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Short Report

Impact of body mass index and metabolic phenotypes on coronary artery disease according to glucose tolerance status

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ABSTRACT

Objective. – This study aimed to examine the impact of obesity, as defined by body mass index (BMI), and a metabolically unhealthy phenotype on the development of coronary artery disease (CAD) according to glucose tolerance status.
Methods. – This population-based retrospective cohort study included 123,746 Japanese men aged 18–72 years (normal glucose tolerance: 72,047; prediabetes: 39,633; diabetes: 12,066). Obesity was defined as a BMI $\geq$ 25 kg/m^2. Metabolically unhealthy individuals were defined as those with one or more of the following conditions: hypertension, hypertriglyceridaemia and/or low HDL cholesterol. A Cox proportional hazards regression model identified variables related to CAD incidence.
Results. – The prevalences of obese subjects with normal glucose tolerance, prediabetes and diabetes were 21%, 34% and 53%, whereas those for metabolically unhealthy people were 43%, 60% and 79%, respectively. Multivariate analysis showed that a metabolically unhealthy phenotype increases hazard ratios (HRs) for CAD compared with a metabolically healthy phenotype, regardless of glucose tolerance status (normal glucose tolerance: 1.98, 95% CI: 1.32–2.95; prediabetes: 2.91, 95% CI: 1.85–4.55; diabetes: 1.90, 95% CI: 1.18–3.06). HRs for CAD among metabolically unhealthy non-obese diabetes patients and obese diabetes patients with a metabolically unhealthy status were 6.14 (95% CI: 3.94–9.56) and 7.86 (95% CI: 5.21–11.9), respectively, compared with non-obese subjects with normal glucose tolerance and without a metabolically unhealthy status.
Conclusion. – A metabolically unhealthy state can associate with CAD independently of obesity across all glucose tolerance stages. Clinicians may need to consider those with at least one or more conditions indicating a metabolically unhealthy state as being at high risk for CAD regardless of glucose tolerance status.

Introduction

Diabetes mellitus and prediabetes are well known to be associated with an increased risk of coronary artery disease (CAD). However, it remains unclear whether the impact of obesity, as defined by body mass index (BMI), and a metabolically unhealthy state reflected by several factors on the incidence of CAD in those with diabetes and prediabetes differ from those in normoglycemic individuals [1,2]. Therefore,we investigated the impacts of obesity and a metabolically unhealthy phenotype individually and in combination on the development of CAD according to glucose tolerance status.

Methods

Data obtained from a nationwide claims database in Japan, consisting of approximately 3,000,000 people belonging to a health-insurance provider for company employees, were analyzed. Details of the study have been described elsewhere [3]. Men aged 18–72 years, who had been followed for at least 3 years between

Abbreviations: BMI, Body mass index; CAD, Coronary artery disease; CVD, Cardiovascular disease; FPG, Fasting plasma glucose; HDL-C, High-density lipoprotein cholesterol; HRs, Hazard ratios; NGT, Normal glucose tolerance.

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1 April 2008 and 31 March 2012, were included and followed up to 31 August 2015.

Of the 173,997 men with available data, 123,746 of them (72,047 with normal glucose tolerance [NGT], 39,633 with prediabetes and 12,066 with diabetes) with no CAD data at baseline but with health examination data, including blood test results, were analyzed. Their classification into NGT, prediabetes or diabetes was based on fasting plasma glucose (FPG), HbA1c levels and claims data as follows: NGT = both FPG < 5.6 mmol/L and HbA1c < 5.7%, and no antidiabetic drug prescription; prediabetes = either FPG 5.6–6.9 mmol/L or HbA1c 5.7–6.4%, or both, and no antidiabetic drug prescription; and diabetes = FPG ≥ 7 0 mmol/L or HbA1c ≥ 6.5%, or both, with no antidiabetic drug prescription or with an antidiabetic drug prescription regardless of FPG or HbA1c. Frequency distributions of prediabetes and diabetes according to diagnostic method are presented in Table S1 (see supplementary data associated with this article online). Metabolically healthy subjects were defined as having none of the following metabolic risk factors: hypertension (systolic blood pressure ≥ 135 mmHg and/or diastolic blood pressure ≥ 85 mmHg, or current use of antihypertensive agents); hypertriglyceridaemia (high plasma triglycerides ≥ 1.7 mmol/L, or current use of pharmacological agents for managing hypertriglyceridaemia); and low plasma levels of high-density lipoprotein cholesterol (HDL-C; < 1.03 mmol/L in men and < 1.29 mmol/L in women). Metabolically unhealthy individuals were defined as having one or more of the above-mentioned risk factors. Obesity was defined as a BMI ≥ 25 kg/m^2, according to the Japan Society for the Study of Obesity [4]. The presence of CAD was determined according to claims using International Classification of Diseases 10th revision (ICD-10) codes for cardiac events, including fatalities but excluding heart failure, and for medical procedures after 1 month of follow-up [3]. A Cox regression model identified variables related to the overall incidence of CAD and according to each glucose tolerance state.

