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Total and high molecular weight adiponectin levels and risk of cardiovascular disease in individuals with high blood glucose levels

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ABSTRACT

Objective: The association of adiponectin levels with cardiovascular disease (CVD) may vary by age and health condition. It is unknown whether adiponectin predicts CVD events among individuals with high blood glucose levels.
Methods: We conducted a nested case–control study among 15,566 men and women aged 40–85 years from four communities, who were free of CVD at baseline. During 192,181 person-years of follow-up, 117 individuals subsequently developed coronary heart disease or ischemic stroke and had high plasma glucose concentrations (fasting/nonfasting $\geq$ 5.6/7.2 mmol/L or treated) at baseline. Controls were randomly selected at a 2:1 ratio and matched for sex, age, blood glucose, year of survey, fasting conditions, and community ($n = 234$). Baseline total and high molecular weight (HMW) adiponectin and their ratio were examined for total subjects and the association with CVD was compared between ages of 40–69 and 70–85 years.
Results: After adjustment for matched variables and traditional risk factors, total and HMW adiponectin and their ratio were not associated with overall risk of CVD. However, significant interactions of the associations between the age groups were found. The highest quartile for HMW adiponectin and HMW/total adiponectin ratio decreased risk of CVD compared with the lowest quartile among middle-aged individuals (multivariable-adjusted odds ratio = 0.33 [95%CI, 0.13–0.83] and 0.47 [0.22–0.98], respectively), while this association was not seen among the elderly.
Conclusions: High HMW adiponectin levels may decrease the risk of CVD in middle-aged adults with high blood glucose.

1. Introduction

Adiponectin is an adipocyte-derived, anti-atherogenic protein that is found as a trimer, hexamer, or as a high-molecular weight (HMW) complex (12–18 subunits) in human plasma, and which plays a role in the regulation of glucose and lipid metabolism [1,2]. Treatment with recombinant full-length adiponectin has been shown to improve insulin resistance, hyperglycemia, and hyperlipidemia in adiponectin-deficient mice [3]. Furthermore, the HMW form of adiponectin was shown to selectively improve insulin resistance, and a low ratio of HMW to total adiponectin was found to be a useful predictor of insulin resistance and metabolic syndrome in clinical studies [4].

However, epidemiological evidence for a protective role of adiponectin against the development of type 2 diabetes and CVD has been limited and inconsistent [5]. Several prospective cohort studies showed that lower adiponectin levels were associated with elevated risk of new onset of type 2 diabetes [6] and incident

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coronary heart disease [7]. In contrast, other studies have reported weak or non-significant associations between low adiponectin levels and cardiovascular disease (CVD) [8], particularly among women [9,10] and the elderly [11]. Furthermore, high adiponectin levels have been associated with an increased risk of CVD among elderly people [12–14].

Taking into consideration the stronger association between glucose abnormalities and CVD events among middle-aged adults than in the elderly [15], we hypothesized that adiponectin levels might also be more strongly associated with CVD events in middle-aged adults than in the elderly. We examined HMW adiponectin levels and the HMW/total adiponectin ratio, which have been shown to be more closely related to insulin sensitivity than total adiponectin [4]. We also hypothesized that adiponectin levels might be more predictive of CVD among individuals with high blood glucose levels, since fasting and non-fasting blood glucose levels were shown to be associated with an increased risk of coronary heart disease and stroke in Japanese men and women aged 40–69 years [16,17]. In the present nested case–control study, we attempted to clarify the association between adiponectin and risk of ischemic stroke and coronary heart disease events among individuals with high blood glucose levels using 12.3 years of follow-up data from approximately 16,000 individuals.

2. Methods

2.1. Study population

The Circulatory Risk in Communities Study (CIRCS) [18] and Ozu Study [19] were prospective cohort studies of Japanese men and women aged 40 years and older in communities across Japan. Baseline surveys were conducted for the CIRCS from 1984 to 1992 in the Ikawa, Kyowa, and Noichi Districts, and from 1996 to 1998 in the Ozu Study. After exclusion of individuals with a history of stoke or coronary heart disease at baseline, 15,566 individuals were followed through the end of 2007 (192,181 person-years), and 263 ischemic strokes and 139 myocardial infarctions occurred among these populations. Of these, we selected 79 ischemic strokes and 52 myocardial infarctions in individuals who had fasting glucose levels $\geq$5.6 mmol/L or non-fasting glucose levels $\geq$7.2 mmol/L or who took medication for type 2 diabetes. In 117 (89.3%) of these cases, frozen blood samples at baseline were available for use in the present study. Controls were randomly selected at a 2:1 ratio among participants with available baseline blood samples and similar glucose levels, but without cardiovascular disease, and were matched for sex, age ($\pm$2 years), year of blood draw, fasting conditions, and community.

