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High-sensitivity C-reactive protein and silent myocardial ischemia in Chinese with type 2 diabetes mellitus

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Abstract

Coronary artery disease (CAD) is a major cause of morbidity and mortality in patients with type 2 diabetes mellitus. When diabetes exists in patients with established CAD, absolute risk for future events is very high. Diabetic patients often have severe, yet asymptomatic, CAD. Although high-sensitivity C-reactive protein (hsCRP) is a strong independent risk factor for cardiovascular events, there is an unclear association between it and silent myocardial ischemia in diabetic patients. In this study, we assess the relationship between hsCRP and silent myocardial ischemia in Chinese with type 2 diabetes mellitus. We designed a cross-sectional study with 225 asymptomatic diabetic patients having no known CAD. Ischemia was assessed by myocardial perfusion imaging. A total of 109 patients (48.4%) was found to have silent myocardial ischemia. Logistic regression analysis revealed age (odds ratio = 4.01, $P = .002$) (95% confidence interval, 1.98-7.44) and hsCRP (odds ratio = 2.58, $P = .005$) (95% confidence interval, 1.33-5.01) to be associated with greater risk of silent myocardial ischemia. Using the American Diabetes Association screening guidelines to evaluate risk, we found silent myocardial ischemia to be equally distributed between diabetic patients with 2 or more cardiac risk factors and those with less than 2 risk factors. Twenty-seven (24.8%) patients with silent myocardial ischemia were missed when the American Diabetes Association guidelines were used alone. High-sensitivity C-reactive protein was associated with silent myocardial ischemia in our study. High-sensitivity C-reactive protein might help detect silent myocardial ischemia in diabetic Chinese who may need aggressive treatment to reduce future CAD morbidity and mortality in Taiwan.

1. Introduction

Coronary artery disease (CAD) is a major cause of death in diabetic patients [1]. Patients with diabetes have more severe CAD and higher incidence of heart failure, myocardial infarction, and cardiac death than those who do not have the disease [2,3]. In diabetes, CAD is often asymptomatic, making early detection very difficult [4,5]. This silent CAD has been associated with increased risk of death [6,7].

Early detection of silent CAD in diabetic patients can be expected to reduce mortality and morbidity of cardiovascular events. The American Diabetes Association (ADA) consensus guidelines [5] recommend performing stress screening for CAD in asymptomatic patients with 2 or more additional CAD risk factors. Despite these recommendations, one well-known study, The Detection of Ischemia in Asymptomatic Diabetics (DIAD), found no association between cardiac risk factors and silent myocardial ischemia in diabetic patients and that selecting only patients who met the ADA guidelines would have failed to identify 41% of patients with silent myocardial ischemia [8].

High-sensitivity C-reactive protein (hsCRP), a sensitive marker for systemic inflammation, has consistently been

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shown to predict incident myocardial infarction, stroke, and cardiovascular death at all levels of the Framingham Risk Score [9]. On the basis of published data from large prospective cohorts [10,11], the Centers for Disease Control and Prevention and the American Heart Association (CDC/AHA) in January of 2003 issued the first set of clinical guidelines for hsCRP as a part of global risk prediction and suggested that the levels of hsCRP of less than 1, 1 to less than 3, and at least 3 mg/L be used to represent low, moderate, and high vascular risk [12]. However, Lloyd-Jones et al [13] recently found no definitive evidence that CRP added substantial predictive value above that provided by risk estimation using traditional risk factors for CAD. The current understanding is largely derived from studies of white persons of European origin. High-sensitivity C-reactive protein levels vary widely among different ethnic subjects and have been reported to be significantly lower in Chinese than in white persons [14]. Therefore, it may be reasonable to assume that the use of hsCRP to define CAD risk might differ among diverse populations. Until now, few studies have investigated the association between hsCRP and CAD in Chinese. In this study, we assessed the relationship between hsCRP and silent myocardial ischemia in asymptomatic Chinese with type 2 diabetes mellitus.

2. Subjects and methods

2.1. Patients

For this study, 225 patients of Han Chinese origin with type 2 diabetes mellitus were recruited at the diabetic clinic in the Metabolism Division at Kaohsiung Medical University Hospital. The hospital's Human Research Ethics Committee approved the design, and informed consent was obtained from each participant.

