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Effects of prediabetes and diabetes on left ventricular and coronary microvascular functions

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ABSTRACT

Background. Coronary flow reserve (CFR) provides independent prognostic information in diabetic patients with known or suspected coronary artery disease. However, there have been no substantial data to evaluate CFR in prediabetics. Accordingly, we aimed to evaluate CFR in subjects with prediabetes using second harmonic transthoracic Doppler echocardiography.

Methods and Results. We measured CFR of 65 subjects with prediabetes, 45 patients with overt type 2 diabetes, and 43 sex and age matched normoglycemic healthy subjects with normal glucose tolerance. Ages, gender, existence of hypertension or hypercholesterolemia, smoking status were similar among the groups. CFR was significantly lower in diabetics (2.15 ± 0.39) than in prediabetics (2.39 ± 0.45) and controls (2.75 ± 0.35); in addition, it was significantly lower in prediabetics than controls. Only 2 (5%) of control subjects had abnormal CFR (<2) but 11 (17%) prediabetic subjects and 19 (42%) diabetic patients had abnormal CFR. We found that only age ($\beta = -0.31$, $P < 0.01$) and presence of the diabetes ($\beta = -0.57$, $P < 0.01$) were significant predictors of lower CFR in a multivariable model that adjusted for other variables. CFR was significantly and inversely correlated with age ($r = -0.15$, $P = 0.04$), fasting glucose level ($r = -0.27$, $P = 0.001$), postprandial glucose level ($r = 0.43$, $P < 0.001$), hemoglobin A1C level ($r = -0.34$, $P < 0.001$), LDL cholesterol level ($r = 0.22$, $P = 0.009$), mitral A velocity ($r = -0.27$, $P = 0.001$) and Tei index ($r = -0.19$, $P = 0.02$), whereas mitral E/A ratio, mitral Em ($r = 0.18$, $P = 0.02$), mitral Em/Am ratio ($r = 0.23$, $P = 0.004$) were significantly and positively correlated with CFR.

Conclusion. CFR is impaired in subjects with prediabetics, but this impairment is not as severe as that in diabetics.

Abbreviations: DM, diabetes mellitus; CFR, coronary flow reserve; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; CV, cardiovascular; TTDE, transthoracic Doppler echocardiography; CAD, coronary artery disease; LVMI, left ventricular mass index; OGTT, oral glucose tolerance test; ADA, American Diabetes Association; FPG, fasting plasma glucose; DT, deceleration time; DTI, Doppler tissue-imaging; IVRT, isovolumic relaxation time; LAD, left anterior descending; BMI, body-mass index; RAAS, renin angiotensin aldosterone system; Hs-CRP, high sensitivity C reactive protein; LV, left ventricular; BP, blood pressure; DPP, Diabetes Prevention Program.

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1. Introduction

Diabetes mellitus (DM) is one of the major coronary risk factors and it affects not only epicardial coronary arteries but also coronary microvasculature. Accordingly, it has been well recognized that patients with type 2 DM have impaired coronary flow reserve (CFR) reflecting coronary microvascular function even in the absence of epicardial coronary atherosclerosis [1–3]. In addition, growing evidence supports that coronary microvascular dysfunction may be an underlying mechanism in patients with symptoms and signs of myocardial ischemia without angiographically detectable coronary artery disease, and even in asymptomatic patients with cardiovascular risk factors [2,4,5]. Furthermore, it has recently been shown that CFR provides independent prognostic information in diabetic patients with known or suspected coronary artery disease and a negative dipyridamole stress echocardiography, and a normal CFR off therapy is associated with better survival in this population [6]. Therefore, CFR measurement offers important diagnostic information about coronary microvascular dysfunction in patients with DM and may be useful for the clinical management and prediction of prognosis for these patients.

Prediabetes, which refers to an intermediate stage between normal glucose tolerance and overt type 2 DM, represents 2 groups of individuals, those with impaired fasting glucose (IFG) and those with impaired glucose tolerance (IGT) [7]. Compared to subjects with normal glucose tolerance, prediabetics are at high risk for developing incident type 2 DM and clinically significant atherosclerotic cardiovascular (CV) disease [8]. The underlying pathophysiological disturbances of excess risk from prediabetes are presumed to be the same as those from diabetes such as insulin resistance and impaired beta cell function [8].

