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Obesity is a determinant of arterial stiffness independent of traditional risk factors in Asians with young-onset type 2 diabetes

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ABSTRACT

Objective: Type 2 diabetes (T2DM) among the young population has become a serious concern globally, presumably due to the rising trend of obesity. Compared to other forms of diabetes, young-onset T2DM experiences more cardiovascular events and other vascular complications although the underlying mechanisms remain largely unknown. Increased arterial stiffness is a hallmark of vasculopathy. We aim to study the clinical and metabolic determinants of arterial stiffness in a cohort of multi-ethnic Asians with young-onset T2DM.

Methods: 179 subjects with T2DM onset age below 30 years old were selected in this cross sectional study. Arterial stiffness was assessed by carotid-femoral pulse wave velocity (PWV).

Results: PWV was correlated with age, duration of diabetes, systolic blood pressure, alanine aminotransferase, urinary albumin-to-creatinine ratio (ACR) and eGFR in bivariate correlation analysis. However, PWV was only significantly correlated with body mass index (BMI), waist circumference, urinary ACR and eGFR after adjustment for age. Overweight individuals with young-onset T2DM had significantly higher PWV levels compared to their lean counterparts (7.3 ± 2.4 m/s vs 6.4 ± 2.3 m/s, $p = 0.072$ and $p < 0.0001$ without and with adjustment for age, respectively). Multivariable regression models revealed that age, BMI, eGFR and usage of insulin were independently associated with PWV. These 4 variables explained 35.5% variance in PWV levels.

Conclusion: Age, BMI, renal function and insulin usage are the main determinants of PWV levels in Asians with young-onset T2DM. Notably, obesity is a modifiable determinant of arterial stiffness independent of high blood pressure, dyslipidemia and hyperglycemia in this population.

1. Introduction

The rising trend of type 2 diabetes (T2DM) among children, adolescents and young adults is becoming a serious concern globally, presumably due to the obesity epidemic [1–3]. Young-onset T2DM accounts for up to 86% of new cases in some ethnic groups [3,4]. In some Asian countries, the prevalence of T2DM in youth has outnumbered type 1 diabetes (T1DM) [5].

Compared to their older-onset counterparts, young-onset T2DM has longer life-time exposure to diabetes and suboptimal response to intensive lifestyle intervention which may contribute to greater propensity for diabetic complications among these patients [6–8]. In corollary, young-onset T2DM is associated with worse prognosis than T1DM. Mortality in individuals with young-onset T2DM is 2-fold higher compared with T1DM of a similar age and diabetes duration and 8- fold higher than age-standardized mortality in the general population [9]. Earlier studies also showed that individuals with young-onset T2DM have worse cardiovascular risk factors than those with T1DM of similar age and cardiovascular death is the major cause of mortality among these patients [7,9]. It is estimated that individuals with young-onset T2DM have an overall 6.15-fold increased risk of any vascular diseases compared to non-diabetic

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population of similar age. A similar pattern has been observed among Asians. A recent study in the Chinese population showed that cardiovascular risk in young-onset T2DM, especially in obese individuals with young-onset T2DM, is significantly higher than that in T1DM [10]. Therefore, prevention and treatment of cardiovascular complications in patients with young-onset T2DM have tremendous clinical, social and economic implications worldwide.

Increased arterial stiffness is a recognized hallmark of vasculopathy and it has an independent predictive value for both fatal and nonfatal cardiovascular events [11,12]. Carotid-femoral pulse wave velocity (PWV) has been considered as a "gold standard" for assessment of arterial stiffness [13]. A large body of evidences support increased PWV as an independent indicator of asymptomatic organ damaged in the continuum of vascular disease and it has been used as an established surrogate measurement of cardiovascular risk in both diabetic and non-diabetic populations [12,14]. An earlier study showed that aortic PWV level in individuals with young-onset T2DM is significantly higher than that in individuals of similar age without diabetes. It is estimated that PWV level of youths with T2DM (average age 15.5 ± 0.4 years) is comparable with that of ~40 years old healthy men, suggesting premature aging of cardiovascular system in these individuals [14]. Similar observation has been made in youths with T2DM (aged 10–23 years old) in SEARCH for diabetes in youth study [15]. Although these studies revealed that patients with young-onset T2DM have significantly worse arterial stiffness compared to the general population and those with T1DM of similar age, the underlying mechanisms of increased arterial stiffness in these patients are largely unknown. In this study, we aim to identify clinical, biochemical and metabolic determinants of arterial stiffness in a cohort of multi-ethnic Asians with young-onset T2DM.

