Atherosclerosis 219 (2011) 322–329

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Plasma total and high molecular weight adiponectin levels and risk of coronary heart disease in women

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ARTICLE INFO

Article history:
Received 24 March 2011
Received in revised form 4 July 2011
Accepted 5 July 2011
Available online 20 July 2011

Keywords:
Adiponectin
Cohort study
Coronary disease
Epidemiology
Risk factors

ABSTRACT

Objective: To examine prospectively the association of total and high molecular weight (HMW) adiponectin, and HMW/total adiponectin ratio with risk of incident coronary heart disease (CHD) in women, and to examine to what extent adjustment for potentially intermediary variables would explain this association.

Methods and results: Among 30,111 women from the Nurses' Health Study, 468 women developed non-fatal myocardial infarction or fatal CHD during 14 years of follow-up. Using risk set sampling, controls were selected 2:1 matched on age, smoking, and date of blood draw. Adjusted for matching factors, parental history of myocardial infarction, hormone replacement therapy, alcohol consumption, physical activity, body mass index, hypertension, and low-density lipoprotein cholesterol levels, the relative risk in the highest versus lowest quintile was 0.50 (95%-CI 0.33–0.75; p trend = 0.001) for total adiponectin, 0.53 (95%-CI 0.35–0.80; p trend = 0.004) for HMW adiponectin, and 0.63 (95%-CI 0.43–0.93; p trend = 0.03) for HMW/total adiponectin ratio. After adjustment for diabetes, HDL-cholesterol, HbA1c, and CRP these associations were attenuated and no longer significant (RRs, 0.84; 95%-CI 0.53–1.33; p trend = 0.62; 0.95; 95%-CI 0.60–1.52; p trend = 0.98; 0.97; 95%-CI 0.64–1.47; p trend = 0.80).

Conclusions: High levels of total and HMW adiponectin, and HMW/total adiponectin ratio are associated with a lower risk of CHD among women. HMW adiponectin and HMW/total adiponectin ratio are not more closely related to risk than total adiponectin. These associations are largely mediated by parameters related to glucose and lipid metabolism and inflammation, especially HDL-cholesterol levels.

1. Introduction

Adiponectin is an adipose tissue-derived collagen-like protein that beneficially affects many pathways that may be relevant for the development of atherosclerosis, including glucose and lipid metabolism, inflammation, endothelial function, as well as thrombogenesis, and it may therefore potentially protect from coronary heart disease (CHD) [1]. However, results from prospective studies in humans provide inconsistent results, with only some showing significant inverse associations between adiponectin and risk of CHD [2–11]. The basis for these inconsistent results are likely due to over adjustment for other biological markers, including glucose, high density lipoprotein cholesterol (HDL-C) and C-reactive protein (CRP), thought to be in the causal pathway between adiponectin and CHD. Further, most prior studies have been conducted among predominantly male populations, and thus, limited information exists for women. In a previous analysis from the Health Professionals Follow-up Study we found a statistically significant inverse association between plasma adiponectin levels and risk of myocardial infarction (MI) among men [2]. In that analysis, adjustment for history of diabetes or plasma levels of hemoglobin A1c (HbA1c) or CRP had little impact, whereas adjustment for HDL-C modestly attenuated the relationship, although it remained statistically significant.

The effects of adiponectin may depend on its quaternary structure in plasma. It was suggested that high molecular weight

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doi:10.1016/j.atherosclerosis.2011.07.011

(HMW) adiponectin may be a better measure of metabolically active adiponectin and therefore more closely related to insulin sensitivity and risk of type 2 diabetes [12,13]. However, in the only report published thus far on HMW adiponectin and risk of incident CHD (including 167 cases and 333 controls over a follow-up period of 4 years), the association was not statistically significant [14].

The aim of the present study was therefore to examine the association of total and HMW adiponectin, and HMW/total adiponectin ratio with risk of incident CHD in the Nurses' Health Study (NHS), a well-described cohort study of women. Because animal studies suggest that adiponectin affects several downstream metabolic pathways that may be relevant for cardiovascular risk, we were particularly interested to examine to what extent adjustment for these potentially intermediary variables related to glucose (HbA1c, history of diabetes) and lipid metabolism (HDL-C) and inflammation (CRP) would explain the inverse association between adiponectin and CHD in a human population.

