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Cardiovascular risk factors and mitral annular calcification in type 2 diabetes

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ABSTRACT

Objective: Mitral annular calcification (MAC) is a degenerative process of the mitral annulus associated with cardiac disease and stroke. Although thought to be more prevalent in type 2 diabetes (T2DM), MAC remains poorly characterized in this population, due to confounding by renal and cardiac disease. Our goal was to study the risk factors for MAC in a sample of T2DM subjects without renal and cardiac disease.

Methods: The Penn Diabetes Heart Study (PDHS) is a cross-sectional study of diabetic individuals without clinical cardiovascular or renal disease. We quantified and analyzed MAC Agatston scores in baseline cardiac CTs from 1753 individuals. Logistic and tobit regression were used to assess MAC's relationship with risk factors and coronary artery calcium (CAC).

Results: MAC was present in 12.0% of subjects, with a median Agatston score of 72.3 [Interquartile range (22.2–256.9)]. Older age, female gender, Caucasian race, and longer diabetes duration were independently associated with both the presence and extent MAC even after controlling for CAC; however, hypertension, hyperlipidemia, tobacco use, CRP levels, and other comorbidities were not associated. CAC was strongly associated with MAC [OR of 4.0 (95% CI 2.4–6.6)] in multivariable models.

Conclusions: Age, female gender, Caucasian race, and diabetes duration were associated with the presence and extent of MAC in T2DM subjects, independent of CAC, which was also strongly associated with MAC. These data suggest that additional mechanisms for MAC formation in diabetics may exist which are distinct from those related to generalized atherosclerosis and deserve further investigation.

1. Introduction

Mitral annular calcification (MAC) represents a degeneration of the fibrous ring of the mitral annulus [1]. It is one of the most common sites of calcification after the coronary arteries [2] and has been increasingly recognized in cardiovascular imaging studies, especially with cardiac CT. Once thought to be a mostly benign process, more recent evidence suggests that MAC is independently associated with cardiovascular disease (CVD) events [3], heart failure [4], stroke [1,5,6], carotid disease [7], and atrial fibrillation [8], as well as cardiovascular mortality [9] and overall mortality [10]. Hence, the burden of MAC in high-risk populations and mechanisms of MAC's association with cardiovascular risk factors and CVD deserve further investigation.

To date, the etiology of MC remains unclear. Histological findings in early disease reveal calcium deposition with apoptotic or necrotic interstitial cell material [11] but the pathogenesis still remains largely unknown. Abnormalities of calcium and phosphate homeostasis, as seen in chronic kidney disease (CKD) and end-stage renal disease (ESRD), may contribute [12,13]. Hemodynamic stress on the mitral annulus as occurs with hypertension and diastolic dysfunction may play a role [2,14,15]. Chronic inflammation may also lead to mitral annular degeneration, or MAC may be simply an extension or manifestation of generalized atherosclerosis [2,16]. A combination of several of these processes is also plausible.

Prior studies have found consistent associations between diabetes and MAC [17,18]. Yet, additional research is required to determine whether MAC may be a clinically useful marker and

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additive to established risk stratification in CVD or stroke risk assessment in diabetes. Because MAC has also been associated with kidney disease – both end-stage kidney disease (ESKD) and milder forms of chronic kidney disease (CKD) [19] – diabetic nephropathy in prior studies might have complicated the study of MAC in diabetics. In addition, many prior studies employed M-mode or 2D echocardiography for a semi-quantitative assessment of MAC, whereas contemporary cardiac CT [18,20] approaches provide a more sensitive and quantitative modality for assessment of MAC. We therefore examined the risk factors for MAC as measured by cardiac CT in patients with T2DM, but without clinical cardiovascular or kidney disease.

2. Methods

2.1. Study participants

Details regarding the Penn Diabetes Heart Study (PDHS) have been published previously [21]. In brief, PDHS recruited a cohort of 2032 subjects with T2DM between 2001 and 2011 from primary care and endocrinology outpatient clinics affiliated with the Hospital of the University of Pennsylvania and the Philadelphia VA Medical Center. The inclusion criteria were a clinical diagnosis of T2DM (defined as fasting blood glucose $\geq$126 mg/dl, 2-h postprandial glucose $\geq$200 mg/dl, or use of oral hypoglycemic agents/insulin in a subject greater than age 40 years), age of 35–75 years, and negative pregnancy test (if female). University of Pennsylvania IRB approval was obtained for this study and informed consent was obtained from all study subjects.