Patients with type 2 diabetes mellitus with no symptoms of CAD were chosen. The ADA criteria were used to diagnose diabetes [4]. Patients were excluded if they had (1) angina pectoris or equivalent symptoms; (2) a history of myocardial infarction, heart failure, or coronary revascularization; (3) electrocardiographic evidence of Q-wave myocardial infarction, or ischemic ST-segment or T-wave changes; (4) previous stress tests or coronary angiographies during the 5 years leading up to enrollment into this study; (5) a recent history of acute infections; (6) chronic inflammation disease; (7) peripheral arterial disease; (8) a history of stroke; or (9) serum hsCRP level of at least 10 mg/L. Individual interviews were held with each patient to obtain information about his or her disease and smoking history. Each patient was evaluated using the Rose questionnaire to confirm the absence of angina. Patients received a complete physical examination and an assessment of the presence and extent of macro- or microvascular complications. Routine blood and urine analyses were done at the same time that studies were done to measure hsCRP levels. Measurements were taken to calculate the body mass index (BMI) and waist-to-hip ratio.

2.2. Study design

Patients were categorized based on the presence of cardiovascular risk factors using current ADA consensus guidelines [5]. These included diabetes and 2 or more of the following: (1) total cholesterol of at least 240 mg/dL, low-density lipoprotein cholesterol of at least 160 mg/dL, or high-density lipoprotein cholesterol (HDL-C) less than 35 mg/dL; (2) blood pressure greater than 140/90 mm Hg; (3) smoking; (4) family history of premature CAD; or (5) micro- or macroalbuminuria. Patients on lipid-lowering or antihypertensive treatment at the time they entered the study were considered to have those risk factors. *Metabolic syndrome* was defined according to the National Cholesterol Education Program definition [15], with a modification in the definition of central obesity (waist circumference: male, >90 cm; female, >80 cm).

Thallium-201 myocardial perfusion imaging (MPI) [16] was performed in all patients. Pharmacologic vasodilator stress was performed by the intravenous infusion of 0.56 mg/kg of dipyridamole over 4 minutes. Two to three millicuries of thallium-201 was injected after the completion of the dipyridamole infusion. Single photon emission computed tomography MPI was started at 5 to 10 minutes after injection of thallium-201. Three hours after the stress test, redistribution imaging was performed. The left ventricle was divided into 17 segments, each classified as normal or abnormal. Result of MPI was defined as *abnormal* when a fixed or reversible perfusion defect involving at least 2 segments of the left ventricle was found. All images were visually analyzed by 2 experienced observers blinded to clinical information.

2.3. Biochemical measurements

Biochemical analyses were done on a Beckman Coulter (Fullerton, CA) biochemical analyzer (SYNCHRON CX-5CE). Serum cholesterol (cholesterol oxidase/peroxidase [CHOD-POD] method), triglyceride (lipose/glucose oxidase/peroxidase [GOD-POD] method), and HDL-C (direct method, polyethylene glycol–penetrated enzymes) were measured. C-reactive protein was measured with a highly sensitive assay (DPC, Los Angeles, CA), and urinary albumin concentrations were measured by immunoturbidimetry (Beckman Instruments, Galway, Ireland).

2.4. Statistical analysis

We used *t* test and 1-way analysis of variance to detect the mean differences between the biochemical data, and adjusted odds ratio (ORs) from logistic regression analysis to measure the effect of factors associated with silent myocardial ischemia of diabetic patients. All *P* values were calculated based on 2-sided tests, with significance defined as having a *P* value less than .05. The SAS software (version 9.12; SAS, Cary, NC) was used to run all statistical operations.

3. Results

This study collected 225 patients with type 2 diabetes mellitus (122 men and 103 women) who were clinically asymptomatic and had no known or suspected CAD. Almost half (109 patients or 48.4%) of those was diagnosed as having abnormal MPI results. The women were found to have a significantly greater frequency of silent myocardial ischemia than the men (59.2% vs 39.3%, $P = .001$) (Table 1). Patients who had silent myocardial ischemia were also significantly older and had significantly higher serum levels of hsCRP than those who did not. There were no significant differences found between the glycemic control, serum lipid profiles, and demographic characteristics between the 2 groups. The prevalence of metabolic syndrome was the same for both groups.

Age (OR = 4.01, $P = .002$) (95% confidence interval [CI], 1.98-7.44) and serum hsCRP levels (OR= 2.58, $P = .005$) (95% CI, 1.33-5.01) were found by multiple logistic regression analysis to be independently associated with silent myocardial ischemia in patients with type 2 diabetes mellitus (Table 2). Fig. 1 shows the prevalence of CAD by serum hsCRP level according to the CDC/AHA guidelines. A significantly increasing trend of CAD was observed with increasing serum levels of hsCRP ($P < .01$).