Analyses were performed using SPSS version 19.0 software (IBM Corp., Armonk, NY, USA), and statistical significance was considered at $P < 0.05$. The Ethics Committee of the Niigata University approved this study.

Results

Baseline characteristics of participants as per glucose tolerance category are presented in Tables S2–S4 (see supplementary data associated with this article online). The prevalences of obese subjects with NGT, prediabetes and diabetes were 21%, 34% and 53%, respectively, whereas the prevalences of metabolically unhealthy people with NGT, prediabetes and diabetes were 43%, 60% and 79%, respectively. The median follow-up duration was 4.1 years. During the study period, 479 CAD events occurred in the overall study population, with 125, 171 and 183 such events in those with NGT, prediabetes and diabetes, respectively. Accordingly, rates of CAD in those subjects were 0.17, 0.50 and 1.40 per 1000 person-years, respectively. Multivariate analysis showed that, compared with those with NGT, hazard ratios (HRs) for CAD in prediabetes and diabetes were 1.47 (95% confidence interval [CI]: 1.16–1.86) and 3.90 (95% CI: 3.07–4.95), respectively. Tables S5–S8 (see supplementary data associated with this article online) present the multivariate-adjusted HRs for CAD according to glucose tolerance category. Table S7 also presents some other definitions of obesity in addition to ≥ 25 kg/m^2 (BMI ≥ 27.5 or ≥ 30.0 kg/m^2).

The presence of a metabolically unhealthy state increased HRs for CAD across all glucose tolerance categories (Table S6). In comparison to those with NGT who were not obese and without a metabolically unhealthy phenotype, the HR for CAD in those with obesity, diabetes and a metabolically unhealthy state was 7.86 (95% CI: 5.21–11.9; Fig. 1, Table S7). Also, non-obese subjects with a metabolically unhealthy state had an approximately two- to threefold increased CAD risk compared with those without a metabolically unhealthy state across all glucose tolerance categories (Table S7). On the other hand, the risk of CAD was not significantly increased in obese individuals without a metabolically unhealthy status (Table S7).

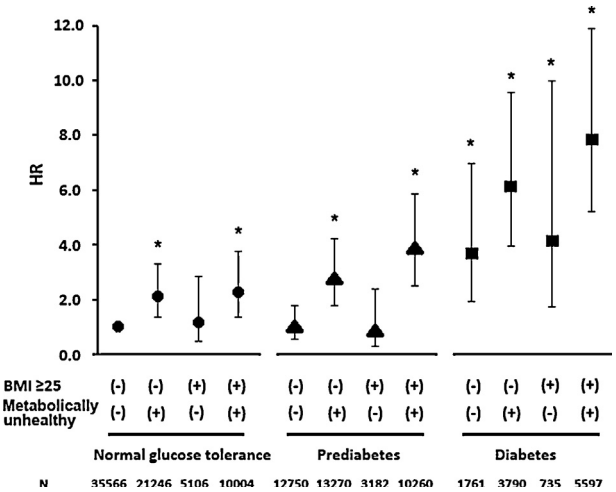

Fig. 1. Impact of obesity and metabolic phenotypes on coronary artery disease, according to glucose tolerance status and adjusted for age, low-density lipoprotein cholesterol (LDL-C), and smoking status. Bars indicate 95% confidence intervals. * $P < 0.05$ vs normal glucose tolerance without a metabolically unhealthy phenotype or obesity. HR: hazard ratio; BMI: body mass index (kg/m^2).

Discussion

Our study investigated the impact of obesity, as defined by BMI, and metabolic phenotype separately and in combination on CAD in Japanese men according to glucose tolerance status. The presence of a metabolically unhealthy state increased the risk for CAD across all glucose tolerance categories.

Obesity is closely linked to risk of diabetes. In fact, the prevalence of obesity is increased in association with worsening of glucose tolerance. Hinnouho et al. [5] showed that both the metabolically healthy obese and metabolically unhealthy obese phenotypes were associated with incidence of cardiovascular disease (CVD), compared with the metabolically healthy normal-weight phenotype. Also, Kim et al. [6] found that the persistently metabolically healthy obese phenotype is associated with incident CVD in Koreans. In our present study, obesity defined by BMI alone was not associated with increases in the development of CAD in any of the glucose tolerance categories. However, the follow-up time was shorter in our study compared with previous studies [5,6]. Thus, our findings may be explained by the shorter observation period. Further studies are needed to clarify the impact of obesity not accompanied by a metabolically unhealthy state on CAD in each glucose tolerance state.

The pattern of body fat distribution is a critical concept when discussing the impact of obesity on CAD. Indeed, Asians including the Japanese have a larger percentage of fat mass at similar BMI levels and a greater proportion of visceral adipose tissue at a total body fat compared with other populations such as Caucasians or blacks. Ito et al. [7] showed that excess accumulation of fat mass, especially in the upper body, and not BMI was related to dyslipidaemia in normal-weight Japanese. Fujimoto et al. [8] revealed that visceral adiposity is an important independent risk

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