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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

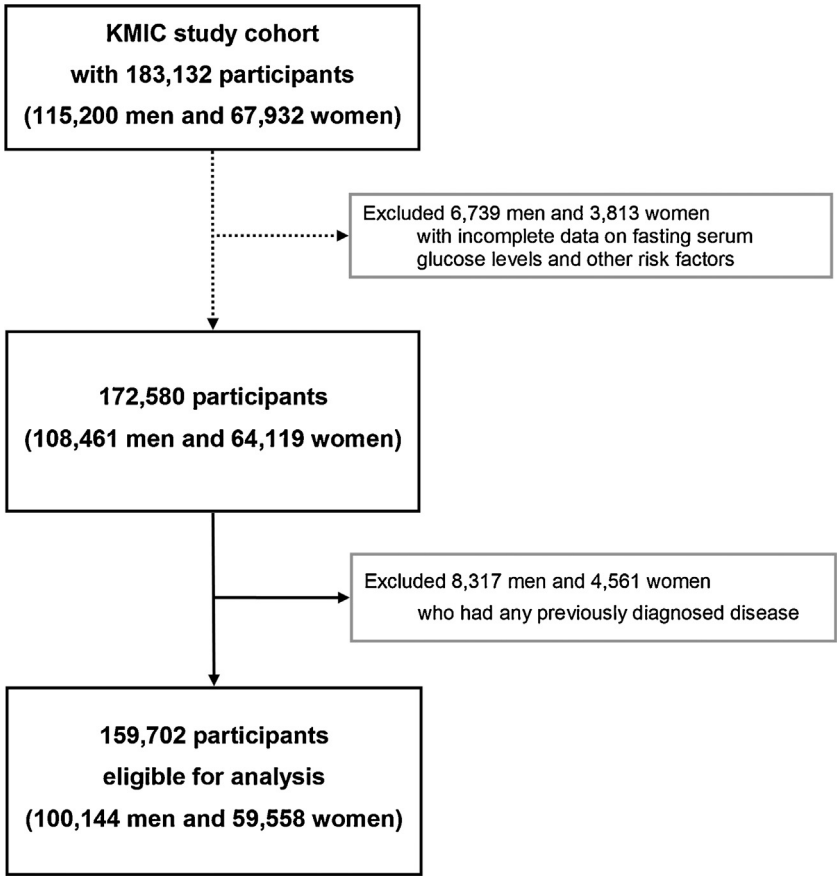

Fig. 1. Flow chart of participants' selection. KMIC, Korea Medical Insurance Corporation.

statistically significant, and all analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA) and R version 3.4.0 (R Development Core Team, Austria).

Results

During the 11-year follow-up, 2503 men and 656 women developed CHD. The general characteristics of the study participants are presented in Table 1 according to the baseline fasting serum glucose categories. The increasing categories of the fasting serum glucose level were associated with a higher mean age, body mass index, total cholesterol level, and systolic and diastolic blood pressures in both sexes.

Table 2 presents the number of events from CHD for 100,144 men and 59,558 women. During the 11-year follow-up, a total of 3159 (2503 in men and 656 in women) CHD events occurred. The crude mortality rates for CHD were 27.6 per 100,000 person-years in men and 5.5 per 100,000 person-years in women.

Fig. 2 shows the Kaplan–Meier curve for survival from CHD according to baseline fasting glucose levels and sex. Among participants with a normal fasting glucose level and IFG level of 100–125 mg/dL, the survival probability from CHD was higher in women than in men (p for log-rank test <0.001). However, among participants with a diabetic fasting serum glucose level, the difference in the survival from CHD between men and women was not significant ($p = 0.934$).

Table 3 shows the HRs for CHD according to baseline fasting serum glucose levels. The HRs in men increased at a diabetic fasting serum glucose level (≥126 mg/dL) compared to a normal fasting serum glucose level (<100 mg/dL), whereas the HRs in women increased from an IFG level ≥110 mg/dL. Compared to men with normal fasting glucose level <100 mg/dL, the multivariable-adjusted HRs in men with IFG level of 110–125 mg/dL and men with diabetic fasting glucose level ≥126 mg/dL were 1.07 (95% CI 0.92–1.25) and 1.92 (95% CI 1.70–2.16), respectively. Among women, the multivariable-adjusted HR in women with IFG level of 110–125 mg/dL and women with diabetic fasting glucose level ≥126 mg/dL were 1.62 (95% CI 1.11–2.36) and 2.85 (95% CI 2.11–3.85), respectively. The sex difference in HRs for CHD was statistically significant (p for interaction with sex = 0.021, multivariable-adjusted model).