A number of factors, including smoking, waist circumference, and BMI, can also influence hsCRP levels. We analyzed the relationship of hsCRP and these factors using analysis of covariance and did not find hsCRP to be associated with smoking ($P = .9587$), waist circumference ($P = .2303$), and BMI ($P = .9323$). After controlling these variables, we still found an association between hsCRP and silent myocardial ischemia (OR= 2.73, $P = .009$) (95% CI, 1.42-5.23).

The ADA guidelines recommend screening only when at least 2 risk factors are present [6]. In our sample, 170 (75.6%) of the patients had at least 2 risk factors, making them candidates for screening (Table 3). Fifty-five (24.4%) patients had 1 or no risk factor and, therefore, fell outside the ADA screening guidelines. However, 27 of these 55 "low-risk" diabetic patients (49.1%), a relatively high frequency, were actually found to have silent myocardial ischemia. Had only the ADA guidelines been used, 24.8% of patients with silent myocardial ischemia would have been missed. In our study, patients with at least 2 risk factors and those with 1 or none had the same actual incidence of silent myocardial ischemia (82/170 or 48.2% vs 27/55 or 49.1%) (P = not significant). Patients with silent myocardial ischemia and those without were not found to be undergoing different types of treatment or taking different medications (Table 4).

Table 1
Clinical characteristics of subjects with type 2 diabetes mellitus

	MPI result		P
	Abnormal (n = 109)	Normal (n = 116)	
Sex (F/M)	61/48	42/74	.003
Age (y)	61.51 ± 8.53	53.91 ± 10.56	.001
BMI (kg/m^2)	26.69 ± 3.98	25.91 ± 3.47	.127
WHR	0.93 ± 0.14	0.90 ± 0.12	.122
WC (cm)	90.03 ± 10.61	89.13 ± 10.73	.537
SBP (mm Hg)	129.30 ± 14.44	125.97 ± 15.61	.107
DBP (mm Hg)	76.81 ± 9.30	77.59 ± 9.37	.542
HbA_{1C} (%)	7.66 ± 1.33	7.58 ± 1.41	.683
Chol (mg/dL)	221.50 ± 67.21	209.7 ± 40.40	.115
TG (mg/dL)	200.04 ± 271.33	198.23 ± 197.89	.955
HDL-C (mg/dL)	47.70 ± 19.71	46.27 ± 56.71	.800
LDL-C (mg/dL)	138.81 ± 63.20	130.51 ± 39.91	.246
Creatinine (mg/dL)	1.04 ± 0.51	0.93 ± 0.32	.062
hsCRP (mg/L)	3.84 ± 6.40	1.76 ± 1.99	.003
Metabolic syndrome (%)[a]	73.4	67.2	.314
Smoking status (%)	18.3	20.7	.737

Data are mean ± SD. WHR indicates waist-to-hip ratio; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA_{1C}, hemoglobin A_{1C}; Chol, cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein-cholesterol.

[a] Metabolic syndrome is described in the text.

Table 2
Logistic regression analysis for silent myocardial ischemia

Predictor	Silent myocardial ischemia		P value
	aOR	95% CI	
Age	4.01	1.98~7.44	.002
Sex	1.66	0.87~3.01	.163
hsCRP	2.58	1.33~5.01	.005
WC	1.00	0.96~1.06	.874
BMI	1.02	0.91~1.13	.780

4. Discussion

We found age and serum hsCRP levels to be strong predictors of silent myocardial ischemia of diabetic patients. Previous reports correlate serum levels of hsCRP, a marker of systemic inflammation and a mediator of atherosclerosis, with cardiovascular disease (CVD) risk [9,11]. It is well

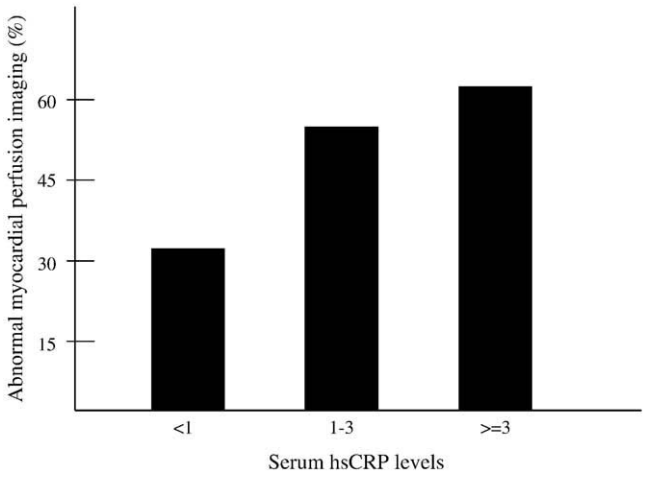

Fig. 1. Prevalence of abnormal MPI by serum hsCRP levels (units are in milligrams per liter).

