarifications on APN values and units.

2.2. Eligibility Criteria

Original studies reporting on the association between circulating APN levels and cIMT were considered eligible. No restriction in regards to population cohort was applied. Abstracts prior to 2011 or abstracts resulting in published work were excluded. Although the search strategy did not restrict articles based on language, at the screening level of potentially eligible articles, we included only English or French records.

2.3. Selection Process

A flow–chart illustrating the review process is presented in Fig. 1. From the initial 3565 studies retrieved (after duplicate removal), 111 original articles and abstracts were independently identified and evaluated in detail by the two first authors (KG and JG), of which 72 pertained to cIMT as an outcome. Discrepancies were resolved through consensus with the corresponding author (SSD). Of those, 26 were excluded due to reasons outlined in Fig. 1, while 9 more articles were included following the updated search, resulting in 55 included articles. All of these articles were written in the English language.

2.4. Data Extraction

Our systematic review and restrictive meta-analysis was performed in accordance with the MOOSE (Meta-analysis of Observational Studies in Epidemiology) guidelines (see Supplementary Material 2). Data extraction was performed independently (KG and JG). Table 1 of Supplementary Material 2 presents study inclusion/exclusion criteria and cIMT definition and method of measurement, while Table 2 of Supplementary Material 2 illustrates a summary of the baseline population characteristics for each included study (country, population, sample size, percent men, age, body mass index, and cIMT measurements). The population from the different studies were categorized into five groups (healthy subjects, general population, and individuals with metabolic, inflammatory, or other chronic diseases). Healthy subjects were defined as having no medical history of disease, while the general population were representative of subjects with and without comorbidities or disease. Table 1 summarizes for each study the type of APN assay used, the type of APN isoform (total or high-molecular weight), blood specimen type (plasma or serum), and APN concentrations. Furthermore, data extraction included parameter effect estimates and covariates used for multivariate analyses (Table 2).

2.5. Data-Analysis Methods

The "sign test" and "vote count" methods were used to provide a crude estimation of the general trend of results for