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Adiponectin is associated with increased mortality and heart failure in patients with stable ischemic heart disease: Data from the Heart and Soul Study

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ABSTRACT

Objective: Serum adiponectin protects against incident ischemic heart disease (IHD). However, in patients with existing IHD, higher adiponectin levels are paradoxically associated with worse outcomes. We investigated this paradox by evaluating the relationship between adiponectin and cardiovascular events in patients with existing IHD.

Methods: We measured total serum adiponectin and cardiac disease severity by stress echocardiography in 981 outpatients with stable IHD who were recruited for the Heart and Soul Study between September 2000 and December 2002. Subsequent heart failure hospitalizations, myocardial infarction, and death were recorded.

Results: During an average of 7.1 years of follow-up, patients with adiponectin levels in the highest quartile were more likely than those in the lowest quartile to be hospitalized for heart failure (23% vs. 13%; demographics-adjusted hazard ratio (HR) 1.63, 95% confidence interval (CI) 1.04–2.56, $p = 0.03$) or die (49% vs. 31%; HR 1.67, 95% CI 1.24–2.26, $p < 0.008$), but not more likely to have a myocardial infarction (12% vs. 17%; HR 0.64, 95% CI 0.38–1.06, $p = 0.08$). The combined outcome of myocardial infarction, heart failure, or death occurred in 56% (136/245) of participants in the highest quartile of adiponectin vs. 38% (94/246) of participants in the lowest quartile (HR 1.54, 95% CI 1.31–2.21, $p < 0.002$). Adjustment for left ventricular ejection fraction, diastolic dysfunction, inducible ischemia, C-reactive protein, and NT-proBNP attenuated the association between higher adiponectin and increased risk of subsequent events (HR 1.43, 95% CI 0.98–2.09, $p = 0.06$).

Conclusions: Higher concentrations of adiponectin were associated with heart failure and mortality among patients with existing IHD.

1. Introduction

Adiponectin is an abundant serum protein that is secreted primarily from adipose tissue [1], with concentrations that are inversely associated with obesity [2]. In animal and in vitro models, adiponectin exerts insulin-sensitizing, anti-inflammatory and anti-atherosclerotic effects [1]. Likewise, in humans low adiponectin levels, such as those seen in obesity, are associated with low HDL [3], hypertension [4], insulin resistance [2,3], and diabetes [2]. Given its connections with cardiovascular disease risk factors, recent population studies have investigated the association of adiponectin with incident cardiovascular events. In patients without previously diagnosed cardiovascular disease, higher levels of adiponectin are thought to be protective against disease [5–7], although this relationship is not consistently present in women [6,8], minorities [9], or the elderly [10].

Despite adiponectin being associated with a favorable cardiovascular risk profile, higher levels of adiponectin have paradoxically been associated with inducible ischemia [11], worse outcomes among patients with acute coronary syndrome [12], and worse outcomes among patients with existing heart failure [10]. The underlying mechanisms of the association between adiponectin and severity of disease in individuals with existing cardiovascular disease are not well understood. In the present study, we further investigated this apparent paradox by evaluating the association between adiponectin and cardiovascular disease outcomes in a cohort of patients with stable ischemic heart disease (IHD).

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2. Methods

2.1. Participants

The Heart and Soul Study is a prospective cohort study designed to investigate the effects of psychosocial factors on health outcomes in patients with stable IHD. Methods have been previously described [13]. Patients were eligible if they had at least 1 of the following: history of myocardial infarction, angiographic evidence of ≥50% stenosis in ≥1 coronary vessels, evidence of exercise-induced ischemia by treadmill ECG or stress nuclear perfusion imaging, or a history of coronary revascularization. Patients were excluded if they were unable to walk one block, had an acute coronary syndrome within the previous six months, or were likely to move out of the area within three years. Between September 2000 and December 2002, 1024 subjects were recruited from 12 outpatient clinics in the San Francisco Bay Area, including 549 (54%) with a history of myocardial infarction, 237 (23%) with a history of revascularization but not myocardial infarction, and 238 (23%) with a diagnosis of coronary disease that was documented by their physician, based on a positive angiogram or treadmill test in over 98% of cases. All participants completed a full-day study including medical history, extensive questionnaires, and an exercise treadmill test with baseline and stress echocardiograms. 12-h fasting serum samples were obtained in the morning prior to stress test and frozen at −80 °C. Of 1024 participants, 39 were excluded from this analysis because frozen serum was not available to perform the adiponectin assay, and 4 were excluded due to lack of complete outcome data, resulting in 981 participants for this analysis. Institutional Review Boards at each site approved this study protocol. All participants provided written informed consent.