Table 3
Prevalence of cardiac risk factors, types of treatment, and medications in study patients

	MPI result				
	Abnormal (n = 109)	Normal (n = 116)	OR	95% CI	*P*
Hypertension					
Yes	75 (71.57)	70 (60.18)	1.45	0.84-2.51	NS
No	34 (28.43)	46 (39.82)			
Dyslipidemia					
Yes	56 (51.38)	67 (57.76)	0.77	0.46-1.31	NS
No	53 (48.62)	49 (42.24)			
Family history of premature CVD					
Yes	8 (7.34)	11 (9.48)	0.76	0.29-1.86	NS
No	101 (92.66)	105 (90.52)			
Smoker					
Yes	14	20	0.71	0.34-1.48	NS
No	95	96			
Micro- or macroalbuminuria					
Yes	37	34	1.24	0.71-2.17	NS
No	72	82			
Cardiac risk factors					
≥2	82 (75.23)	88 (75.86)	0.97	0.53-1.78	NS
<2	27 (24.77)	28 (24.14)			

NS indicates not significant.

known that a number of factors, particularly smoking [17] and BMI [18], can influence serum CRP levels. Various medications also have several effects on the CRP levels. Angiotensin-converting enzyme inhibitor (ACEI) [19], statins [20], and thiazolidinediones (TZDs) [21] decrease the CRP levels, whereas hormone replacement therapy (HRT) in postmenopausal women increases them [22]. Our results found an association between hsCRP levels and silent myocardial ischemia in diabetic patients after adjusting for smoking status, BMI, and the medications including ACEI, statins, TZDs, and HRT.

Chinese are generally thought to be at low risk for CAD [23,24]. In fact, the prevalence rate of CAD has been reported to be significantly lower in Chinese with type 2 diabetes mellitus than in diabetic white persons [25]. An expert panel of the CDC/AHA has suggested that hsCRP may be an adjunct to major cardiovascular risk factors [12]. However, there have been few studies on the relationship between hsCRP and CAD in Chinese. In one of the studies, Wang et al [26] found that hsCRP could predict CAD in Chinese. In another, increased expression of hsCRP was associated with increased risk of CVD in Chinese [27]. Recently, Pu et al [28] found that hsCRP can potentially be used for the screening of CAD in patients with type 2 diabetes mellitus. Our study found that a significantly increasing trend of silent myocardial ischemia in diabetic patients was observed with increasing hsCRP levels according to the CDC/AHA guidelines ($P < .01$) (Fig. 1). Therefore, hsCRP might play an important role in CAD in diabetic Chinese and might be useful for screening for CAD.

Recent guidelines for CAD management in diabetes are based on the premise that most patients with diabetes are at high risk for future CAD events. Grundy et al [29] reported that diabetic patients with established CAD should be placed in the category of very high risk and deserve intensive therapy. It is also very important to detect silent myocardial ischemia in diabetic patients because they are also at very high risk and in need of aggressive treatment. In our study, there was no difference in prevalence of silent myocardial ischemia between patients with 2 or more risk factors and those with less than 2 risk factors. Selecting only patients who met the ADA guidelines would have failed to identify 24.8% of patients with silent myocardial ischemia, a finding similar to that of the DIAD study [8] and of Scognamiglio et al [30].

We did not find demographics or traditional cardiac risk factors to be associated with silent myocardial ischemia. This might reflect the impact of treatment with statins (56%) and ACEI/angiotensin receptor blocker (78.9%) as well as generally aggressive control of blood pressure (mean, 127/77 mm Hg) and glucose (hemoglobin A_{1c}, 7.6%). Although diabetic patients with metabolic syndrome are at high risk of CVD [31,32], we did not find an association between metabolic syndrome and silent myocardial ischemia in our subjects.

