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Influence of sex on the incidence of potential coronary artery disease and long-term outcomes in asymptomatic patients with diabetes mellitus

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ABSTRACT

Background: Diabetic patients often have coronary artery disease (CAD) without symptoms. It is known that females tend to have silent or less chest pain and worse prognoses when they develop acute coronary syndrome. Thus, sex differences may impact long-term outcomes in diabetes mellitus (DM) patients with silent myocardial ischemia (SMI). The present study aimed to assess the influence of sex on long-term outcomes in DM patients with SMI.

Methods: A total of 461 consecutive asymptomatic and self-sufficient DM patients seen at our hospital from 2011 to 2017 were prospectively reviewed. Patients underwent an ergometer exercise test. When the exercise test was positive or the patient could not achieve 90% of their target heart rate, coronary angiography was performed. The primary endpoint was major adverse cardiac and cerebrovascular events (MACCEs), including death, non-fatal myocardial infarction, and stroke.

Results: SMI was diagnosed in 81 patients. The median follow-up duration from diagnosis was 35 (15–57) months. The incidence of SMI was similar in females and males [34/170 (20%) vs. 47/291 (16.2%), $p = 0.36$]. Enrolled patients were divided into four groups according to sex and the presence/absence of SMI. Female patients with SMI showed worse clinical outcomes. After adjustment for age and coronary risk factors, female SMI was independently associated with MACCEs [hazard ratio 2.59, 95% confidence interval 1.07–5.68, $p = 0.024$], while male SMI was not.

Conclusions: Female SMI was associated with worse long-term outcomes in DM patients. Early diagnosis of potential SMI and appropriate care are required in female DM patients. (UMIN000038340).

1. Introduction

Coronary artery disease (CAD) is a major cause of morbidity and mortality in diabetic patients. Diabetes mellitus (DM) patients often have obstructive CAD without symptoms, and this is called silent myocardial ischemia (SMI). It has been shown that 10–50% of patients with diabetes have SMI [1–4]. Aggressive screening for CAD in asymptomatic patients is not recommended in guidelines [5–7]; however, CAD is implicated in 60–80% of deaths in diabetic patients and is 2–4 times more common in diabetic patients than in the general population [8]. To improve clinical outcomes, the high-risk patient group among asymptomatic DM patients should be clarified.

It is known that females are more likely to have silent or less chest pain when they develop acute coronary syndrome (ACS) [9]. Furthermore, patients without chest pain or discomfort tend to present later and have worse mortality rates compared with those presenting with more typical symptoms of ACS [10]. Nearly two-thirds of deaths from heart attacks in females occur among those who have no history of chest pain [11]. Thus, female patients with DM may also tend not to have symptoms, even if they have critical CAD. To make matters worse, female may be at risk for coronary microvascular disease. It might be associated with an increased risk of cardiovascular events. Female have smaller and stiffer hearts and cardiac vessels, suffering a greater extent of atherosclerosis and endothelial dysfunction. The etiology of coronary atherosclerosis in female is different compared to male. Consequently, females may have worse clinical outcomes than asymptomatic male DM patients with SMI. The present study aimed to determine the influence of sex on the incidence of

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potential CAD and long-term outcomes in asymptomatic patients with DM.

2. Methods

2.1. Study population

Outpatients with DM who visited the diabetes department at the Fuji Hospital between July 2011 and August 2017 were prospectively enrolled. All patients were asymptomatic and self-sufficient in daily life. Patients with DM were identified as those requiring treatment with nutritional modification, oral medications, and/or insulin. The diagnosis of DM was based on the American Diabetes Association (ADA) criteria [12].

2.2. Study design and protocol

All patients underwent a cycle ergometer exercise test. A 12-lead electrocardiogram (ECG) was used and continuously monitored during the test, and blood pressure was recorded at rest and every 1 min during exercise and recovery. The stress test was considered positive when a horizontal or down-sloping ST-segment with a depression >1 mm occurred [5].

The test was considered inconclusive if the patient failed to reach 90% of the target heart rate calculated according to his or her age. Coronary angiography (CAG) was performed when the exercise test was positive or inconclusive. A significant lesion was defined as stenosis of more than 50%. SMI was diagnosed based on the exercise stress test results and detection of a significant lesion during the CAG. SMI patients were treated with medications and/or revascularization with percutaneous coronary intervention (PCI) or coronary artery bypass grafts (CABG). The treatment strategy was left to the discretion of the heart team, which consisted of two interventional cardiologists, three general cardiologists, and two surgeons.

