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Retinal microvascular abnormalities are associated with early carotid atherosclerotic lesions in hospitalized Chinese patients with type 2 diabetes mellitus

Lian-Xi Li [a,1], Mei-Fang Li [a,1], Jun-Xi Lu [a,1], Li-Li Jia [b], Rong Zhang [a], Cui-Chun Zhao [c], Ying Ren [c], Yin-Fang Tu [a], Ying Shen [a], Fang Liu [a], Yu-Qian Bao [a], Wei-Ping Jia [a,*]

[a] Department of Endocrinology and Metabolism, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Shanghai Clinical Center for Diabetes, Shanghai Diabetes Institute, Shanghai Key Laboratory of Diabetes Mellitus, Shanghai Key Clinical Center for Metabolic Disease, 600 Yishan Road, Shanghai, 200233, China
[b] Department of ophthalmology, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, 600 Yishan Road, Shanghai 200233, China
[c] Department of VIP, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, 600 Yishan Road, Shanghai 200233, China

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ABSTRACT

Objective: Controversies concerning the association of retinal microvascular abnormalities (RMAs) with atherosclerosis in patients with diabetes exist. The objective of this study was to investigate the association between RMAs and carotid atherosclerotic lesions in Chinese inpatients with type 2 diabetes.

Methods: This cross-sectional study involved 2870 type 2 diabetic patients including 1602 men aged 15–90 years and 1268 women aged 17–88 years. Both retinal arteriosclerosis (RA) and diabetic retinopathy (DR) were determined by digital fundus photography using a standardized protocol. RMAs are defined as the presence of either RA or DR. Carotid atherosclerotic lesions including carotid intima-media thickness (CIMT), carotid atherosclerotic plaque and stenosis were assessed and compared between patients with and without RMAs based on Doppler ultrasound. The association of RMAs with carotid atherosclerotic lesions was analyzed by linear and binary logistic regression analyses.

Results: The CIMT values in both male and female diabetics with RMAs were significantly greater than in those without RMAs after controlling for age (0.88 ± 0.21 vs. 0.77 ± 0.20 mm for men, $p = 0.002$; and 0.84 ± 0.19 vs. 0.76 ± 0.21 mm for women, $p = 0.002$). The prevalence of carotid plaque was also markedly higher in patients with RMAs than in those without RMAs after adjusting for age (54.3% vs. 23.9% for men, $p < 0.001$; 48.4% vs. 32.0% for women, $p = 0.046$). However, no significant difference was observed in the prevalence of carotid stenosis in either men or women with or without RMAs. After controlling for multiple confounding factors, RMAs were independently associated with increased CIMT in both men (β: 0.067,95% CI: 0.026–0.269, $p = 0.018$) and women (β: 0.087, 95% CI: 0.058–0.334, $p = 0.005$) with type 2 diabetes, and they were also closely associated with the presence of carotid plaque (OR: 2.17, 95% CI: 1.54–3.05, $p < 0.001$ for men; OR: 1.38, 95% CI: 0.91–2.08, $p = 0.129$ for women) in men with type 2 diabetes.

Conclusions: RMAs were closely associated with early carotid atherosclerotic lesions in hospitalized Chinese patients with type 2 diabetes. Our results suggested that changes in retinal microvasculature may play a role in the pathogenesis of atherosclerosis and may be used as an indicator of early atherosclerosis in patients with type 2 diabetes.

1. Introduction

Many studies have documented the association of atherosclerosis with alterations in the structure and function of microcirculation in the heart, brain, retina, skin, and kidney (Irving et al., 2002; Kong et al., 2012; Nagaoka et al., 2005; Sartore et al., 2013; Yoon et al., 2010). Of these microvascular systems, the retinal microvasculature offers a unique window of opportunity to non-invasively analyze the systemic microcirculation in vivo (Liew et al., 2007; Wong et al., 2004). Retinal microvascular abnormalities (RMAs), such as arteriolar narrowing and retinopathy, have been found to be closely associated with atherosclerosis and cardiovascular diseases (Klein et al., 2002; Wang et al., 2006, 2008). For example, two previous studies have revealed that retinal arteriosclerosis (RA), as indicated by retinal arterial narrowing, is associated not only with coronary microvascular disease, but also with coronary macrovascular disease (Wang et al., 2006; Wang et al., 2008).

Competing interests: The authors declare that they have no competing interests.

* Corresponding author at: Department of Endocrinology and Metabolism, Shanghai Jiaotong University Affiliated Sixth People's Hospital, 600 Yishan Road, Shanghai 200233, China. Tel.: +86 21 64369181x58922; fax: +86 21 64368031.
E-mail address: wpjia@sjtu.edu.cn (W-P. Jia).

[1] These authors contributed equally to this work.

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However, other studies have found no evident association of retinal microvascular changes with atherosclerotic lesions (Klein et al., 2000; van Hecke et al., 2006; Wong et al., 2003). For example, van Hecke et al. investigated the relationship between RMAs and the carotid intima-media-thickness (CIMT) in subjects with normal glucose metabolism, impaired glucose metabolism, and type 2 diabetes and found that only retinal venular dilatation was associated with increased CIMT after adjustment for age, sex and glucose tolerance status (van Hecke et al., 2006). However, this association was lost statistical significance after additional adjustment for cardiovascular risk factors (van Hecke et al., 2006). Furthermore, there may be racial differences in the association of RMAs with atherosclerotic lesions, and the prevalence and characteristics of RMAs are largely unknown in Chinese type 2 diabetics.

Therefore, our aims were to investigate the association between RMAs and carotid atherosclerotic lesions, including CIMT, carotid plaque and stenosis, and to assess the prevalence and characteristics of RMAs in Chinese subjects with type 2 diabetes.

