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Obesity paradox: Differential effects on cancer and noncancer mortality in patients with type 2 diabetes mellitus

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ABSTRACT

Objective: To investigate associations between body mass index (BMI) and cause-specific mortality in patients with type 2 diabetes mellitus (T2DM).
Methods: Prospective follow-up of a nationally representative cohort of 89,056 Taiwanese patients with T2DM recruited since 1995. Vital status was matched with the National Death Certificate Database until the end of 2006. Self-reported body weight and height were used to calculate BMI, which was treated either as a continuous or categorical variable (underweight, <18.5; normal, 18.5–22.9; overweight, 23.0–24.9; obesity I, 25.0–29.9; and obesity II, ≥30.0 kg/m^2). Causes of death were classified as all-cause, cancer, diabetes complications (macrovascular and microvascular), and other. Cox regression was used to estimate the hazard ratios.
Results: A total of 26,951 patients (30.3% of the cohort) died during follow-up (cancer 5.4%, diabetes complications 17.4%, and other causes 7.5%). As a continuous variable, BMI was inversely associated with mortality from all-cause, cancer, diabetes complications, and other causes, with respective adjusted hazard ratios (95% confidence intervals) of 0.942 (0.939–0.946), 0.966 (0.958–0.975), 0.935 (0.930–0.939), and 0.942 (0.935–0.949). Compared to normal weight, underweight was significantly predictive for any of causes of death, while overweight, obesity I, and obesity II were all significantly associated with mortality in an inverse pattern. After excluding patients with a follow-up duration <2 years, most BMI categories were not significantly predictive of mortality from cancer, suggesting a potential bias of cancer-induced weight loss.
Conclusions: The obesity paradox, mainly observed in noncancer mortality, exists in patients with T2DM, suggesting a survival advantage in obese diabetic patients.

1. Introduction

Obesity is associated with leptin resistance and may cause vascular or myocardial injury through its adverse effects on hemodynamics and cardiovascular structure and function [1]. Epidemiological studies have also demonstrated obesity as an independent risk factor for diabetes, hypertension, dyslipidemia, cardiovascular disease (CVD) and cancer [1–4]. However, the effects of obesity on mortality are not as well defined. Some studies have suggested a U-shaped or J-shaped association with increased mortality in people who are either underweight or obese [5,6]. In contrast, in recent years, a higher body weight has been shown to improve the survival of patients with a variety of clinical conditions including cardiovascular (hypertension, heart failure, coronary heart disease and peripheral arterial disease) and noncardiovascular (elderly, end-stage renal disease, dialysis, advanced cancers, chronic obstructive lung disease, rheumatoid arthritis and acquired immune deficiency syndrome) diseases, a phenomenon referred to as the "obesity paradox" [1,2].

Whether the obesity paradox can be seen in Asian populations is not clear. A recent Taiwanese study supported the existence of the obesity paradox in the general population [7]. Tsai et al. followed up 4440 subjects aged 53 years and older from a nationally representative cohort of Taiwanese people for 4 years and showed that the underweight condition was significantly predictive for all-cause mortality, but obesity did not significantly change the mortality risk [7]. This study evaluated all-cause mortality during a short period

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and could not conclusively determine whether the obesity paradox phenomenon could be seen in specific causes of death. To the best of our knowledge, no prospective follow-up studies evaluating whether the obesity paradox exists in patients with type 2 diabetes mellitus (T2DM) have been conducted.

The purpose of the present study was to evaluate whether the obesity paradox existed in Taiwanese patients with T2DM by analyzing the relationship between baseline body mass index (BMI) and cause-specific mortality in a large and nationally representative cohort of patients after 12 years' follow-up.

2. Methods

2.1. Study subjects

Because more than 96% of the total population of Taiwan has been covered by the compulsory and universal National Health Insurance (NHI) since March 1995, almost all diabetic patients have been using the NHI. The assembly of such a national sample was described in detail elsewhere [8–10]. In brief, a total of 256,036 diabetic patients were identified from 66 hospitals and clinics located throughout Taiwan from 1995 to 1998. To create a cohort of 90,000 patients for long-term follow-up, 128,572 cases from the 256,036 patients were randomly selected for questionnaire interview, assuming a predicted response rate of 70%.