The registry was conducted in accordance with the principles of the Helsinki Declaration. The study protocol was approved by the institutional review board. Written informed consent was obtained from each patient.

2.3. Definition and data collection

All patients underwent a laboratory analysis, chest radiogram, 12-lead ECG, and cardiac ultrasonography. The body mass index (BMI), hemoglobin A1c (HbA1c) levels, estimated glomerular filtration rate (eGFR), and brain natriuretic peptide (BNP) levels were also measured. The disease duration of DM was defined as the time of first diagnosis of DM by a laboratory analysis including a blood sugar test, HbA1c level test, and/or an oral glucose tolerance test, up to enrollment in the study. Diabetic retinopathy was defined as the appearance of progressive dysfunction of the retinal vasculature secondary to chronic hyperglycemia. A screening examination was performed on every patient by an ophthalmologist. Exclusion criteria included inability to perform the ergometer exercise test, typical angina, and chest pain. The primary endpoint was major adverse cardiac and cerebrovascular events (MACCEs), including death, non-fatal myocardial infarction, and stroke.

2.4. Statistical analysis

Quantitative variables were presented as mean ± standard deviation, and categorical variables were presented as percentages. Continuous variables were compared with the Student *t* test or the Mann-Whitney *U* test, and a Fisher's extract test or a chi-square test was used for categorical data, as appropriate. Univariable and multivariable Cox's proportional hazards regression models were used to identify significant predictors of long-term MACCEs. The variables with a p-value < 0.1 on the univariate analysis were entered into the multivariable analysis. Multivariable analysis was performed using stepwise selection methods. All p-values < 0.05 were considered statistically significant. Statistical analyses were performed using JMP Pro version 14 software (SAS Institute Inc., Cary, North Carolina, USA).

3. Results

A total of 461 consecutive outpatients with DM were enrolled (291 men and 170 women). The mean age was 61 ± 15 years. The average disease duration was 7.9 ± 8.4 years. Fig. 1 shows the flowchart of the enrolled patients. A total of 134 patients showed a positive ECG result or were unable to complete the exercise test due to fatigue or dyspnea. A total of 81 patients were diagnosed with SMI based on the exercise stress test and CAG, as explained in the Methods. Thirty-eight voluntary patients underwent CAG despite a negative exercise test. None of them had a significant coronary lesion.

Clinical baseline characteristics according to sex are shown in Table 1. There was no significant difference in age. Compared to female patients, male patients were more likely to be smokers, to have hyperuricemia, lower estimated glomerular filtration rates, and lower left ventricular ejection fractions. The incidence of SMI was similar in females and males.

The baseline clinical characteristics of SMI and non-SMI patients were also compared (see Supplemental Table 1). SMI patients were older than non-SMI patients. The mean duration of diabetic disease was significantly longer in SMI patients than in non-SMI patients. Compared to patients without SMI, those with SMI showed a greater rate of insulin use, chronic kidney disease, retinopathy, and hypertension, as well as higher BNP values and lower left ventricular ejection fractions.

Enrolled patients were divided into four groups (female SMI, male SMI, female non-SMI, and male non-SMI) as shown in Fig. 1. Baseline characteristics of the SMI patients according to sex are summarized in Supplemental Table 2. There were no significant differences in age between the groups. Female patients with SMI had a higher rate of insulin use and higher HbA1c. Male patients with SMI showed a greater prevalence of hyperuricemia, and smoking.

The average SYNTAX score in 81 diabetic patients with SMI was 13.6 ± 9.3. Forty-one SMI patients were treated with percutaneous coronary intervention and four patients were treated with bypass graft surgery after diagnosis. Thirty-six patients were treated with medication alone.