We also demonstrated differences in the mean levels of baseline risk factors between men with and without diabetes compared to women with and without diabetes (Supplementary Table 1). Differences in the baseline levels of the body mass index, systolic blood pressure, and total cholesterol among participants with and without diabetes were significantly greater in women than in men.

Discussion

This was a longitudinal study with a large sample size and long-term follow-up period, which enabled us to investigate the

Table 1
Baseline characteristics of 100,144 men and 59,558 women.

	Fasting serum glucose level, mg/dL				
	<100	100–109	110–125	≥126	p for trend
Men					
N (%)	80,167 (80.1)	11,865 (11.8)	4815 (4.8)	3297 (3.3)	
Fasting serum glucose, mg/dL	86.2 ± 7.7	103.8 ± 2.8	115.5 ± 4.3	161.5 ± 38.1	<0.001
Age, years	44.5 ± 6.6	45.7 ± 6.5	46.7 ± 6.6	48.0 ± 6.4	<0.001
Body mass index, kg/m^2	23.3 ± 2.4	23.8 ± 2.5	23.9 ± 2.5	24.2 ± 2.5	<0.001
Total cholesterol, mg/dL	192.4 ± 31.9	198.2 ± 34.1	200.2 ± 35.6	206.6 ± 40.7	<0.001
Systolic blood pressure, mmHg	124.1 ± 13.3	128.6 ± 14.7	131.5 ± 15.5	132.2 ± 16.2	<0.001
Diastolic blood pressure, mmHg	81.3 ± 9.2	84.1 ± 9.7	85.6 ± 10.0	86.1 ± 10.2	<0.001
Current smoker (%)	44,701 (55.8)	6593 (55.6)	2661 (55.3)	1791 (54.3)	0.382
Women					
N (%)	55,222 (92.7)	3045 (5.1)	810 (1.4)	481 (0.8)	
Fasting serum glucose, mg/dL	84.0 ± 7.5	103.5 ± 2.7	115.0 ± 4.2	157.9 ± 35.2	<0.001
Age, years	42.2 ± 6.1	44.3 ± 6.7	45.7 ± 6.7	46.7 ± 6.8	<0.001
Body mass index, kg/m^2	22.2 ± 2.4	23.1 ± 2.7	23.8 ± 2.7	24.2 ± 3.0	<0.001
Total cholesterol, mg/dL	188.1 ± 31.7	199.2 ± 35.1	206.3 ± 38.1	214.8 ± 43.1	<0.001
Systolic blood pressure, mmHg	115.6 ± 12.0	121.3 ± 14.5	125.1 ± 16.4	127.5 ± 17.4	<0.001
Diastolic blood pressure, mmHg	75.2 ± 8.8	78.8 ± 9.7	81.2 ± 10.3	82.7 ± 11.0	<0.001
Current smoker (%)	172 (0.3)	16 (0.5)	1 (0.1)	4 (0.8)	0.030

Values are expressed as mean ± standard deviation or number (%).

Table 2
Total CHD, fatal and, non-fatal CHD during the 11-year follow-up.

		Men						Women					
		All events		Fatal events		Non-fatal events		All events		Fatal events		Non-fatal events	
	ICD-10 codes	No. of events	Crude rates/100,000 p-y	No. of events	Crude rates/100,000 p-y	No. of events	Crude rates/100,000 p-y	No. of events	Crude rates/100,000 p-y	No. of events	Crude rates/100,000 p-y	No. of events	Crude rates/100,000 p-y
CHD	I20-I25	2503	234.7	297	27.6	2206	206.8	656	101.1	36	5.5	620	95.6
Acute MI	I21	870	81.6	261	24.3	609	57.1	96	14.8	30	4.6	66	10.2
Angina pectoris	I20	1274	119.4	20	1.8	1254	117.6	444	68.4	5	0.8	439	67.7
Other CHD	I22-I25	359	33.7	16	1.5	343	32.2	116	17.9	1	0.1	115	17.7

ICD, international classification of diseases; p-y, person-years; CHD, coronary heart disease; MI, myocardial infarction.