2. Subjects and methods

2.1. Subjects

SMART2D study (Singapore Study of MAcro-angiopathy and Micro-Vascular Reactivity in Type 2 Diabetes) aims to investigate traditional and novel risks factors associated with vascular complications in patients with T2DM. Inclusion and exclusion criteria of SMART2D have been described elsewhere [16]. We define young-onset T2DM with a cut-off onset age of 30 years old or below [9]. By Jan 2014, 1930 subjects with T2DM have been recruited in SMART2D. Among them, 180 subjects were identified as having diabetes onset age before 30 years old (age at diagnosis of T2DM). Onset age of diabetes was self-reported. A research nurse would trace their hospital medical record if the patients were uncertain of their age of T2DM diagnosis. SMART2D study complies with principles laid by Helsinki Declaration and it has been approved by the domain- specific ethical committee under Singapore National Healthcare Group. Informed written consent has been obtained from each participant.

Singaporeans have been found to have higher percentage of body fat compared with Caucasians with the same body mass index (BMI) [17]. Therefore, we defined overweight by the Asian- specific BMI cutoff of 23 kg/m^2 in this study [18].

2.2. Ascertainment of type 2 diabetes

Diagnosis and classification of diabetes were based on American Diabetes Association (ADA) criteria 2012 [19]. Ascertainment of T2DM was mainly based on review of medical history and exclusion of type 1 diabetes (T1DM)and those in the category of "other" types of diabetes (mainly secondary diabetes). The prevalence of anti-GAD antibody was only 30–40% in Asian population with T1DM [10,20]. Therefore, the presence of autoantibodies was not a prerequisite for defining T1DM in our cohort. Adopting the same criteria by Luk et al., we defined T1DM as presence of diabetic ketoacidosis and/or requirement for continuous usage of insulin within 1 year of diagnosis [10]. To further ascertain the duration between diabetes diagnosis and starting time of insulin usage, we reviewed the electronic medical record manually in all the patients with young-onset diabetes with BMI below 25. One of the subjects was re-classified as T1DM because of initiation of insulin treatment within one year after diagnosis of diabetes and was excluded from the following data analysis.

2.3. Clinical and biochemical measurement

Blood pressure was measured by a sphygmomanometer. BMI was calculated as body weight (kg)/ (height (m) × height (m)). Creatinine was measured by enzymatic method on Roche/Hitachi cobas c system (Roche Diagnostic GmbH, Mannheim, Germany) and estimated glomerular filtration rate (eGFR) was calculated based on Modified Diet in Renal Disease (MDRD) formula which performed well in patients with diabetes [21]. Urinary albumin was measured by a solid phase competitive chemiluminescent enzymatic immunoassay (Immulite, DPC, Gwynedd, UK). HbA1c was quantified by Point-of-care Immunoassay Analyzer which has met NGSP performance standard (DCA Vantage Analyzer, Siemens AG, Erlangen, Germany). HDL-cholesterol and LDL-cholesterol were quantified by enzymatic methods using Kodak Ektachem chemistry slides. Total triglycerides, activities of alanine aminotransferase (AST), aspartate aminotransferase (ALT) were quantified by enzymatic colorimetric method on Roches/Hitachi cobas c system. Carotid-femoral PWV was measured by the foot- to- foot method (SphygmoCor, AtCor Medical, Sydney, Australia) and it has been widely adopted as a "gold standard" for the assessment of aortic stiffness [13]. Taking into account that the direct carotid-to-femoral distance is about 20% longer than the actual anatomical distance traveled by pulse wave, we adjusted PWV by a scaling factor of 0.8 in data analysis as recommended by ESH/ESC new guideline [12].

2.4. Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD) and categorical variables were expressed as proportions. Plasma triglycerides, ALT, AST and urinary albumin-to-creatinine ratio (ACR) were expressed as median (inter-quartile) and log-transformed before data analysis as their distributions were skewed. Differences between lean and overweight subjects were compared by Student's t test or χ^2 test where appropriate. Given that the age differed significantly between lean and overweight subjects, between- group differences in BMI, blood pressure, lipids profile, ALT, AST, renal function and PWV was further compared after adjustment for age. Bivariate relationship between clinical, biochemical variables and PWV was first analyzed by Pearson correlation analysis, followed by general linear models to adjust for age.

We employed multivariable linear regression models to study clinical, biochemical and metabolic variables which might independently determine variances in PWV. In our models, PWV was entered as dependent variable. Age was the most important determinant of arterial stiffness so it was entered as the independent variable [11]. Gender and ethnicity were entered as the main confounders (model 1). Selection of covariates was based on pathophysiology of arterial stiffness and suggestions from prior literature. On the basis of model 1, age of diabetes onset and HbA1c were entered to adjust for disease burden and glycemic control (model 2). Duration of diabetes was highly correlated with age