Although substantial evidence supports the contention that prediabetes is associated with endothelial dysfunction, atherosclerotic vascular disease and target-organ damage [9,10], there is only one study with relatively small sample size investigating CFR in these patients [11]. In the present study, we measured CFR in normoglycemic subjects with normal glucose tolerance, in subjects with prediabetes, and in patients with overt type 2 DM using transthoracic Doppler echocardiography (TTDE).

2. Methods

2.1. Study population

The overall study population consisted of 153 subjects: 65 subjects with prediabetes, 45 patients with overt type 2 DM, and 43 normoglycemic subjects with normal glucose tolerance. Demographic and clinical data of the groups are shown

Table 1 – Demographic and biochemical characteristics of the study groups.

	Prediabetics (65)	Diabetic Patients (45)	Controls (43)
Clinical History and Features			
Age (year)	51.4 ± 8.6	51.6 ± 7.2	50.4 ± 8.5
Male/female (n/n)	26/39	19/26	18/25
Hypertension (n, %)	20 (30)	15 (33)	8 (19)
Hypercholesterolemia (n, %)	20 (30)	19 (42)	14 (33)
Current smoker (n, %)	6 (9)	3 (7)	4 (9)
BMI (kg/m^2)	31.4 ± 4.8	30.6 ± 4.9	29.3 ± 4.5
BMI ≥ 30 kg/m^2 (n, %)	40 (62) †	28(62)†	17 (40)
Waist circumference (cm)	104.0 ± 12.5	104.5 ± 8.5	101.1 ± 12.7
Hip circumference (cm)	113.4 ± 13.9†	107.5 ± 9.9	100.8 ± 8.3
SBP (mmHg)	130.8 ± 13.3*	138.5 ± 19.9	138.1 ± 9.1
DBP (mmHg)	76.3 ± 10.5†	79.6 ± 14.0	83.4 ± 6.5
Heart rate (bpm)	79.4 ± 8.5	90.0 ± 14.1	76.7 ± 8.8
Premature menopause (n, %)	5 (8)	6 (13)	8 (19)
Treatment and Laboratory			
OAD (n, %)	-	41 (90)	-
Beta blockers (n, %)	3 (5)	2 (4)	4 (9)
RAAS blockers (n, %)	12 (18)	21 (46)†¶	7 (16)
CCB (n, %)	5 (8)	5 (11)	2 (5)
Lipid-lowering drugs (n, %)	14 (22)	24 (53)†¶	12 (28)
Fasting glucose (mg/dL)	109.4 ± 5.4‡	152.1 ± 42.3‡§	94.0 ± 5.9
2-h glucose in OGTT (mg/dL)	147.5 ± 38.8‡	–	103.3 ± 21.1
Hemoglobin A1C (%)	5.8 ± 0.5	7.4 ± 1.9‡§	5.5 ± 0.6
Triglyceride (mg/dL)	168.4 ± 93.5	163.1 ± 90.7	147.4 ± 77.9
Total Cholesterol (mg/dL)	203.2 ± 40.9†	201.6 ± 45.6†	181.1 ± 38.1
HDL Cholesterol (mg/dL)	50.3 ± 12.4	48.0 ± 9.7	50.3 ± 13.2
LDL Cholesterol (mg/dL)	122.6 ± 36.6†	121.7 ± 39.3†	104.0 ± 25.8
Hs-CRP (mg/dL)	3.03 ± 3.07	3.23 ± 6.11	2.94 ± 2.90

* P < 0.05 vs. diabetics; †: P < 0.05 vs. controls; ‡: P < 0.001 vs. controls. ¶: P < 0.05 vs. prediabetics; §: P < 0.001 vs. prediabetics. Abbreviations: BP: blood pressure; OGTT: oral glucose tolerance test; HDL: high-density lipoprotein; LDL: low-density lipoprotein; hsCRP: high-sensitivity C-reactive protein.