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Longer rewarming time in finger cooling test in association with HbA1c level in diabetics

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ABSTRACT

Objective: To assess if rewarming time in finger cooling test (FCT) as an indicator of microvascular dysfunction is abnormal in patients with type 2 diabetes mellitus (T2DM).
Methods: Forty-three T2DM patients and 48 healthy controls with similarly distributed baseline demographic, clinical and laboratory parameters were subjected to FCT involving 60-second index finger immersion into water at 4 °C. Finger temperature was measured before FCT (baseline-T), immediately after cooling stimulus (T0), and at one-minute intervals until baseline-T recovery. Temperature decline amplitude was calculated as the difference between T0 and baseline-T, and rewarming time as time elapsed from T0 to baseline-T recovery.
Results: T2DM patients compared with healthy controls had statistically similar baseline-T, significantly larger temperature decline amplitude, significantly lower T0, and significantly longer rewarming time. In T2DM patients, rewarming time positively correlated with T2DM duration ($r = 0.513$, $p < 0.001$) and glycated hemoglobin (HbA1c) level ($r = 0.446$, $p = 0.003$), which also were its independent predictors in multivariate regression analysis.
Conclusions: Patients with T2DM display abnormal FCT results suggestive of microvascular dysfunction, with T2DM duration and HbA1c level independently predicting rewarming time.

Introduction

By synthesizing biologically active substances that regulate vascular tone, the vascular endothelium plays a pivotal role in maintaining normal blood vessel function (Babushkina et al., 2015). Assessment of endothelial dysfunction, which is a predictor of increased mortality in patients with type 2 diabetes mellitus (T2DM), is therefore clinically relevant. To this end, in addition to measuring levels of circulating endothelial-derived/associated markers, such as soluble *E*-selectin and circulating endothelial progenitor cells (Abebe and Mozaffari, 2010), a wide range of noninvasive vascular reactivity tests have been developed, including flow-mediated dilatation (FMD) of brachial artery for conduit arteries (Deanfield et al., 2005), peripheral artery tonometry (*endo*-PAT) for digital arteries (Bonetti et al., 2004), and digital thermal monitoring (DTM) or laser Doppler imaging (LDI) for microcirculation (resistance arteries and arterioles) (Correa et al., 2010; Gul et al., 2009; Ahmadi et al., 2009).

Among DTM assessments, which are based on cold, ischemia or heat mediated skin temperature change as stressor (Gul et al., 2009; Chen et al., 1999; Roustit et al., 2011), the convenient and inexpensive finger cooling test (FCT) is commonly used in clinical practice. FCT assessment is based on skin rewarming progression after cooling stimulus withdrawal. Cold exposure induces artery constriction and decreases skin temperature, which gradually increases after cooling stimulus withdrawal. Thus, a longer rewarming time reflects stronger artery constriction and impaired microcirculatory function. FCT has been used for Raynaud's phenomenon diagnosis (Roustit et al., 2011) and to evaluate microcirculatory function in hypertensive patients (Wollersheim et al., 1987) and abnormal FCT has been associated with risk factors for cardiovascular diseases and metabolic syndrome score (Liu and Bluemke, 2009; Veijalainen et al., 2013).

Although evaluation of vascular function in patients with T2DM has attracted increasing attention, it has mainly focused on macro- but not microcirculation. The present study therefore aimed at testing the hypothesis that rewarming time in FCT may be: 1. longer in T2DM patients, who often have microcirculatory dysfunction; and 2. associated with T2DM duration and glycated hemoglobin (HbA1c) level. If the hypothesis proves valid, FCT might be used to clinically evaluate microcirculatory function.

Materials and methods

The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a prior approval by the Ethics

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Committee of the Second Affiliated Hospital of Nanchang University. Informed consent was obtained from each participant.

Subjects

From March to July 2015, the present study enrolled 43 consecutive inpatients with T2DM diagnosed as serum glucose ≥7.0 mmol/L, or 2-h glucose levels in oral glucose tolerance test ≥11.1 mmol/L. Exclusion criteria were: hypertension, acute coronary syndrome, malignant arrhythmia, heart failure, and severe hepatic or renal dysfunction.

Levels of fasting glucose, serum total cholesterol (TC), high-density lipoprotein cholesterol (HDL—C), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), HbA1c, creatinine (Cr) and blood urea nitrogen (BUN) were measured. T2DM duration was defined as time elapsed since diagnosis of diabetes.

Concurrently, 48 healthy subjects as per routine physical examination were included as controls. Information on age, gender, body mass index (BMI) and family history of cardiovascular disease and blood pressure (BP) were collected for all participants.

No participants were on medications that might affect vascular activity, such as beta-blockers and calcium channel blockers. All T2DM patients received glucose-lowering treatment: 11 patients were on only insulin, 15 on insulin plus oral hypoglycemic agents; and 17 on only oral hypoglycemic agents. Oral hypoglycemic agents included sulphonylurea, metformin, thiazolidinedione, acarbose, glipizide and dipeptidyl peptidase-4 inhibitors at physician's discretion.