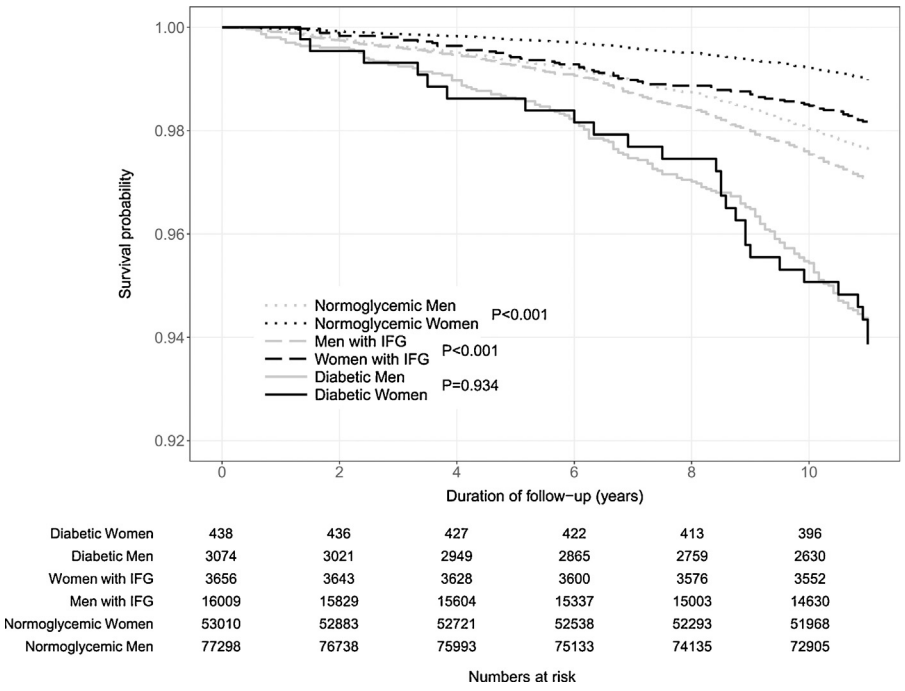

Fig. 2. Survival probability from coronary heart disease events according to baseline fasting serum glucose levels and sex during the 11-year follow-up. Normoglycemic, baseline fasting serum glucose level <100 mg/dL; impaired fasting glucose (IFG), 100 mg/dL ≤ baseline fasting serum glucose level <126 mg/dL; diabetic, baseline fasting serum glucose level ≥126 mg/dL. Values for *p* denote the results of the log-rank test for sex differences for each fasting serum glucose level.

relationship between several fasting serum glucose levels and the incident risk of CHD in men and women. The relative risks of CHD in women increased from a prediabetic range (≥110 mg/dL), whereas those in men increased at a diabetic range (≥126 mg/dL). Women had higher HRs for CHD than men, and differences in HRs between men and women were statistically significant. Previous studies have reported that the relative risk of cardiovascular disease increases more in women than in men [9,10,19,20]. Our findings are in agreement with the results of previous studies that showed that the diabetic range of fasting serum glucose was associated with a more significant CHD risk in women than in men after adjusting for major cardiovascular risk factors.

Moreover, the interesting aspect of our study is that the prediabetic range of fasting serum glucose was associated with CHD only in women. Few studies have investigated the sex difference on the CHD risk in association with hyperglycemia lower than the diabetic range. The Framingham study reported that the incidence of cardiovascular disease was positively associated with casual blood glucose levels in nondiabetic women, whereas such an association was not observed in men [21]. A prospective study reported that asymptomatic hyperglycemia, defined as the top 5% of the casual blood glucose distribution (≥126 mg/dL), was a significant risk factor for mortality due to CHD in women but not in men [22]. The Hoorn study, which examined the association between the continuous blood glucose concentration and cardiovascular disease mortality, showed no clear, consistent differences between men and women [23]. Differences in the glucose assay methods, endpoint measurements, and small number of events in the previous studies may have contributed to these inconsistencies.