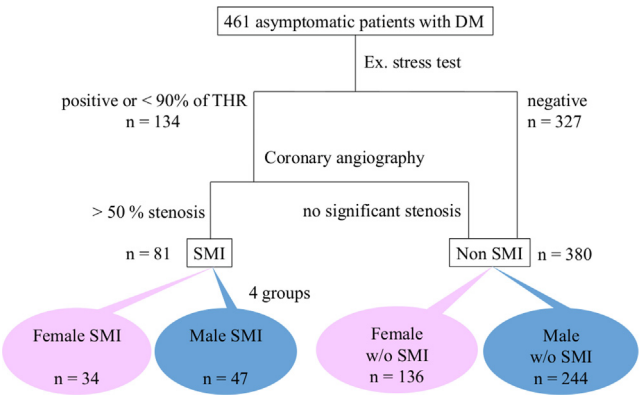

Fig. 1. Flowchart. The flowchart of the study is shown. DM, diabetes mellitus; SMI, silent myocardial ischemia; THR, target heart rate.

Table 1
Baseline clinical characteristics of diabetic patients according to sex.

Variables	Female (n = 170)	Male (n = 291)	*p* value
Age (years)	62.3 ± 14.5	60.1 ± 14.8	0.10
Body mass index (kg/m^2)	24.9 ± 5.8	25.4 ± 5.1	0.46
Duration since diagnosis of DM (months)	7.9 ± 8.1	7.9 ± 8.5	0.96
Insulin use	41 (24.1)	63 (21.7)	0.55
Retinopathy	43 (25.3)	56 (19.2)	0.086
HbA1c (%)	8.7 ± 2.5	8.6 ± 2.6	0.88
eGFR (ml/min/1.73 m^2)	85.1 ± 31.8	76.7 ± 24.3	0.003*
BNP (pg/ml)	34.3 ± 57.3	30.6 ± 43.2	0.55
Left ventricular ejection fraction (%)	72.7 ± 7.3	69.1 ± 8.6	<0.001*
SMI	34 (20.0)	47 (16.2)	0.36
Medical history			
Hypertension	94 (55.3)	158 (54.3)	0.84
Dyslipidemia	85 (50.0)	160 (55.0)	0.30
Hyperuricemia	9 (5.3)	46 (15.8)	<0.001*
Chronic kidney disease (>stage 3a)	7 (4.1)	24 (8.2)	0.064
Smoking	52 (30.6)	222 (76.3)	<0.001*
Prior myocardial infarction	7 (4.1)	27 (9.3)	0.025*
Statin use	57 (33.5)	75 (25.8)	0.082

Data are expressed as n (%) or mean ± standard deviation (SD).
DM, diabetes mellitus; HbA1c, hemoglobin A1c; eGFR, estimated glomerular filtration rate, BNP, brain natriuretic peptide; SMI, silent myocardial ischemia.
* Statistically significant difference.

The duration from enrollment to the final follow-up was 15–57 months (median 35 months) in the overall cohort. There were 12 deaths, three cases of non-fatal myocardial infarction, and six stroke events during the follow-up period. In univariable Cox regression analyses for MACCEs, the value of HbA1c was not independently associated with MACCEs [hazard ratio 1.08, 95% confidence interval 0.96–1.20, p = 0.15]. Female patients with SMI had worse clinical outcomes than female non-SMI patients, while male SMI patients and non-SMI patients had a similar prognosis (Fig. 2). After adjustment for age and coronary risk factors, female SMI was independently associated with MACCEs [hazard ratio (HR) 2.59, 95% confidence interval (CI) 1.07–5.68, p = 0.024], while male SMI was not (Table 2).

4. Discussion

The present study investigated the impact of sex on the incidence of potential CAD and the long-term outcomes in asymptomatic SMI patients with DM. The major findings were as follows: [1] the incidence of SMI was similar in males and females with DM [2], the female patients with SMI had worse clinical outcomes compared to female patients without SMI, while male patients with SMI and male patients without SMI showed a similar prognosis [3], female sex and SMI were independently associated with worse clinical outcomes in diabetic patients.

SMI was diagnosed in 17.5% of DM patients in the present study. In published reports, the prevalence of SMI varies widely, from <10% to 50% [1,2] depending on the patient population. In recent studies, the incidence of SMI is reported to be 20–35% [3,4]. In most of the previous studies [13,14], patients were screened for SMI using myocardial perfusion scintigraphy or an exercise stress test alone. The strength of the present study was that all patients with a positive or inconclusive finding on the exercise stress test underwent CAG with catheterization, as shown in Fig. 1.