2. Methods

2.1. Study population

The NHS is a prospective cohort investigation involving 121,700 female U.S. registered nurses who were 30–55 years old at baseline in 1976. Information about anthropometry, health and disease is assessed biennially, and information about diet is obtained every four years using self-administered questionnaires [15]. The questionnaires and the validity and reproducibility of measurements have been described previously [16]. From 1989 to 1990, a blood sample was requested from all participants in the NHS, and 32,826 women provided one. Participants who provided blood samples were similar to those who did not. Among the 30,111 women without cardiovascular disease (CVD) or cancer prior to 1990, we identified 468 women with incident non-fatal MI or fatal CHD between date of blood drawing and June 2004. Using risk-set sampling [17], we randomly selected controls in a 2:1 ratio who were individually matched for age, smoking status, fasting status and date of blood sampling from participants free of CVD at the time of diagnosis of the index case. Study physicians blinded to the participant's exposure status confirmed the diagnosis of MI on the basis of the criteria of the World Health Organization (symptoms plus either diagnostic electrocardiographic changes or elevated levels of cardiac enzymes). Deaths were identified from state vital records and the National Death Index or reported by the participant's next of kin or the postal system. Fatal CHD was confirmed by an examination of hospital or autopsy records, by the listing of CHD as the cause of death on the death certificate, if CHD was the underlying and most plausible cause, and if evidence of previous CHD was available. The study protocol was approved by the review boards of Brigham and Women's Hospital and Harvard School of Public Health.

2.2. Measurement of biochemical variables

Blood samples were collected in liquid sodium heparin tubes, placed on ice packs, stored in Styrofoam containers, returned to our laboratory by overnight courier, centrifuged, and divided into aliquots for storage in liquid-nitrogen freezers (−130 °C or colder). Total (TC), low-density lipoprotein (LDL-C) cholesterol, HDL-C, and triglycerides (TG) were measured with standard methods using reagents from Roche Diagnostics and Genzyme with coefficients of variation (CVs) of 1.7%, 2.5%, 1.8%, and 3.1%, respectively. CRP and HbA1c levels were quantified using an immunoturbidimetric technique on the Hitachi 911 analyzer, with a CV of 1.4%, and 2.6%, respectively. Total and HMW adiponectin levels were measured using a commercially available enzyme linked immunosorbent assay method from ALPCO Diagnostics Inc. (Salem, NH), with CVs of less than 15%. The laboratory used is certified by the NHLBI/CDC Lipid Standardization program. Total and HMW adiponectin levels were available for 455 cases and 911 controls. For covariates when information was missing, we assigned the median level within the cohort (TC, $n = 18$; LDL-C, $n = 37$; HDL-C, $n = 18$; TG, $n = 98$; CRP, $n = 34$; HbA1c, $n = 28$).

In a reliability study among 20 men from the Health Professionals Follow-up Study (a cohort study similar to the NHS) with 2 blood measurements taken 1 year apart, within-person plasma HMW adiponectin levels tended to decrease over the 1-year period from geometric mean plasma levels of 2.86 mg/L (95%-confidence interval 2.21–3.69 mg/L) to 2.56 mg/L (95%-CI 1.93–3.39 mg/L; p based on Student's paired t-test, 0.04); however, there was excellent reliability in the 2 measurements (intraclass correlation coefficient based on log-transformed levels, 0.91; 95%-CI 0.79–0.96). Total adiponectin had similar excellent reliability and was not substantially affected by transport conditions [18].

2.3. Statistical analysis

Plasma levels of total and HMW adiponectin, and HMW/total adiponectin ratio were categorized into quintiles based on control participants, and unconditional logistic regression adjusted for matched variables (age, 5-year categories; smoking status, never, past, or current; fasting status, yes or no; and month of blood draw, 5 categories) was used to investigate the association with incidence of CHD. Linear trend tests across categories were conducted using median log-transformed adiponectin levels of controls. We also estimated the multivariable-adjusted relative risk associated with a difference in log-transformed continuous adiponectin levels of log(2), which corresponds to 2-fold higher adiponectin levels on the original scale. In multivariable models, we further adjusted for family history of MI before age 60 years (yes/no), alcohol intake (nondrinker; 0.1–4.9, 5.0–14.9, 15.0–29.9, or ≥30.0 g/d; or missing), body mass index (BMI, <20, 20–24, 25–29, 30–34, or ≥35 kg/m^2), history of hypertension (yes/no), physical activity (quintiles), hormone replacement therapy use (yes/no), and LDL-C levels (quintiles). We examined the impact of potential intermediate biomarkers by adding history of diabetes (yes/no), or plasma levels of HDL-C, HbA1c, or CRP (all in quintiles) separately and in combination to our models. Conditional logistic regression provided essentially the same results and hence, are not reported. With risk-set sampling, the odds ratio derived from logistic regression directly estimates the incidence (hazard) rate ratio, and, therefore, the relative risk [17,19]. Additional analyses were stratified by alcohol intake (non-drinkers versus moderate drinkers), BMI (<25 kg/m^2 versus ≥25 kg/m^2), and age (<60 years versus ≥60 years), and interactions tested using cross product terms.

p values presented are 2-tailed and $p < 0.05$ was considered statistically significant. Analyses were performed using SAS software, version 8.2 (SAS Institute Inc., Cary, NC).

3. Results

Cases had a significantly higher BMI and were more likely to have a history of hypertension or diabetes and to use cholesterol lowering drugs (Table 1). Alcohol consumption was significantly lower among cases. Cases had significantly lower plasma levels of total and HMW adiponectin, and a lower HMW/total adiponectin ratio. TC, LDL-C, TG, CRP, and HbA1c levels were significantly higher and HDL-C levels significantly lower among cases than among controls.