Cold exposure and temperature detection

Finger temperature was measured using an infrared electronic thermometer (DT 8806S, CEM, China) with a distance of 10 mm between the thermometer and padded surface of the right index finger. FCT was performed in a room with a temperature of 22–23 °C and humidity of 50–60%. Before the test, no subjects had drunk coffee for at least 4 h, and all relaxed in a sitting position for 15 min. At first, index finger temperature was measured twice and the average was recorded as baseline temperature (baseline-T). Then, the index finger was immersed up to the proximal interphalangeal joint into water at 4 °C for 60 s. At the end of the cold stress, water on the finger was absorbed with a soft paper tissue and the temperature of the cooled finger was measured immediately (T0). Then, the finger temperature was measured at 60 seconds intervals until the temperature returned to baseline value. Temperature decline amplitude (difference between T0 and baseline-T) and rewarming time (time elapsed from T0 to baseline-T) were calculated (Isii et al., 2007).

Bioelectrical impedance analysis

A tetrapolar impedance meter (HBF-371, V-BODY OMRON) was used to measure the percentage of body fat mass (Wu et al., 2015; Bosy-Westphal et al., 2008).

Statistical analysis

Statistical analysis was conducted using the IBM SPSS Version 18.0 (SPSS Science, Chicago, IL, USA). Data are expressed as means ± standard deviation (SD) for continuous variables and analyzed by *t*-test, while categorical variables are presented as n (%) and analyzed using Chi-square test or a Fisher's exact test. Univariate correlation analyses and multivariate linear regression analyses were performed to evaluate factors associated with rewarming time. Independent variables in the multivariate linear regression model included age, sex, BMI, family history of CVD, body fat mass, baseline temperature, temperature decline amplitude, T0, T2DM duration as well as blood biochemical parameters including fasting glucose, HbA1c, TC, HDL—C, LDL-C, and TG. A two-sided p-value < 0.05 was considered statistically significant.

Results

There were no significant differences in the distributions of age, gender, BMI, body fat mass, family history of CVD and serum lipids between the two groups. All T2DM patients had normal hepatic and renal function. Fasting blood glucose level was significantly higher in T2DM patient than in healthy controls; and 35 out of the 43 T2DM patients had HbA1c level > 7%, reflecting poor blood glucose control.

Baseline-T was statistically similar between the two groups. However, temperature decline amplitude was larger and T0 was lower in the T2DM group than in healthy controls. More importantly, rewarming time was significantly longer in T2DM group as compared with healthy controls (Table 1).

Pearson's correlation analysis showed a positive correlation between rewarming time and T2DM duration ($r = 0.513$, $p < 0.001$) or HbA1c levels ($r = 0.446$, $p = 0.003$) in patients with T2DM (Fig. 1). A negative correlation was found between rewarming time and T0 ($r = -0.276$, $p = 0.035$) in patients with T2DM (Fig. 2).

Table 1
Comparison of baseline characteristics and FCT results between the T2MD and healthy control groups.

	T2DM ($n = 43$)	Healthy ($n = 48$)	p
Male gender	23 (53.5)	25 (52.1)	0.893
Age (years)	60.12 ± 8.86	59.48 ± 8.79	0.732
BMI (kg/m^2)	23.80 ± 3.34	24.22 ± 2.97	0.522
Body fat mass (%)	27.70 ± 7.51	28.91 ± 5.07	0.372
Family history of CVD	22 (51.2)	29 (60.4)	0.375
TC (mmol/l)	4.85 ± 1.19	4.73 ± 0.98	0.590
HDL (mmol/l)	1.17 ± 0.26	1.23 ± 0.27	0.300
LDL (mmol/l)	2.57 ± 0.81	2.51 ± 0.54	0.669
TG (mmol/l)	1.56 ± 0.92	1.73 ± 0.53	0.274
FBG (mmol/L)	8.82 ± 3.32	4.89 ± 0.83*	<0.01
HbA1c (%)	8.81 ± 2.16	–	–
Baseline-T (°C)	33.79 ± 1.36	33.76 ± 1.81	0.934
T0 (°C)	17.28 ± 3.72	18.70 ± 2.76*	0.041
T decline amplitude (°C)	16.51 ± 3.35	15.07 ± 3.06*	0.035
Re-warming time (minutes)	7.23 ± 3.68	5.73 ± 1.98*	0.020

Data are presented as mean ± SD or n (%). T2DM, type 2 diabetes mellitus; BMI, body mass index; CVD, cardiovascular disease; HbA1c, glycated hemoglobin; FBG, fasting blood glucose; TC, total cholesterol; HDL, high density lipoprotein; LDL, low density lipoprotein; TG, triglyceride; T0, finger temperature at 0 min after finger cooling test; Baseline-T, Baseline temperature of the index finger; T decline amplitude, the difference between T0 and baseline-T.

* $p < 0.05$.