A total of 93,484 (response rate, 72.7%) patients completed the interview. After excluding patients with type 1 diabetes mellitus (T1DM), a total of 89,056 patients identified as T2DM were included into the study. The information abstracted from the questionnaire for this study included age, sex, diabetes duration, self-reported body weight and height, insulin use, hypertension, smoking and living region. BMI was calculated as body weight in kg divided by squared body height in meters; and was classified as underweight, normal, overweight, obesity I, and obesity II, using the following respective cutoffs recommended for Asian populations [11]: $<$18.5, 18.5–22.9, 23.0–24.9, 25.0–29.9, and $\geq$30.0 kg/m^2.

2.2. Ascertainment of vital status

In Taiwan, every resident has a unique identification number, and events like birth, death, marriage, or migration should be registered in the household registration offices. If a person dies, a death certificate should be issued by a physician, and this certificate should be reported to the household registration offices within 30 days as required by law. Data from death certificates, including the unique identification number, date of birth, sex, and date and cause of death, have been computerized since 1971 and can be used for academic research. Causes of death have been coded according to the ninth revision of the International Classification of Diseases (ICD-9) in Taiwan since 1981.

Specific causes of death were first classified into the following categories (Classification I) according to ICD-9: cancer (140–208); diabetes mellitus (250); cardiopulmonary disease (401–429); stroke (430–438); diseases of arteries, arterioles, and capillaries (440–448); nephropathy (580–589); infection (001–139, 320, 321, 326, 421, 460–466, 480–487, 510, 513, 551, 567, 590, 599, 680–686, 711, 730); digestive diseases (520–579 excluding 551); accidents (800–949); suicide (950–959); other causes (codes other than the above); and all-cause, as have been used in our previous study [8]. Causes of death were then divided into the following categories (Classification II) for analyses: (1) all-cause, (2) cancer, (3) diabetes complications (including diabetes mellitus; cardiopulmonary disease; stroke; diseases of arteries, arterioles and capillaries; and nephropathy as mentioned above), and (4) other causes (causes other than cancer or diabetes complications).

2.3. Statistical analyses

Analyses were conducted using SAS statistical software, version 9.1 (SAS Institute, Cary, NC). *P*-values less than 0.05 were considered statistically significant.

All patients were followed up from recruitment until the end of 2006. Baseline characteristics for patients who died and patients who survived were compared for both sexes by Chi-square test for categorical variables and by Student's *t* test for continuous variables.

Mortality rates were computed using a person-years denominator. The person-years of follow-up for each patient were calculated as the duration from the date of recruitment until the end of 2006 for those who were alive or to the date of death for those who died. Age was divided into less than 65 years and 65 years or older. Age- and sex-specific mortality rates with regard to different categories of BMI were calculated.

Survival curves for different categories of BMI were plotted by the Kaplan–Meier method for both sexes and both age categories. The logrank test was used to test the significance of the survival difference among the different categories of BMI.

Cox proportional hazards models were used to estimate the hazard ratios and their 95% confidence intervals for BMI (as a continuous variable) and BMI subgroups (as a categorical variable using a BMI of 18.5–22.9 kg/m^2 as the reference BMI) for the different causes of death according to classification II, i.e., all-cause, cancer, diabetes complications, and other. Models were created for both sexes. Age, sex, diabetes duration, insulin use, hypertension, smoking, and living region were treated as potential confounders. Living regions were defined as urban for the Metropolitan Taipei area (including the city of Taipei and the county of Taipei) and other administratively designated cities across Taiwan or as rural for administratively designated counties and offshore islands.

To minimize potential bias due to illness-induced body weight loss, sensitivity analyses were also performed for the above Cox regression models after excluding patients who died within 2 years of follow-up.

To examine whether similar results could be seen in younger and older patients, Cox regression models were further created in patients aged less than 65 years and 65 years or older, separately, and for both sexes, together and separately.

3. Results

Table 1 compares the baseline characteristics between patients who died and those who survived at the end of follow-up. Approximately 30.3% of patients died during the 12-year follow-up. Patients who died were characterized by older age, male predominance, longer diabetes duration, lower BMI, and greater prevalence of insulin use, hypertension, smoking, and living in rural areas. The findings were similar when analyzing men and women separately.

Specific causes of death are shown in Table 2. For both sexes, approximately 5.4% died of cancer, 17.4% died of diabetes complications, and 7.5% died of other causes.

Table 3 shows the calculated mortality rates for the different categories of BMI by age and sex. Except for those aged 65 years or older (both sexes combined, men, and women) and those less than 65 years old (women only), all the other analyses showed a decreasing mortality rate with increasing BMI.

Fig. 1 shows the survival curves with regard to different categories of BMI in both sexes for patients of all ages. Increasing mortality was observed with decreasing BMI (logrank test, $P < 0.0001$). Because similar trends were observed for all subgroups