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Association between resistin levels and cardiovascular disease events in older adults: The health, aging and body composition study

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ABSTRACT

Objective: Prospective data on the association between resistin levels and cardiovascular disease (CVD) events are sparse with conflicting results.
Methods: We studied 3044 aged 70–79 years from the Health, Aging, and Body Composition Study. CVD events were defined as coronary heart disease (CHD) or stroke events. «Hard » CHD events were defined as CHD death or myocardial infarction. We estimated hazard ratio (HR) and 95% confidence intervals (CI) according to the quartiles of serum resistin concentrations and adjusted for clinical variables, and then further adjusted for metabolic disease (body mass index, fasting plasma glucose, abdominal visceral and subcutaneous adipose tissue, leptin, adiponectin, insulin) and inflammation (C-reactive protein, interleukin-6, tumor necrosis factors-α).
Results: During a median follow-up of 10.1 years, 559 patients had « hard » CHD events, 884 CHD events and 1106 CVD Events. Unadjusted incidence rate for CVD events was 36.6 (95% CI 32.1–41.1) per 1000 persons-year in the lowest quartile and 54.0 per 1000 persons-year in the highest quartile (95% CI 48.2–59.8, P for trend < 0.001). In the multivariate models adjusted for clinical variables, HRs for the highest vs. lowest quartile of resistin was 1.52 (95% CI 1.20–1.93, P < 0.001) for « Hard » CHD events, 1.41 (95% CI 1.16–1.70, P = 0.001) for CHD events and 1.35 (95% CI 1.14–1.59, P = 0.002) for CVD events. Further adjustment for metabolic disease slightly reduced the associations while adjustment for inflammation markedly reduced the associations.
Conclusions: In older adults, higher resistin levels are associated with CVD events independently of clinical risk factors and metabolic disease markers, but markedly attenuated by inflammation.

1. Introduction

Resistin has received much attention in recent years as an emerging biomarker involved in pathways of adiposity, insulin resistance and inflammation [1–3]. Resistin is mainly secreted by inflammatory cells in humans and associated with the presence of atherosclerosis [2,3]. Prospective data on the association between resistin levels and cardiovascular disease (CVD) events are increasing with conflicting results [4–7]. A recent meta-analysis including 7 studies reported that circulating resistin levels were associated with mortality, especially in high-risk individuals, such as patients with diabetes [8]. Diabetic patients have been reported

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to have higher levels of resistin compared to non-diabetic patients, suggesting some specific role of resistin in this high-risk population [9,10]. In older adults, inflammatory markers, such as interleukin-6 (IL-6), C-reactive protein (CRP), and tumor necrosis factor-alpha (TNF-alpha) have been independently associated with CVD events with an incremental improvement of prediction [11,12]. Some recent data suggest that resistin levels were associated with incident CVD events independently of inflammatory markers [13]. However, controversies persist whether the association between circulating resistin levels and CVD events is independent of metabolic disease or inflammatory markers.

A previous study within the Health Aging, and Body Composition Study (Health ABC Study) has shown an association between resistin levels and heart failure (HF) events in the elderly population [14]. In this present study, we aim at describing the association between serum resistin levels and CVD events among older adults of the Health ABC Study. We explored whether the association between resistin levels and CVD events might be confounded or attenuated by metabolic disease or inflammatory markers.

2. Materials

2.1. Study design and population

We analyzed data from the Health ABC study, a prospective cohort study of 3075 community-dwelling men and women aged 70–79 years enrolled between April 1997 and June 1998, and who were without overt physical disability at enrollment. Participants were identified from a sample of white and black Medicare-eligible adults living in designated zip coded areas surrounding Pittsburgh, PA, and Memphis, TN, USA. Details of eligibility and exclusion criteria have been previously described [15]. All participants gave written informed consent and the local Institutional Review Boards approved the protocol. We excluded 31 participants with missing data for resistin. The final sample consisted of 3044 participants.