To identify strokes and coronary heart disease events, medical records were reviewed by trained nurses and physicians [20]. Incident strokes were validated based on the National Survey of Stroke criteria [21], which require a constellation of neurological deficits that present rapidly and persist for at least 24 h (or until death). For each subtype of stroke, i.e. subarachnoid hemorrhage, intracerebral hemorrhage, or ischemic stroke, a definitive diagnosis was established based on data from computer tomographic (CT) scans, magnetic resonance images (MRI), or autopsy.

Incident myocardial infarctions were confirmed in the medical records using the criteria of the MONICA project [22], which require electrocardiogram results, cardiac enzyme measurements, and/or autopsy. On the basis of the combined findings available for review, diagnoses of "definite myocardial infarction" and "possible myocardial infarction" were made. In the absence of a diagnosis of myocardial infarction, deaths that occurred within 1 h of onset were regarded as sudden cardiac deaths.

This study was approved by the Ethical Committees of Ehime University Graduate School of Medicine and University of Tsukuba.

2.2. Measurements

A self-administered questionnaire was completed by participants at baseline that included medical history, smoking and alcohol consumption habits, and time since the last meal. Blood pressure was measured on the right arm with subjects in a sitting position after resting at least 5 min by a trained technician using a standard mercury sphygmomanometer. Body mass index (BMI, kg/m [2]) was calculated as weight divided by height squared.

Subjects were considered to be fasting if blood was collected more than 8 h after the last meal. Total cholesterol and triglycerides were measured using conventional methods certified by the Osaka Medical Center for Health Science and Promotion, a member of the Cholesterol Reference Method Laboratory Network (CRMLN) [23]. Hypertension was defined as systolic and diastolic blood pressures $\geq$140/90 mmHg or the use of medication to treat hypertension. Hyperlipidemia was defined as total cholesterol $\geq$5.70 mmol/L, triglycerides $\geq$1.70 mmol/L, or the use of medication to treat dyslipidemia. Type 2 diabetes was defined as a fasting glucose level $\geq$7.0 mmol/L, a non-fasting glucose level $\geq$11.1 mmol/L, or the use of medication to treat diabetes.

Total and HMW adiponectin were measured using an enzyme-linked immunosorbent assay (ELISA) kit (SEKISUI Medical Co., LTD., Tokyo, Japan) [24]. The intra-assay coefficient of variation was 5.4% for total adiponectin (mean = 3.98 μg/mL) and 5.0% for HMW adiponectin (mean = 1.08 μg/mL). The lower limit for adiponectin detection was 0.038 ng/mL.

Covariates, including medical history, smoking status (current smoker, former smoker, or never smoked), and regular alcohol consumption (regular drinker, former drinker, or never drank) were determined using a self-administered questionnaire. Use of medications for hypertension or diabetes mellitus (yes/no) was determined by the question, "Have the following conditions been treated by physicians?" with hypertension, diabetes mellitus, and hyperlipidemia offered as potential responses.

2.3. Statistical analysis

With a mean of 12.3 years of follow-up time, person-years were calculated as the period from the date of baseline to that of the first endpoint (death, emigration, or loss) or until December 31, 2007.

Because of skewed distribution, total and HMW adiponectin values were log-transformed in analysis. When comparing means, medians, and percentages of variables between cases and controls, the unpaired t test, the Wilcoxon rank sum test, and the χ^2 test were used, respectively. Odds ratios and 95% confidence intervals (CIs) were calculated using a modified Poisson regression analysis adjusting for matched variables of sex, age (continuous), and community [25]. Furthermore, we constructed multivariable-adjusted models using smoking status (current smoker, others), alcohol consumption (regular alcohol drinker, others), and medications or past history of hypertension or diabetes (yes/no) as covariates. A test for linear trends was also performed using median values for total and HMW adiponectin grouped by quartile and adjusted for the same covariates. We examined interactions between adiponectin levels and subgroups with an interaction term (subgroup $\times$ adiponectin levels) using median values for each quartile in the multivariable-adjusted model.

Statistical significance was assumed at $P < 0.05$. All statistical analyses were performed using SAS software, version 9.2 (SAS Institute, Inc., Cary, North Carolina, USA).