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Original article

Sex difference in the effect of the fasting serum glucose level on the risk of coronary heart disease

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ABSTRACT

Objective: Diabetic women have a greater relative risk of coronary heart disease than diabetic men. However, the sex difference in the effect of fasting serum glucose levels below the diabetic range on the risk of coronary heart disease is unclear. We investigated whether the association between nondiabetic blood glucose levels and the incident risk of coronary heart disease is different between men and women.
Methods: The fasting serum glucose levels and other cardiovascular risk factors at baseline were measured in 159,702 subjects (100,144 men and 59,558 women). Primary outcomes were hospital admission and death due to coronary heart disease during the 11-year follow-up.
Results: The risk for coronary heart disease in women significantly increased with impaired fasting glucose levels (≥110 mg/dL) compared to normal glucose levels (<100 mg/dL), whereas the risk for coronary heart disease in men was significantly increased at a diabetic glucose range (≥126 mg/dL). Women had a higher hazard ratio of coronary heart disease associated with the fasting serum glucose level than men (p for interaction with sex = 0.021).
Conclusions: The stronger effect of the fasting serum glucose levels on the risk of coronary heart disease in women than in men was significant from a prediabetic range (≥110 mg/dL).

Introduction

Type 2 diabetes is one of the fastest growing public health problems worldwide [1–3]. Diabetes is a risk factor for cardiovascular disease, and the risk of coronary heart disease (CHD) in diabetic individuals is at least 2-fold greater than that in non-diabetic individuals [4–6]. Glucose level cut-offs for diagnosing diabetes are mainly based on what has been considered a threshold for microvascular complications such as retinopathy [7]. There is still a limited scientific understanding of the relationship between a wide range of blood glucose levels and macrovascular complications.

Women have a lower cardiovascular mortality rate than men [8]. Interestingly, women with diabetes have an increased relative risk of CHD compared to women without diabetes, which is approximately twice as high as that in men with diabetes [9–14]. These findings assert that diabetes weakens the advantages of being female. However, few studies have investigated the effect of the sex difference and fasting serum glucose levels below the diabetic range on the risk of CHD. Therefore, we investigated the association between fasting serum glucose levels and the incident risk of CHD, and we evaluated whether the association between nondiabetic blood glucose levels and the risk of CHD is different between men and women.

Materials and methods

Study population

Data were collected from the Korea Medical Insurance Corporation (KMIC) study. The KMIC provides health insurance to civil service workers, teachers, and their dependents in South Korea. Of the entire South Korean population (approximately 43 million in 1990), 4,603,361 (11%) were insured by KMIC, including 1,213,594 workers and their 3,389,767 dependents in 1990. All insured workers are required to participate in biennial medical examinations performed by the KMIC. The KMIC study

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cohort consisted of 115,200 men and 67,932 women aged 35–59 years who underwent health examinations in 1990 (95% participation rate) and 1992 (94% participation rate). The study was composed of a 25% random sample of male workers and all female workers [15]. Data on fasting serum glucose levels and major cardiovascular risk factors for 108,461 men and 64,119 women were available. After excluding 8317 men and 4561 women who reported any diagnosed diseases at baseline, we enrolled 100,144 men and 59,558 women for the analyses (Fig. 1). The study was approved by the Institutional Review Board of Severance Hospital at Yonsei University.

Data collection

The KMIC biennial examinations were conducted in a standard manner by medical staff at local hospitals. In 1990, examinations were conducted at 416 hospitals. Participants' smoking history, alcohol consumption, physical activity, and health status were assessed by self-administered questionnaires in 1992. Participants' weight, height, fasting serum glucose level, total cholesterol level, and systolic and diastolic blood pressures were measured in 1990 and 1992, and the values were averaged for analysis. Each hospital that participated in the assessments followed internal and external quality control procedures, as stipulated by the Korean Society of Quality Control in Clinical Pathology [16,17].