2.2. Biomarker measurements

In the Health ABC Study, baseline blood samples were obtained after overnight fasting, frozen at −70 °C, and shipped to the core laboratory at the University of Vermont. Serum resistin concentration was measured on EDTA plasma at the University of Pennsylvania using a commercially available human resistin enzyme-linked immunosorbent assay (ELISA) from Linco Research St Louis MO (EZHR-95K). Intra- and interassay coefficients of variation for this assay are 4.5% and 7.4%, respectively (Millipore website Linco Research, Inc. Human Resistin ELISA. Available at: www.millipore.com/catalogue/item/ezhr-95k.). Each sample was diluted 1:10 before the assay was performed using assay buffer from the kit. The lowest 5% extreme values were repeated. The laboratory technicians who performed the assays were blinded to participant characteristics and the cardiovascular outcomes assessment. Measures of IL-6, CRP and TNF-α were done in duplicate using a high-sensitivity ELISA (R&D Systems, Inc., Minneapolis, Minnesota). Blind duplicate analyses (n = 150) for IL-6, CRP and TNF- α showed interassay coefficients of variation of 10.3%, 8.0% and 15.8%, respectively. Serum leptin was measured using the Sensitive Human Leptin RIA Kit (product number SHL-81K) from Linco Research, Inc. (St. Charles, MO). The intra-assay CV was 3.7–7.5% and the inter-assay CV is 3.2–8.9%. Adiponectin concentrations were measured in duplicate by radioimmunoassay (Linco Research Inc). Insulin was measured from serum at baseline using a Microparticle Enzyme Immunoassay (MEIA) on the Abbot IMx (Abbott Laboratories Diagnostics Division, South Pasadena, CA).

2.3. Study outcomes

All participants were asked direct questions every 6 months to detect the incidence of any interim CVD events which included coronary heart disease (CHD) and stroke events. Using algorithms mirroring those of the Cardiovascular Health Study, CVD events were adjudicated based on interview, review of all hospital records, death certificates and other documents by a panel of experts blinded to the results of resistin. CHD events were defined as acute myocardial infarction [MI], coronary death, hospitalization for angina, or coronary revascularization (angioplasty of coronary arteries and coronary artery bypass graft surgery). As done in previous publications, we also analyzed separately hard CHD events, defined as nonfatal MI and CHD death (including fatal MI) and soft CHD events, defined as hospitalization for angina and coronary revascularization [16]. Stroke event was defined as any hospitalization for fatal or nonfatal stroke. Follow-up time was defined by the time from baseline visit until the first event date for those who presented an event or was censored at the last contact date for those who did not have any event or to last follow-up. Among Health ABC participants who were alive at 10 years (median follow-up for this analysis), 73 were lost to follow-up (2.4% of the cohort – this is the % censored by 10 years due to FU loss – in other words, 97.6% had complete FU data by 10 years).

2.4. Covariates

Covariates included sociodemographic variables (age, gender, race), physical and biological parameters, including smoking status (current, past, or never smokers), body mass index (calculated as weight in kilograms divided by the height in meters squared), total cholesterol, high-density lipoprotein cholesterol, and creatinine (all measured by a calorimetric technique on a Johnson & Johnson Vitros 950 analyzer, New Brunswick, New Jersey). Hypertension was defined by self-report and use of antihypertensive medications, or measured blood pressure, with systolic of 140 mm Hg or higher, diastolic of 90 mm Hg or higher, or both. Participants were considered as having diabetes if they reported a physician diagnosis of diabetes, and/or if they were taking insulin or an oral diabetes medication, and/or if their fasting plasma glucose was ≥126 mg/dl in accord with the American Diabetes Association criteria in place near the start of the Health ABC Study (in 2002) [17,18]. The use of cardiovascular medication (statin, aspirin, angiotensin-converting enzyme [ACE] inhibitors or angiotensin receptor blocker [ARB]) was identified using Iowa Drug Information System codes. Preexisting CVD was defined as a diagnosis of CHD (angina, prior myocardial infarction [MI], angioplasty of coronary arteries, or coronary artery graft surgery), stroke or transient ischemic attack, peripheral arterial revascularization, carotid artery disease, heart failure. Abdominal visceral and subcutaneous adipose tissue areas at the lumbar (L4-L5) level were measured with computed tomography (CT). Areas were calculated by multiplying the number of pixels of a given tissue type by the pixel area using imaging software (RSI Systems). Visceral fat was manually distinguished from subcutaneous fat by tracing along the fascial plane defining the internal abdominal wall. Body mass index (BMI) was categorized as normal weight if BMI was ≤ 24.9 kg/m^2, overweight if BMI between 25.0 kg/m^2 and 29.9 kg/m^2 and obesity if BMI ≥ 30.0 kg/m^2. We defined the inflammation severity according to the number of inflammatory markers (CRP, TNF-α, IL-6) above the 3rd tertile of the distribution within the Health ABC Study [12].