Previous studies have reported the risk for silent myocardial ischemia of diabetic patients to range from 9% to 60% for non-Chinese [33,34]. Although the present study does not intend to investigate the actual prevalence of silent myocardial ischemia in Chinese with type 2 diabetes mellitus, we did find a high frequency (48.4%) of silent myocardial ischemia in diabetic Chinese who have been previously thought to be at low risk for CAD. We speculate that this wide range reported is due to differences in the methods of selecting patients, screening techniques, and ethnicity. In our study, patients were carefully screened to ensure there was no clinical reason to suspect CAD. The Rose questionnaire was used to confirm the absence of angina. Myocardial perfusion imaging is reported to be a strong predictor of short- and long-term risks of coronary events in patients with diabetes [35,36]. We used MPI, as was done in the DIAD study [8], to detect silent myocardial ischemia of all patients.

Table 4
Types of treatment and medications

	MPI		
	Abnormal (n = 109)	Normal (n = 116)	*P*
Type of treatment			
OAD	97 (89%)	113 (88.8%)	NS
TZD	21 (19.3%)	23 (19.8%)	NS
Insulin	1 (0.9%)	1 (0.9%)	NS
Both	11 (10.1%)	12 (10.3%)	NS
Medications			
β-Blocker	14 (12.8%)	17 (14.7%)	NS
ACEI/ARB	86 (78.9%)	90 (77.6%)	NS
CCBs	55 (50.5%)	60 (51.7%)	NS
Diuretics	41 (37.6%)	45 (38.8%)	NS
Statins	61 (56%)	64 (55.2%)	NS
HRT[a]	10 (16.4%)	8 (19.0%)	NS

OAD indicates oral antidiabetic drug; ARB, angiotensin receptor blocker; CCBs, calcium channel blockers.

[a] Women only.

Exercise treadmill testing (ETT) is currently the most commonly used means of diagnosing and stratifying risk patients suspected of having CAD. Retrospective studies have previously shown that MPI variables have incremental diagnostic and prognostic value over ETT variables [37, 38]. However, ETT is limited in that it requires that the patient have some capacity for exercise. In our study, the diabetic patients were old and many were limited in their capacity for exercise. Therefore, we used MPI to screen for silent myocardial ischemia in asymptomatic Chinese with type 2 diabetes mellitus. The overall specificity of MPI is suboptimal, which is due largely to a failure to recognize image attenuation artifacts. Attenuation artifacts are common in patients with high BMI, although the differences in BMI between diabetic patients with normal and abnormal MPI findings were not significant (Table 1).

This study has some limitations. First, not all the patients with silent myocardial ischemia underwent angiographic coronary evaluation. Of the 2 patients receiving coronary angiography, one had 2-vessel disease and the other had 3-vessel disease (data were not shown). Recently, Boden et al [39] reported that the addition of percutaneous coronary intervention as an initial management strategy in patients with stable CAD did not reduce the risk of death, myocardial infarction, or other cardiovascular events. Diabetic patients with silent myocardial ischemia might not necessarily receive percutaneous coronary intervention. Second, MPI has been reported to be limited in its ability in women, as it has been found to produce false-positive results due to breast attenuation and small left ventricular chamber size [40]. Despite this limitation, many studies have reported women with an abnormal MPI finding to be at significantly increased risk for cardiac events [41-47]. Berman et al [41] found that the greater the abnormality of the MPI is, the greater is the risk of cardiac death in men and women, with diabetic women appearing to be at greater risk of cardiac death than diabetic men for any MPI result. Because diabetic women are at 8 times greater risk of cardiovascular death than nondiabetic women, MPI may be used to provide accurate information for the diagnosis and prognosis of ischemic heart disease in diabetic women [48]. Third, our study enrolled diabetic patients of Han Chinese origin in Taiwan. Differences in socioeconomic status, literacy, and access to health care might not make our results representative of Chinese populations found in other parts of the world. Fourth, because this study is cross-sectional, we could not determine whether silent myocardial ischemia is the cause or the result of high hsCRP levels in diabetic patients. A prospective study is needed to clarify the relationship between hsCRP and silent myocardial ischemia in Chinese with type 2 diabetes mellitus. Because there has been no large-scale study defining the relationship between silent myocardial ischemia and cardiac events in asymptomatic diabetic patients, all the patients of the present study will have at least 3 years of follow-up evaluation to clarify their conditions.

In conclusion, our study found an association between hsCRP level and silent myocardial ischemia in diabetic patients. Diabetic patients with silent myocardial ischemia are at very high risk and need aggressive treatment. High-sensitivity C-reactive protein might help detect silent myocardial ischemia in patients with type 2 diabetes mellitus in Taiwan.

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