Main outcome measures

Primary outcome measures were incidence and mortality of CHD. CHD was defined by the International Classification of Diseases, 10th revision (ICD-10) codes I20-I25 [angina pectoris, acute myocardial infarction (MI), subsequent acute MI, other acute ischemic heart disease, and chronic ischemic heart disease]. Non-fatal outcomes were ascertained from diagnoses from health insurance claims data, and fatal outcomes were collected from causes of death on death certificates from the National Statistical Office. For individuals with more than one event, whether fatal or non-fatal, only the first event was used in the analyses. The follow-up period was 11 years from January 1, 1993 to December 31, 2003.

Statistical analysis

Data are expressed as means with standard deviations or frequencies with percentages. We stratified study participants into four groups: normal fasting glucose level <100 mg/dL, impaired fasting glucose (IFG) level of 100–109 mg/dL, IFG level of 110–125 mg/dL, and diabetic fasting serum glucose level ≥ 126 mg/dL. The IFG group was divided into two stages that corresponded to the old and new American Diabetes Association criteria: fasting glucose levels of 100–109 and 110–125 mg/dL [18]. We used a log-rank test to evaluate differences in the cumulative survival among the groups according to baseline fasting glucose levels and sex. The independent effects of fasting serum glucose levels on CHD were analyzed using the Cox proportional hazard models, after adjusting for age, body mass index, blood pressure, total cholesterol level, and cigarette smoking status. A log-likelihood ratio test was performed to test the significance of the interaction term of sex with the fasting serum glucose levels for CHD. Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated for the incident risk of CHD. Values of $p < 0.05$ were considered

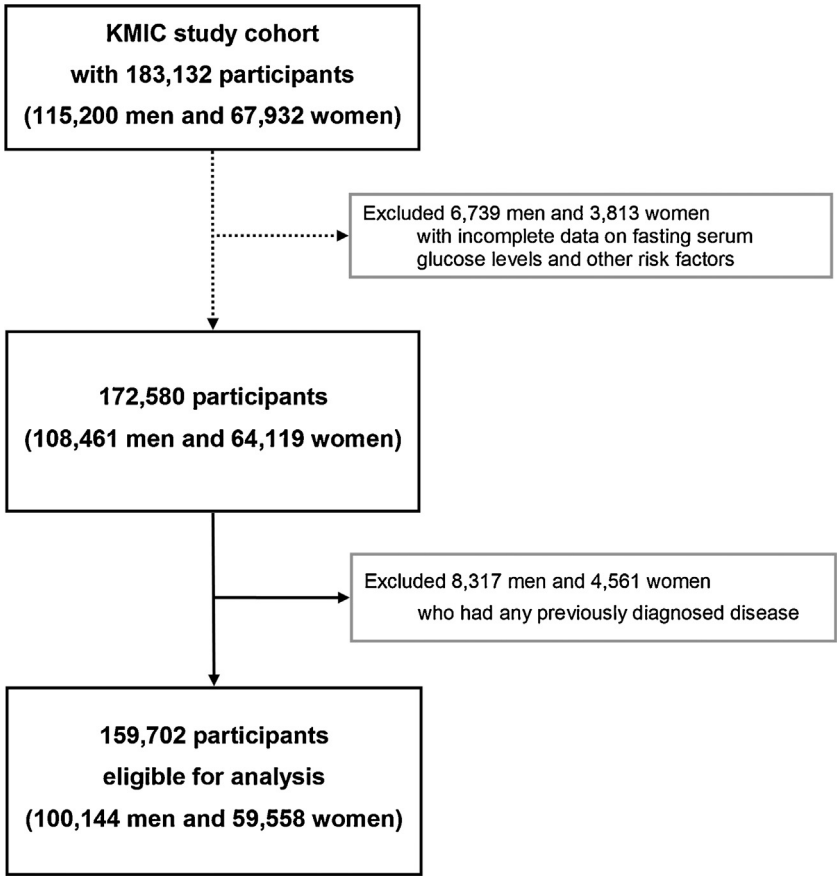

Fig. 1. Flow chart of participants' selection. KMIC, Korea Medical Insurance Corporation.

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