MAYO CLINIC

Risks for Cardiovascular and Cardiac Deaths in Nonobese Patients With Diabetes and Coronary Heart Disease

Tetsuro Tsujimoto, MD, PhD; Hiroshi Kajio, MD, PhD; and Takehiro Sugiyama, MD, MSHS, PhD

Abstract

Objective: To assess whether obese diabetic patients with coronary heart disease (CHD) have a lower risk for cardiovascular or cardiac mortalities than do nonobese diabetic patients with CHD.

Patients and Methods: We conducted a prospective cohort study using data from the National Health and Nutrition Examination Survey 1999-2010 and followed up the study participants from the survey participation date until December 31, 2011. For primary analyses, we built Cox proportional hazard models restricted to diabetic patients with CHD; unadjusted and adjusted hazard rates of cardiovascular mortality were compared between obese and nonobese participants.

Results: A total of 3,056 diabetic participants (504 with and 2,552 without CHD) and 22,556 nondiabetic participants (953 with and 21,603 without CHD) aged 20 to 79 years without malignant disease were included. Follow-up was completed in 99.8% of study participants. Hazard ratio (HR) for cardiovascular mortality for diabetic participants with CHD was significantly lower among the obese than among the nonobese (adjusted HR, 0.38; 95% CI, 0.18-0.82; P=.01); these findings were not observed in diabetic participants without CHD. Among nondiabetic participants, cumulative event rates for cardiovascular deaths were not significantly different between the obese and the nonobese, regardless of CHD status. Similar results for cardiac mortality were observed in both diabetic and nondiabetic participants.

Conclusion: Obesity in diabetic patients with CHD was associated with lower cardiovascular and cardiac mortality risks compared with absence of obesity. That is, nonobese patients having diabetes and CHD may have an increased risk for serious cardiovascular events.

O besity, an important risk factor for diabetes and cardiovascular diseases, has been increasing in epidemic proportions worldwide.[1,2] In addition, a recent study has suggested that obesity may be associated with increased risk of cancer.[3] However, the obesity paradox, association between obesity and reduced mortality or cardiovascular events compared with that in absence of obesity, has been reported among patients with several comorbidities, such as coronary heart disease (CHD).[4-7] In addition, some studies have suggested that the obesity paradox might be present after diabetes has developed[8-10]; however, others have reported otherwise.[11,12] The conflicting results for the obesity paradox in diabetes may be

attributed to patient selection bias and incomplete adjustment.[13,14] Moreover, the results for the obesity paradox in diabetes may be different between patients with and without CHD.[4,5]

In this study, using nationally representative data, we assessed whether obese diabetic patients with CHD have a lower risk of cardiovascular or cardiac mortalities compared with nonobese diabetic patients with CHD. In addition, to assess the coronary risk among diabetic populations with CHD, we investigated cardiac mortalities in obese and nonobese populations. Similar analyses were conducted in diabetic populations without CHD, nondiabetic populations with CHD, and nondiabetic populations without CHD.

From the Department of Diabetes, Endocrinology, and Metabolism, Center Hospital (T.T., H.K.), Department of Clinical Study and Informatics, Center for Clinical Sciences (T.S.), National Center for Global Health and Medicine, and Department of Public Health/Health Policy, the University of Tokyo (T.S.), Tokyo, Japan.

PATIENTS AND METHODS

Data Source and Study Population

This was a prospective cohort study using data from the US National Health and Nutrition Examination Survey (NHANES).[15] Written informed consent was obtained from all participants. The National Center for Health Statistics Research Ethics Review Board approved the NHANES protocols.[16] The NHANES was conducted by the National Center for Health Statistics at the Centers for Disease Control and Prevention. It uses a stratified, multistage probability sampling design, which enabled representation of the US civilian noninstitutionalized population.[15] In this study, data were collected at home and mobile examination centers (MECs). Blood specimens were collected during an MEC examination.

Among the population participating in the NHANES during the period 1999 to 2010, the unweighted response rate of household interviews was 80.6% and that of MEC examination was 77.1%.[17] We focused on participants aged 20 to 79 years, which resulted in a sample number of 29,725. We excluded those with missing information on body mass index (BMI; n=1,849) and those with BMI of less than 15 kg/m^2 (n=11) because these participants may have other comorbidities. In addition, we excluded those with a history or comorbidities of cancer (n=2,115) and those with diabetes at age less than 20 years (n=138) to avoid the possible effects of genetic or autoimmune diseases. We prospectively followed up the study participants from the date of survey participation for interviews until December 31, 2011.

Definition of Diabetes, Obesity, and CHD

We defined diabetes using 1 of the following 3 criteria: previous diagnosis of diabetes, intake of antidiabetic medications or insulin, or glycated hemoglobin (HbA1c) level of 6.5% or more.[18] Participants who did not satisfy any of these 3 criteria were defined as without diabetes. We extracted information on BMI, calculated as weight (kg) divided by height (m) squared, from the MEC measurements in the 1999-2010 NHANES. Among the study participants, *obesity* was defined as a BMI of 30 kg/m^2 or more. *Coronary heart disease* was defined as a previous diagnosis of CHD, myocardial infarction, or angina pectoris.

Outcome Measures

The main outcome measures were cardiovascular and cardiac mortalities. In addition, we assessed noncardiovascular and all-cause mortalities. We used the abovementioned mortality follow-up data provided in the Public-use Linked Mortality Files.[19] To identify causes of deaths occurring in participants in or after 1999, the NHANES used the *International Classification of Diseases, Tenth Revision* codes.[20] The specific codes used were I00 to I09, I11, I13, and I20 to I51 for causes of death from diseases of the heart (cardiac death) and I60 to I69 for causes of death from cerebrovascular diseases. *Cardiovascular death* was defined as death from cardiac and cerebrovascular diseases. *Noncardiovascular death* was defined as any death due to noncardiovascular causes.

Other Measurements

We extracted data on potential confounders, including age, sex, race and ethnicity, educational attainment, smoking status, hypertension, hyperlipidemia, and HbA1c level. Race and ethnicity were classified into 4 categories: non-Hispanic white, non-Hispanic black, Mexican American, and others including other Hispanics, Asian, and multiracial participants. We classified educational attainment as more than high school, high school graduation or General Education Development certificate, or less than high school. *Hypertension* was defined as either a previous diagnosis of hypertension or intake of antihypertensive medications. *Dyslipidemia* was defined as a previous diagnosis of hyperlipidemia or intake of lipid-lowering medications. The HbA1c level was measured upon MEC examination in this survey.

Statistical Analyses

Demographic data were presented as numbers with proportions (%) or means with SDs. Both diabetic and nondiabetic participants were divided according to the presence or absence of CHD. Study participants with obesity were compared with those without obesity using *t* test for continuous variables and chi-square test for categorical variables. For primary analyses of cardiovascular and cardiac