2.2. Measurement of adiponectin

Total serum adiponectin level was determined by immunoassay of thawed fasting serum samples (Linco, Millipore, St. Charles, MO). Each sample was assayed in duplicate, and adiponectin level was calculated as the average of two measurements. The lowest detectable measurement for adiponectin was 145.4 pg/mL. The inter-assay coefficient of variation for this multiplexed immunoassay was 14.2–21.8%, and the intra-assay coefficient of variation was 1.4–7.9%. No significant cross-reactivity was observed within the panel [11].

2.3. Outcome ascertainment

Annual telephone interviews were conducted with participants or their proxy to inquire about interval hospitalization or death. For any reported event, medical records, electrocardiograms, death certificates, autopsy, and coroner's reports were obtained. Each event was adjudicated by 2 independent and blinded reviewers. In the event of disagreement, the adjudicators conferred, reconsidered their classification, and requested consultation from a third blinded adjudicator.

The primary outcome was a composite of myocardial infarction, heart failure, or death from any cause. Secondary outcomes were the individual components of myocardial infarction, heart failure, and death from any cause. Myocardial infarction was defined using standard diagnostic criteria [14]. Heart failure was defined as hospitalization or emergency department visit for heart failure. Death was verified by death certificates.

2.4. Other patient characteristics

Demographic characteristics, medical history, and smoking status were assessed by self-report questionnaire. We measured weight and height and calculated the body mass index (BMI) (kg/m^2). Participants were asked to bring their medication bottles to the study appointment, and research personnel recorded all current medications. Medications were categorized using Epocrates Rx (San Mateo, CA). Total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, insulin, glucose, glycosylated hemoglobin, creatinine, and high sensitivity C-reactive protein (CRP) were determined from 12-h fasting serum samples. Insulin levels were measured with a Linco Multiplex immunoassay (Millipore, St. Charles, MO). Levels of the amino terminal fragment of the prohormone brain-type natriuretic peptide (NT-proBNP) were determined using Roche Diagnostics Elecsys NT-proBNP electrochemiluminescence immunoassay (Elecsys proBNP, Roche Diagnostics, Indianapolis, IN). Estimated glomerular filtration rate (eGFR) was calculated using the abbreviated Modification of Diet in Renal Disease (MDRD) Study equation [15].

Participants underwent symptom-limited exercise stress testing according to a standard Bruce protocol (those unable to complete the standard protocol were converted to a manual protocol) with continuous 12-lead electrocardiogram monitoring. Prior to exercise, participants underwent complete resting two-dimensional echocardiograms with all standard views using an Acuson Sequoia ultrasound system (Siemens Medical Solutions, Mountain View, CA) with a 3.5-MHz transducer and Doppler ultrasound examination. Standard two-dimensional parasternal short-axis and apical two- and four-chamber views were obtained during held inspiration and were used to calculate the left ventricular ejection fraction [16]. Diastolic dysfunction was defined as pseudonormal or restrictive filling on mitral inflow [13]. At peak exercise, precordial long- and short-axis and apical two- and four-chamber views were obtained to assess for wall motion abnormalities. We defined exercise-induced ischemia as the presence of one or more new wall motion abnormality at peak exercise that was not present at rest [11]. A single experienced cardiologist (NBS), who was blinded to the results of the adiponectin assays and clinical histories, interpreted all echocardiograms.

2.5. Statistical analysis

Participants were divided into quartiles on the basis of serum adiponectin level. Baseline participant characteristics across quartiles were compared using analysis of variance (ANOVA) for continuous variables and χ^2 test for dichotomous variables. We compared the frequency of outcomes across quartiles using the χ^2 test. We compared rates of the primary outcome as well as myocardial infarction, heart failure, and death between quartile IV vs. quartile I in multivariate Cox regression models adjusted for baseline demographics (age, sex, race), clinical risk factors (diabetes, systolic blood pressure, diastolic blood pressure, eGFR, beta-blocker use, aspirin use, and statin use), metabolic markers (BMI, hemoglobin A1c, insulin, glucose, total cholesterol, HDL, and triglycerides), and measures of cardiac disease severity (LV ejection fraction, diastolic dysfunction, inducible ischemia, log C-reactive protein, log-NT-proBNP). We further examined risk associated with the continuous value of adiponectin level after log-transformation to normalize the distribution, and expressed risk per standard deviation (SD) increase (0.8 μg/mL) of log adiponectin using the same multivariate Cox regression models. We tested for interactions between adiponectin and age, sex, race, BMI, diabetes, serum creatinine, and left ventricular ejection fraction. Analyses were performed using Statistical Analysis Software (version 9.2; SAS Institute Inc., Cary, NC).