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ORIGINAL ARTICLE

Leptin, Adiposity, and Mortality: Results From the National Health and Nutrition Examination Survey III, 1988 to 1994

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Abstract

Objective: To determine whether leptin is related to all-cause and cardiovascular (CV) mortality in older adults.

Patients and Methods: Participants 60 years and older with plasma leptin level measurements from the National Health and Nutrition Examination Survey III (1988-1994) and mortality data linked to the National Death Index were included. We created sex-specific tertiles of leptin (men: 4.2-7.7 μg/L; women: 11.5-21.4 μg/L) to identify the effect of leptin on all-cause and CV mortality. We also determined whether leptin predicted mortality in patients with obesity. We classified obesity using 4 possible definitions: body mass index 30 kg/m^2 or greater; body fat 25% or more in men and 35% or more in women; waist circumference 102 cm or greater in men and 88 cm or greater in women; and waist-hip ratio 0.85 or higher in women and 0.95 or higher in men. Sex-specific proportional hazard models were used to assess the effect of leptin on all-cause and CV mortality.

Results: Of 1794 participants, 51.6% were women; the mean age was 70.3±0.4 years, and the follow-up period was 12.5 years with 994 deaths (469 were CV deaths). All-cause mortality in the highest leptin tertile was significant neither in men (hazard ratio [HR], 1.23; 95% CI, 0.93-1.63) nor in women (HR, 0.97; 95% CI, 0.68-1.40). CV mortality was the highest in the highest leptin tertile in men (HR, 1.69; 95% CI, 1.06-2.70) but not in women (HR, 1.21; 95% CI, 0.73-1.98). Evaluating the effect of leptin in subgroups of different obesity definitions, we found that high leptin levels as predict CV mortality in men as measured by waist circumference or body fat.

Conclusion: Elevated leptin level is predictive of CV mortality only in men. Leptin may provide additional mortality discrimination in obese men.

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The proportion of older adults in the United States is rapidly increasing,[1] and the coexisting public health epidemic paralleling this rise is that of obesity.[2] Obesity affects many chronic diseases such as hypertension, dyslipidemia, and coronary artery disease[3] and leads to premature death and years of life lost.[4] Older adults with obesity surviving past age 60 are at an increased risk of physical limitations, impairments in activities of daily living, and institutionalization,[5,6] all of which can affect quality of life.

Leptin is a key product of the obese gene, leading to suppression of appetite and reduction of food intake.[7] People with obesity are known to have leptin resistance, which is reflected by elevated concentrations in those with higher levels of fat mass.[8] Leptin plays an active role in cytokine and adipokine metabolism, which may be involved in the development of cardiovascular (CV) disease and frailty.[9] It may be partially mediated through the release of proinflammatory cytokines, such as tumor necrosis factor α, interleukin 1, and interleukin 6.[10] Some studies[11] have advocated that leptin should be considered a component of the metabolic syndrome, which itself is associated with increased risk of death.[12]

There have been few population-based studies describing the relationship between leptin and mortality in older adults,[13,14] and the mechanistic effects in an aging human are

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incompletely understood. Aging is associated with functional decline, frailty, and disability, and physical activity is known to mitigate the effects of this pathway.[5,15,16] The purpose of this study was to identify whether leptin levels predict long-term CV and all-cause mortality in community-dwelling older adults. A secondary aim was to determine whether leptin provided any additional discriminatory effort to predict death in a subset of older adults with obesity.

PATIENTS AND METHODS

Study Design and Population

We performed a secondary analysis using data from the National Health and Nutrition Examination Survey (NHANES) because leptin and mortality data were unavailable in other waves of the NHANES. All data were publicly available online at http://www.cdc.gov/nchs/nhanes.htm. Briefly, NHANES III is a population-based study of noninstitutionalized adults in the United States. The survey was conducted by the Centers for Disease Control and Prevention between October 1988 and October 1994. The study design was complex and stratified, and it oversampled minorities and older adults. All data were initially downloaded in March 2013 and updated in November 2013. Data were de-identified. The study was exempt for purposes of research.

There were 39,095 sampled participants, of which we excluded 31,320 (80.1%) who were younger than 60 years. Of the remaining 7775 participants, 6178 (79.5%) consented to be interviewed and were examined by a physician at a mobile examination center. All races (non-Hispanic white, non-Hispanic black, and Hispanic American) were included. A total of 1694 (27.4%) participants without complete anthropometric and bioelectrical impedance data were excluded. We initially identified 4484 in our cohort.

Demographic Characteristics

All questionnaires or interviews were performed by trained staff, with automated data collection according to validated protocols in English or Spanish. If participants were unable to answer, proxies were asked to assist. Participant age was self-reported from an initial screening questionnaire and verified against an age verification chart. Any differences were reconciled using a protocol. Age at screening was considered baseline age. Education and race were both self-reported; education was dichotomized as 12 years or less and more than 12 years. All comorbidities used in this analysis were ascertained by self-report. Smokers were considered ever smokers if they answered the question "Have you ever smoked at least 100 cigarettes in your lifetime" affirmatively. Current smokers answered the question "Do you smoke cigarettes" affirmatively. The level of physical activity was assessed using metabolic equivalent (MET) intensity levels on the basis of the Compendium of Physical Activities Report.[17] All participants completed a questionnaire of leisure time physical activity and its frequency in the past month. High activity level was defined as MET levels greater than 6 for 3 or more times per week; moderate activity level as MET levels ranging from 3 to 6, 5 or more times per week; and low activity level as MET levels that did not meet criteria for either group.

Anthropometric Measures

Weight was measured in kilograms using a calibrated digital scale. All variables were measured in centimeters. Height was measured using a stadiometer, with the participant standing after deep inhalation and weight distributed equally on both feet. Waist circumference (WC) was measured by palpating the right iliac crest, crossing the midaxillary line, and placing the measure around the trunk's body at minimal respiration in the standing position. Hip circumference was assessed above the hips at the side seams of the pants at maximum extension of the buttocks. The waist-hip ratio (WHR) was the ratio of waist to hip circumference, and body mass index (BMI) was calculated as the weight in kilograms divided by the height in meters squared. All procedures were performed on the right side of the body, except in cases it was physically impossible. For quality assurance purposes, replicates (to allow for alternative methods to estimate variance) and data review were performed (http://www.cdc.gov/nchs/nhanes.htm).

Body Composition Measures

NHANES III used a Valhalla 1990B Bio-Resistance Body Composition Analyzer (Valhalla Scientific), and data were converted using sex-specific predictive equations[18] to calculate fat-free mass and total body water. Total body fat was the difference between weight and fat-free

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