Myocardial ischemia is often asymptomatic in patients with DM and it is frequently at an advanced stage when the patient presents at the clinic. Even in populations with normal findings on ECG and echocardiography, elevated event rates are still observed in diabetic patients when compared to non-diabetic individuals. In spite of the high prevalence of hypertension, dyslipidemia, smoking habits and previous myocardial infarction, LVEF was higher than expected values in asymptomatic DM patients in the present study. Direct visualization of the coronary arteries is preferred because patients with diabetes frequently have diffuse, multivessel CAD.

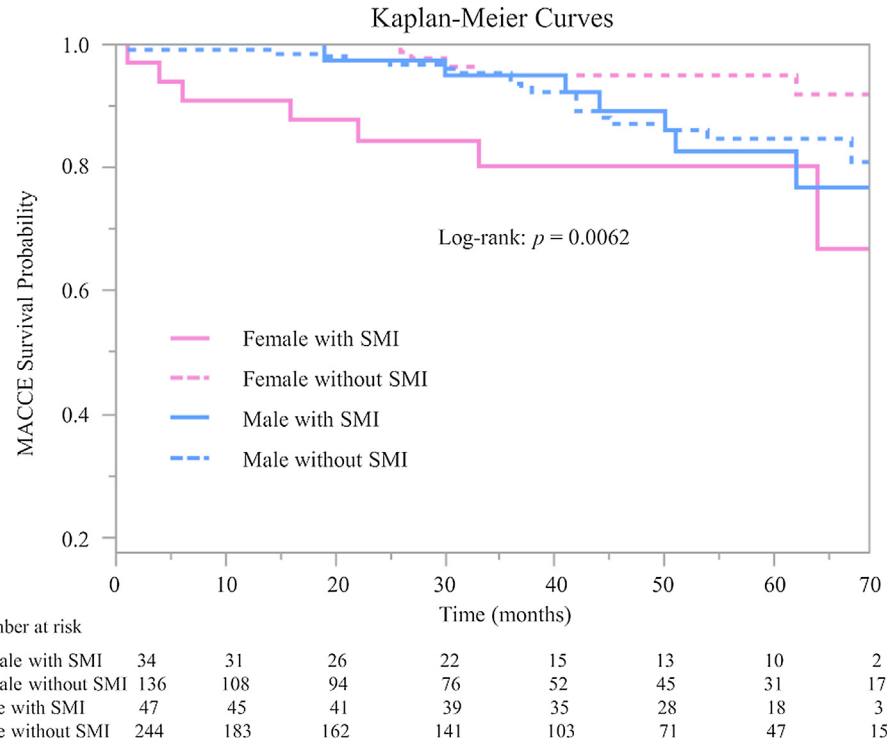

Fig. 2. Kaplan-Meier curves comparing MACCE survival probability based on sex and SMI. Females with SMI show the worst outcomes compared to the other groups. MACCE, major adverse cardiac and cerebrovascular events, including death, non-fatal myocardial infarction, and stroke; SMI, silent myocardial ischemia.

Table 2
Univariable and multivariable Cox regression analyses for MACCE in DM.

Variables	Univariable				Multivariable			
	Hazard Ratio	95% Confidence Interval		*p* value	Hazard Ratio	95% Confidence Interval		*p* value
Age (years)	1.07	1.04	1.11	<0.001*	1.07	1.03	1.10	<0.001*
Male without SMI	1.03	0.55	1.93	0.919				
Female with SMI	3.07	1.31	6.35	0.011*	2.59	1.07	5.68	0.024*
Female without SMI	0.35	0.12	0.81	0.013*				
Male with SMI	1.27	0.52	2.72	0.572				
Hypertension	1.41	0.74	2.76	0.296				
Dyslipidemia	0.80	0.43	1.52	0.507				
Hyperuricemia	1.33	0.54	2.85	0.498				
CKD (>3a)	5.11	2.36	10.1	<0.001*	3.58	1.60	7.50	0.001*
Smoking	1.17	0.61	2.34	0.634				

MACCE, major adverse cardiac and cerebrovascular event; SMI, silent myocardial ischemia; CKD, chronic kidney disease.
* Statistically significant difference.