2. Patients and methods

2.1. Subjects and study design

This cross-sectional study was approved by the ethics committee of Shanghai Jiao Tong University Affiliated Sixth People's Hospital. Written informed consent was obtained from all subjects. From January 2007 to June 2009, 3598 patients with type 2 diabetes who were hospitalized in our department were consecutively observed. All subjects underwent an interview and gave a history of hypertension and medication and cardio-cerebrovascular events (CCEs), alcohol consumption and smoking status. The definition of hypertension, smoking, and alcohol use has been described in previous studies (Li et al., 2012, 2013a,b). Based on our previous studies (Li et al., 2012, 2013a,b), CCEs were defined as a history of myocardial infarction, angina, angioplasty, coronary artery bypass surgery, transient ischemic attack, ischemic, or hemorrhagic stroke. Of the 3598 patients, 505 subjects were excluded because of a lack of carotid ultrasound data and/or complete clinical data. Of the remaining 3093 patients, retinal photographs were available for 2875 individuals. Of these, photographs of five subjects could not be evaluated. Ultimately, 2870 patients were included in the present study.

2.2. Physical examination and laboratory measurements

Physical examinations, including weight, height, waist circumference, hip circumference and blood pressure, were performed according to our previous protocol (Li et al., 2012, 2013a,b). Body mass index (BMI) was calculated as weight divided by height squared. Waist-to-hip ratio (WHR) was calculated as waist circumference divided by hip circumference.

Blood samples were obtained after an overnight fast and 2 h after breakfast. We determined the glycosylated hemoglobin A1C (HbA1c), fasting plasma glucose (FPG), 2 h postprandial plasma glucose (2 h PPG), fasting C-peptide (FCP), 2 h postprandial C-peptide (2 h PCP), total triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), aspartate aminotransferase (ALT), alanine aminotransferase (AST), γ-Glutamyltransferase (γ-GT), blood urea nitrogen (BUN), creatinine (Cr), uric acid (UA), and C-reactive protein (CRP) by standard laboratory protocols.

The 24 h urinary albumin excretion (UAE) was determined as the mean of the values obtained from three separate early morning urine samples during the period of hospitalization. The ΔCP represents the difference between the value of 2 h PCP and FCP and was calculated as value of 2 h PCP minus FCP. The estimated glomerular filtration rate (eGFR) was calculated using the simplified MDRD formula: eGFR) = $186.3\times$ (Serum creatinine)$^{-1.154}\times$ (age)$^{-0.203}$ ($\times$0.742 if female) (National Kidney Foundation, (2002).

2.3. Ultrasonography measurements

Carotid atherosclerotic lesions were measured with carotid ultrasonography as described previously (Li et al., 2013a,b). Briefly, each subject was examined in a supine position with their head turned 45 degrees from the site being scanned. Carotid arteries including the common carotid arteries, the bifurcation, the external carotid arteries, and the internal carotid arteries were examined bilaterally to assess the presence of atherosclerotic plaque and stenosis and measure CIMT. The IMT was defined as the distance between the leading edge of the lumen-intima echo and the leading edge of the media adventitia echo. The CIMT was defined as the mean of the right and left IMT of the common carotid artery. Based on the Mannheim consensus, atherosclerotic plaque was defined as focal structures encroaching into the arterial lumen of 0.5 mm or 50% of the surrounding IMT value or IMT of > 1.5 mm (Touboul et al., 2004). Carotid stenosis was defined as any degree of narrowing in either the internal, external or common carotid arteries by carotid plaques (Li et al., 2012, 2013a,b). The reproducibility of measurements of carotid atherosclerotic lesions has been reported in our previous study (Li et al., 2013a,b).

2.4. Digital nonmydriatic fundus photography and image analysis

Retinal photographs of each subject were taken according to a standardized protocol described in our previous study (Li et al., 2012). Briefly, following 5 minutes of dark adaptation, fundus photography was performed at each site with a 45° digital nonmydriatic camera (Canon CR6-45NM). The retinal photographs covered the disc, macula, and temporal vasculature of each retina. The photographs were digitized and stored as bitmap images. The fundus photographs were analyzed by an experienced ophthalmologist who was blinded to participant characteristics to identify RA and diabetic retinopathy (DR). The intra-observer reproducibility was determined using a Spearman correlation coefficient. The intra-observer correlation coefficients were 0.94 for the identification of RA and 0.98 for the identification of DR.

According to Scheie's classification (Scheie, 1953), RA was defined as the presence of broadening of the light reflex from artery, arterial narrowing, arteriovenous compression, and 'copper' or 'silver' wiring. DR was defined as present if any of the following lesions were detected: microaneurysms, hemorrhages, soft exudates, hard exudates, neovascularization, and laser photocoagulation scars (1991). RMAs were defined as the presence of either RA or DR. Mild RMAs were defined as either stage 1–2 RA in Scheie's classification, or background changes of DR (Fig. S1). Severe RMAs were defined as either stage 3-4 RA in Scheie's classification, or proliferative changes of DR, or the presence of laser photocoagulation scars (Fig. S1).

2.5. Statistical analysis

All analyses were performed with SPSS 15.0 for windows software. P values <0.05 were considered to be statistically significant, and p values <0.1 were considered to be a significant trend. The data are presented as the mean ± S.D, percentages or medians (interquartile range) in the case of a skewed distribution. For continuous variables with normal distribution, two-tailed independent sample t tests were used to compare between two groups, and one-way ANOVA with LSD was used to compare among multi-groups. If the data were not distributed normally, the Mann–Whitney *U* test and Kruskal–Wallis H test were used. The χ^2 test was