The reason why hyperglycemia has a greater relative risk for CHD in women than in men is unclear. Several mechanisms may explain why hyperglycemia has a greater adverse effect in women than in men. Hyperglycemia may have a stronger additive or synergistic effect on overweight, hypertension, hypercholesterolemia, and smoking in women than in men. A previous study reported that the increased risk of cardiovascular disease in diabetic women can be mediated in part by the loss of a woman's usually favorable lipoprotein profile in the presence of diabetes [24]. Our study's results corroborate these explanations, because they showed that differences in the baseline levels of the body mass index, systolic blood pressure, and total cholesterol level among participants with and without diabetes were significantly greater in women than in men (Supplementary Table 1). These findings were also consistent with those of a previous study, which reported that differences in the levels of blood pressure and lipids between individuals with and without diabetes were significantly

Table 3
Hazard ratios for coronary heart disease according to baseline fasting serum glucose levels.

Baseline fasting serum glucose level (mg/dL)	Men			Women		
	Number of events	Age-adjusted HR (95% CI)	Multivariable-adjusted HR[a] (95% CI)	Number of events	Age-adjusted HR (95% CI)	Multivariable-adjusted HR[a] (95% CI)
<100	1850	1.00	1.00	562	1.00	1.00
100–109	317	1.16 (1.04–1.29)	1.00 (0.90–1.12)	49	1.36 (1.04–1.77)	1.17 (0.90–1.52)
110–125	161	1.30 (1.12–1.51)	1.07 (0.92–1.25)	19	2.05 (1.41–2.98)	1.62 (1.11–2.36)
≥126	175	2.38 (2.12–2.68)	1.92 (1.70–2.16)	26	3.61 (2.68–4.86)	2.85 (2.11–3.85)

p-value for interaction with sex = 0.021, multivariable-adjusted model. CI, confidence interval; HR, hazard ratio.
[a] Adjusted for age, body mass index, blood pressure, total cholesterol level, and cigarette smoking status.

greater in women than in men [25]. This would potentially explain why the attenuation of HRs for CHD was considerably greater in women than in men after multivariable adjustment. The sex difference in the CHD risk related to the fasting serum glucose level may be mediated in part by differences in the levels of other cardiovascular risk factors [26,27].

Another possible explanation for the sex difference in the effect of diabetes on the CHD risk is the persistently more favorable survival rate for women without diabetes than for men without diabetes [20]. In the present study, there was a marked male predominance in the CHD incidence among participants with nondiabetic glucose levels, whereas the gap between men and women was almost eliminated among participants with diabetic fasting glucose levels (Fig. 1). In addition, previous studies have indicated that the greater risk of CHD associated with diabetes in women may indicate a treatment bias that favors men [28–32]. Men with diabetes or a history of cardiovascular disease are more likely to receive aspirin, statins, or antihypertensive drugs than women do. The excess relative risk of CHD in women with diabetes may be due to the more aggressive treatment of cardiovascular risk factors in men with diabetes than in women with diabetes.

Several possible limitations of the present study should be considered. First, there was no objective information on anti-diabetic medications for this study population. Thus, individuals who indicated that they had any previously diagnosed disease were excluded. Second, an oral glucose tolerance test was not performed in the current study, and insulin levels were not measured. Although the 2-hour glucose tolerance test is a better predictor for cardiovascular mortality than the fasting glucose test [33], the fasting serum glucose test is recommended for use in mass screening, as it is easier and faster to perform, more convenient, and less expensive. Third, the accuracy of diagnoses from health insurance claims data and death certificates may be considered. A previous study analyzing validity of diagnosis in Korean national health insurance claims data has reported that the accuracy for diagnosing acute MI was more than 70% [34]. Fourth, the present study was performed in only middle-aged Korean men and women, which may limit the generalizability of our results to other populations.

In conclusion, women had a higher hazard ratio of CHD associated with fasting serum glucose than men. The stronger effect of fasting serum glucose levels on the CHD risk in women was significant from a prediabetic range ($\geq$110 mg/dL). These findings suggest that more careful glycemic control may be needed in women with hyperglycemia to prevent CHD.

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Conflict of interest

The authors declare that they have no conflict of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:10.1016/j.jjcc.2017.07.013.

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