We excluded those with clinical coronary artery disease (defined as myocardial infarction, coronary revascularization, angiographic coronary disease or positive stress test), insulin use prior to age 35, a serum creatinine >2.5 mg/dl and a weight >300 lb (136.4 kg). Of 2032 subjects originally recruited, several individuals were excluded from this analysis: 143 individuals did not have a cardiac CT either because of withdrawal from the study or technical issues related to the scanner; of those with CT scans, 12 individuals had uninterpretable studies for MAC and 124 had missing covariate data. Thus, a sample of 1753 with complete data remained for analysis. Individuals with missing covariate data and no CT scans were similar to those with all available data based on age, gender, and race.

2.2. Clinical parameters

Participants were evaluated at Penn's Clinical and Translational Research Center (CTRC) after a 12-h overnight fast. All individuals underwent a detailed questionnaire for medical information and anthropometric measurements. Standard lipid panels were measured in real-time in Penn's Center for Disease Control-certified lipid laboratory using enzymatic assays (Hitachi 912, Roche Diagnostic Systems Inc., NJ, USA) in lipoprotein fractions after ultracentrifugation (β-quantification technique). C-Reactive Protein (CRP) levels were measured using two different assays over time: the initial 1000 participants had CRP measured using a high-sensitivity latex turbidimetric immunoassay (Wako Ltd., Osaka Japan), whereas the later 1032 were measured by a BNII nephelometer (Dade-Behring, Newark DE). A subset of PDHS CRP samples ($n = 35$) was measured using both assays with a Spearman rho correlation of 0.94 between samples and small systematic difference in levels (with mean $\pm$ SDs of 1.02 ± 0.50 mg/L vs. 1.03 ± 0.50 mg/L). Linear regression was used to adjust original assay results to reflect the more recent assay. Laboratory test results were generated by personnel blinded to the clinical characteristics and CT data of study participants. The MDRD estimated GFR evaluation was not applied because the vast majority of PDHS participants (>95%) had eGFR values of >60 mL/min/1.73 m^2 and this estimation lacks sensitivity and discrimination in mild kidney dysfunction [22].

2.3. Cardiac CT measurements

CT studies and global Agatston MAC scores were performed using an Imatron C-150 CT scanner (GE-Imatron, South San Francisco, CA). Scans were obtained using a single breath hold and with section thickness of 3 mm, field of view of 35 cm, and matrix of 512×512 to reconstruct raw image data. Images were calibrated to a standard phantom attenuation. MAC was defined as the presence of calcium visually seen along the mitral annulus in 3 orthogonal views; a specific Hounsfield cut point was not used. MAC was quantified using the Agatston scoring method provided by AquariusNET viewer software (TeraRecon, INC. Foster City, CA). Two trained readers interpreted all of the studies and were blinded to all other subject data. Five percent of the studies were randomly reassigned to be re-read by each reader and 5% to the other reader for quality control. The intra-reader kappa statistics were 0.96 (95% CI 0.87–1.00) and 0.90 (95% 0.76–1.00). The inter-reader kappa statistic for the presence of MAC was 0.87 (95% CI 0.73–1.00). Quantification of MAC Agatston scores was performed by 3 readers, who had an interclass correlation coefficient of 0.98 on a subset of 25 randomly selected studies. Coronary artery calcium (CAC) was quantified by the Agatston method as previously described [23]

2.4. Statistical analysis

Data are reported as median (interquartile range = IQR) or mean $\pm$ standard deviation for continuous variables and as proportions for categorical variables. For univariate comparisons of cardiovascular risk factors between individuals with and without MAC, the chi-square test, the Student's *t*-test and the Wilcoxon rank sum test were used. We used logistic regression and tobit regression for multivariable analysis of MAC data. Logistic regression was used to test the association of CVD risk factors with the presence of MAC; tobit conditional regression of $\ln(\text{MAC} + 1)$ was used to assess the association of risk factors with both the presence and quantity of MAC scores. Tobit regression is useful in situations with zero scores but also a marked skew and has been used for other similar distributions such as with CAC [23]. Tobit combines logistic regression of the presence of MAC (any MAC present vs. no MAC) with a linear regression (of log-transformed MAC) when MAC is present to produce a single estimate for the relationship of risk factors with MAC data.

Initial covariates were obtained from univariate analysis and included: age, gender, race and variables that were different between those with and without MAC with a p value cut point of <0.2. Plasma triglyceride and CRP levels were log-transformed. Backward stepwise elimination was used to obtain variables in the final model which were significantly associated with MAC (with a p value above 0.05 warranting elimination). We also examined the association of the presence of CAC and CAC Agatston scores with MAC using logistic and tobit regression models, respectively. All analysis was done using STATA version 12.0 software (Statacorp, College Station, Texas).

3. Results

3.1. Characteristic of the study sample

The mean age of the full study sample was 60 years (IQR 52–66 years); 36% were female, 61% were Caucasian, and 33% were African