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Review

Leptin and coronary heart disease: A systematic review and meta-analysis

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ABSTRACT

Introduction: Leptin, an adipose tissue-derived hormone, plays a central role in regulating human energy homeostasis. The role of leptin in regulating blood pressure, activating the sympathetic nervous system, insulin resistance, platelet aggregation, arterial thrombosis, angiogenesis, and inflammatory vascular responses suggests that leptin may have a close relationship with the development of coronary heart disease (CHD). However, no conclusive data are available to determine the association between leptin and CHD.

Methods: The PubMed, EMBASE and Cochrane databases were surveyed for original studies describing the association between leptin and CHD outcome from the date of publication of each database through March 2013. The data were extracted by two investigators independently.

Results: The meta-analysis reported here was comprised of eight original articles with a total of 21,064 participants (10,842 men, 10,222 women) and 2053 CHD events. The odds ratio for the sociodemographic-adjusted study reported here was 1.57 (95% confidence interval, 1.14–2.16) and 1.72 (95% confidence internal, 1.03–2.87) in males and females, respectively. Further adjustment for additional cardiovascular risk factors resulted in an odds ratio of 1.36 (95% confidence interval, 0.98–1.88) in males and 1.50 (95% confidence interval, 0.93–2.42) in females. Sensitivity analysis restricted to sociodemographics-adjusted studies with high methodological quality indicated an estimate of 1.47 (95% confidence internal, 1.06–2.04) in males and 1.85 (95% confidence internal, 0.61–5.63) in females. Sensitivity analysis restricted to cardiovascular risk factor-adjusted studies showed no significant differences in both males and females.

Conclusion: The results of the meta-analysis represents the most precise and accurate estimate of the relationship between leptin and CHD. Although the associations of leptin and CHD were not statistically significant both in male and female overall, males with high levels of leptin should be paid more attention to. Our findings highlight the need for additional well-designed and gender-specific prospective studies to evaluate the role of leptin on the development of CHD.

Contents

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1. Introduction

Leptin, an adipose tissue-derived hormone, plays a central role in regulating human energy homeostasis and is hypothesized to be an "adiposity signal" for the long-term regulation of body weight by the brain [1,2]. In accordance with this postulated role, leptin levels increase with obesity and correlate strongly with percent body fat in males and females. Also leptin concentrations are higher in women than in men. One possible explanation is that the actions of leptin are blocked by testosterone and increased by ovarian steroids [3]. The role of leptin in regulating blood pressure, activating the sympathetic nervous system, insulin resistance, platelet aggregation, arterial thrombosis, angiogenesis, and inflammatory vascular responses [4–13] suggests that leptin may have a close relationship with the development of coronary heart disease (CHD). Currently, CHD is a major cause of death, and epidemiological studies suggest that the numbers of death per year are on the rise [14]. To date, a plethora of studies aiming at the association between leptin and CHD have been published but the results of these reports were inconsistent [15–22]. Moreover, there are very few meta-analysis examining the relationship between leptin and CHD according to gender. Given the inconsistency of prior results, we performed a systematic review and meta-analysis of the current evidence for the relationship between leptin and CHD in both males and females.

2. Methods

2.1. Literature search

The procedures for conducting the meta-analysis of observational studies were performed as previously reported [23]. We conducted a review of literature from the PubMed, EMBASE, and Cochrane library databases. The date range from publication of each database through March 2013. These databases were searched for studies describing the association between leptin and incident CHD outcomes, including acute myocardial infarction (AMI), angina pectoris, angina, cardiovascular disease (CVD), and ischemic heart disease (IHD). In addition, we also reviewed the reference lists from each article and/or review. To focus our search, we searched for English literature pertaining to CHD in adult humans.

2.2. Selection criteria

The articles were included if they 1) consisted of original studies (e.g., not review articles, meeting abstracts, editorials, or commentaries); 2) consisted of cohort or case–control studies; and 3) reported risk estimates for the association between leptin and CHD outcomes. The title and the abstract of each article was reviewed for the initial screening step. Following this initial step, potential articles were included in our full-text review process. This full-text review process was performed by two independent investigators in a blinded fashion. Any discrepancies that were found were resolved by consensus or consultation with a third author.

2.3. Data extraction

For each identified article, in a blinded fashion, two of the study investigators extracted information pertaining to the study characteristics (citation, study name, authors, publication year), participant characteristics (location, number, mean age or age range, gender), leptin assessment, CHD outcomes (specific endpoints, methods for diagnosis, follow-up years, duration), analysis strategy (statistical models, covariates), and multivariable-adjusted risk estimates (including data to calculate its precision, such as 95% confidence interval (CI), standard error (SE), or *P* values). Study quality was assessed by the scale of the Newcastle-Ottaw [24], which involved evaluation of selection bias, study design and analysis, measurements of exposure and outcome, and generalizability of results. We defined studies of high or low quality based on the median overall score among all studies.

2.4. Data synthesis

The included studies reported relative risks (RR) for cohorts or odds ratios (ORs) for case–control studies. The ORs were assumed to approximate RR. Individual studies reported risk estimates for leptin based on various categories (e.g., tertiles, quartiles, quintiles, or specific thresholds). To provide a consistent approach to meta-analysis, risk estimates for each study were transformed to determine the baseline distribution of leptin values as previously described [25]. Briefly, log risk estimates were transformed with the comparison between top and bottom tertiles being equivalent to 2.718 times the log risk ratio for a 1-standard deviation (SD) increase. These scaling methods assume that the exposure is normally distributed and that the association with disease risk is log-linear. The conversion factor of 2.718 is the difference in the medians between the top and bottom thirds of the standard normal distribution. Additional conversions were used to determine differences in the medians of extreme quartiles or quintiles. The SEs of log ORs and log RRs were calculated by using reported data on precision and were similarly standardized. Publication bias was assessed using the Egger's linear regression method.

3. Results

3.1. Literature search

Our search strategy resulted in the identification of 2043 articles (Fig. 1). Following the extensive review of the title and abstracts of the articles, only 74 full-text articles were evaluated. After the final