Associations of Serum C-Peptide Level with Body Fat Distribution and Ever Stroke in Nondiabetic Subjects

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Background: Although elevated serum C-peptide level as an indicator of insulin resistance increases the obesity-associated risk of cardiovascular disease among diabetic patients, evidence indicating that serum C-peptide level is associated with stroke in nondiabetic subjects is limited. The aim of this study is to evaluate the association between serum C-peptide level and ever stroke in nondiabetic subjects and investigated the associations of serum C-peptide level with body fat distribution and stroke events among nondiabetic subjects. *Methods:* This study was a population-based cross-sectional study that included 7030 participants aged 12-85 years. Body fat distribution was determined by dual-energy X-ray absorptiometry. Serum C-peptide level was measured using the radioimmunoassay method. The association between serum C-peptide level and body fat distribution was evaluated by multiple linear regression models. Logistic regression analysis was performed to calculate the odds ratio (OR) of serum C-peptide level being associated with ever stroke. *Results:* A total of 103 nondiabetic subjects reported having a stroke. Logistic regression analysis revealed a high-serum C-peptide level significantly associated with ever stroke among nondiabetic subjects (OR: 3.71, 95% confidence interval: 1.78-7.75). Meanwhile, in multiple linear regression analysis, serum C-peptide level was positively associated with total and regional fat distribution among nondiabetic subjects. *Conclusion:* The serum C-peptide level is strongly associated with the ever stroke in nondiabetic subjects and significantly associated with total and regional body fat distribution. **Key Words:** Serum C-peptide—stroke—body fat distribution—serum insulin—fasting plasma glucose.

Introduction

The obesity epidemic has become a major health problem worldwide. Obesity is a well-established major risk factor of type 2 diabetes and is associated with stroke.[1] Obesity causes a number of metabolic disturbances that can induce premature cardiovascular disease and increase an individual's chances of suffering from other chronic diseases.[2] Insulin resistance plays an important role in the development of type 2 diabetes. Obesity-induced insulin resistance can initially enhance insulin secretion from pancreatic β-cells. However, prolonged insulin resistance leads to reduced insulin secretion in direct response to hyperglycemia, eventually leading to type 2 diabetes.[3] On the other hand, diabetes is recognized as an inflammatory disease caused by obesity.[4] The weak inflammatory response often present in obesity affects both insulin secretion and β-cell function and may, thus, contribute to the development of type 2 diabetes. Several epidemiologic studies show that increased body mass index (BMI) as a measure of excessive body fat increases the relative risk of developing type 2 diabetes.[5] In addition, larger waist circumference (WC) and waist-to-hip ratio (also referred to as abdominal or central

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obesity) are associated with an increased risk of type 2 diabetes.[6] Ectopic fat is associated with a relatively large amount of visceral fat and can be described as central fat. Visceral fat secretes elevated amounts of proinflammatory cytokines such as tumor necrosis factor and interleukin-6.[7] The adipose tissue in proximity to the vasculature and heart are implicated in the development of vascular dysfunction; thus, they might contribute to hypertension and CVD.[8]

Serum C-peptide was previously considered an inactive peptide. It is currently known as a useful marker of β-cell function.[9] However, a few recent studies suggest that C-peptide is an active peptide hormone with an important physiologic function.[10] Serum C-peptide may improve microvascular blood flow.[11] Furthermore, basal C-peptide levels are significantly elevated among patients with metabolic syndrome and diabetes.[12] Epidemiologic studies report that serum C-peptide level is independently associated with CVD, cancer, and total mortality.[13] In addition, several studies focus on the association between serum C-peptide level and BMI in the development of type 2 diabetes in patients. However, the metabolic characteristics of serum C-peptide are receiving increasing attention.

Despite the fact that serum C-peptide as a marker of insulin resistance and obesity—specifically type 2 diabetes—has been widely studied, the pathogenesis of these metabolic disorders and their influences on the development of stroke remain unknown among nondiabetic subjects. Therefore, the aim of the present study was to evaluate the association between serum C-peptide level and ever stroke events independent of serum insulin and fasting plasma glucose (FPG) level. Furthermore, we hypothesized that serum C-peptide is an intermediary factor between obesity and low-grade inflammation and may be associated with stroke events in nondiabetic subjects.

Materials and Methods

Subjects

This study was based on data from the National Health and Nutrition Examination Survey 1999-2004, which is a population-based program designed to assess the health and nutritional status of children and adults in the United States. Clusters of households were observed at 2-year intervals. A representative cross-sectional sample comprising a total of 38,077 US residents was selected through a stratified multistage probability sampling process. Of them, 31,126 were interviewed and 29,402 were examined in the Mobile Exam Center (MEC). All participants provided written informed consent, and the study was approved by the Institutional Review Board of the Centers for Disease Control and Prevention (Atlanta, GA).

Information Collection

The survey included a home interview and health examination. During the home interview, the participants were asked about their daily physical activity, dietary habits, disease history, and general health status. Physical activity included questions about exercise, sports, and physically active hobbies in leisure time. The participants reported whether they had engaged in vigorous or moderate-intensity physical activity during the past 30 days. If respondents responded with a "yes" for vigorous activity, but did not give at least one example of a vigorous activity or reported a duration of less than 10 minutes, then the answer was recoded as "no". Smoking status was categorized as never, former, or current smoking status. Furthermore, smokers were asked about the number of cigarettes smoked per day, age at which they had started smoking, and total number of years of smoking. Drinkers were defined as participants who reported consuming at least 12 alcoholic beverages during the past 12 months, such as whiskey, beer, wine, and wine coolers. Education level was classified as below high school, high school diploma, or college or above on the basis of their responses.

Anthropometrics Measurements

MEC provided a standardized environment for the collection of high-quality data. The health technicians verified body measurement instrument calibration in the field, and performing the equipment calibration checks is monitored. The height, weight, and WC were measured according to a standard protocol. Height was measured using an electronic stadiometer and weight using a digital scale connected to the integrated survey information system. The WC was measured using a metal tape. BMI was calculated as the weight in kilograms divided by the square of the height in meters (kg/m^2).

Dual-Energy X-ray Absorptiometry Measurements

Dual-energy X-ray absorptiometry (DXA) is the method most widely used to assess body composition. In the study, whole-body DXA scans (Hologic QDR 4500 A fan beam densitometer; Hologic, Inc., Bedford, MA) were performed to estimate body fat distribution.[14] All scans were analyzed using Hologic Discovery software version 12.1. The results for each participant were reviewed by the Department of Radiology of the University of California, San Francisco. Total, arm, leg, trunk, subtotal, android, and gynoid fat masses in grams were measured, and fat distribution as the percent of body fat (%fat) in each region was used in the study. The body lean mass and the percent of body lean (%lean) were also obtained.