There could be several explanations for the different patterns of symptoms in patients with DM, including different thresholds of pain sensitivity, psychological denial, or the presence of autonomic neuropathy leading to sensory denervation [15]. Autonomic neuropathy is a common feature of diabetes, and abnormalities of the autonomic nerve fibers have been demonstrated histologically in DM patients who died after painless myocardial infarction. Furthermore, DM patients with SMI show evidence of diffuse abnormalities on m-iodobezylguanidine imaging, suggesting that abnormalities of pain perception may be linked to sympathetic denervation [16]. In previous reports, the main factors predictive of SMI in the general population are hypertension, history of cardiovascular diseases, and diabetes duration [17]. In the diabetic population, other predictors such as retinopathy and established coronary or peripheral artery disease have also been reported [18]. These predictors were consistent with the findings of the present study. However, previous studies did not focus on the influence of sex on the incidence of SMI in diabetic patients. The present study clarified that female sex was not associated with the incidence of SMI in diabetic patients.

The mechanism behind the influence of sex on of long-term outcomes in diabetic patients with SMI should be discussed. The female patients with SMI had worse clinical outcomes compared to female patients without SMI, while male patients with and without SMI showed a similar prognosis. Kaplan-Meier curves showed that the prognosis in female SMI patients was worse than in male SMI and male non-SMI patients. Interestingly, female non-SMI patients had better clinical outcomes than any other group. There are several explanations for these findings. Several studies [9] have provided data on the possible differences in ACS presentation according to sex. Studies from large cohorts suggest that approximately one-third of patients present without chest pain or discomfort [11]. The absence of chest pain or discomfort with ACS is more common in women than in men [9]. Increased age is another factor associated with asymptomatic ACS. Female, elderly DM patients with SMI may not experience typical chest pain or discomfort when they suffer from ACS. The delay in diagnosis due to the absence of symptoms may worsen the outcomes. Thus, threshold of pain sensitivity is one possible mechanism behind the sex difference in long-term outcomes. Another explanation is physical activity. Previous research [19] has shown that females with DM engage in less leisure time physical activity than males. Low levels of physical activity may progress atherosclerosis, especially in SMI patients.

Based on the findings from the present study, more aggressive screening for SMI is needed in asymptomatic female DM patients. They should be examined using minimally invasive test such as exercise test first. If the result is positive or not determinable, coronary angiography should be performed to diagnose SMI. High-risk groups, such as females with SMI, should be examined for coronary ischemia regularly because we know that they may not experience symptoms, even when they have fatal heart ischemia.

There were several limitations to the present study. Firstly, our study was conducted in a single center and relatively small number of patients. The number of cardiovascular events was small because the study population consisted of outpatients who were asymptomatic, self-sufficient in daily life, and without frailty. In this perspective, the present study should be considered a provocative pilot study to be confirmed in larger patient dataset or multicenter collaboration. Patients with a negative result on the exercise test did not have to undergo CAG under our protocol. However, we performed CAG on 38 patients despite a negative exercise test result and none of them had a significant coronary stenotic lesion. Although the patients who had positive ECG stress test were scheduled for coronary angiography in the present study, the generally recommended clinical practice in this patient subset is cardiac perfusion or coronary CT imaging. Thus, the application of a more conservative diagnostic algorithm could have obtained different results. The presence of diabetic ketoacidosis or hyperglycemic hyperosmolar state might impact on the cardiovascular events. However, the information of such diabetic state was not available in the present study. Further research is needed to clarify the sex differences regarding diabetic patients with SMI.

In conclusion, long-term outcomes were worse in asymptomatic SMI patients with DM. Therefore, female DM patients should be examined for potential CAD and more carefully in our daily practice.

CRediT authorship contribution statement

Chisato Sato: Investigation, Writing - original draft. **Kohei Wakabayashi:** Formal analysis, Investigation, Methodology, Project administration, Supervision, Writing - review & editing. **Naoko Ikeda:** Investigation, Writing - review & editing. **Yuki Honda:** Investigation, Writing - review & editing. **Ken Sato:** Investigation, Writing - review & editing. **Toshiaki Suzuki:** Investigation, Writing - review & editing. **Keita Shibata:** Investigation, Writing - review & editing. **Kaoru Tanno:** Writing - review & editing.

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Disclosures

The authors have no conflicts of interest to disclose.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2020.100504.

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