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Non-compressible arterial disease and the risk of coronary calcification in type-2 diabetes

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ABSTRACT

Objective: Ankle–brachial index (ABI) screening is recommended for the detection of asymptomatic peripheral arterial disease (PAD) in at-risk populations, including diabetics. A low ABI identifies obstructive lower extremity vascular disease and predicts CVD events and increased mortality. A high ABI represents non-compressible arterial disease (NCAD), and is also associated with increased mortality and vascular events. Our objective is to investigate whether low and high ABI have distinct patterns of association with cardiovascular disease (CVD) risk factors and subclinical atherosclerosis in individuals with type-II diabetes mellitus.
Methods: The Penn Diabetes Heart Study (PDHS) is a prospective observational cohort of diabetic individuals without clinically evident CVD. Multivariate logistic and Tobit linear regression were used to compare CVD risk factors and coronary artery (CAC) among 1863 subjects with PAD (ABI $\leq$ 0.9), NCAD (ABI $\geq$ 1.4 or non-compressible) or normal ABI (0.91–1.39).
Results: Compared to those with normal ABI, PAD was associated with smoking, obesity, and lower HDL-c; while diabetes duration and reduced renal function were associated with NCAD. Both PAD and NCAD were independently associated with increased CAC compared to those with normal ABI, and these relationships were not attenuated in multiply adjusted models.
Conclusion: NCAD bears a distinct relationship to traditional CVD risk factors among diabetics, though like PAD is independently associated with increased CAC. These findings support the recognition of NCAD as a high-risk phenotype and provide additional relevance to ABI screening in diabetics.
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1. Introduction

Ankle–brachial index (ABI) screening is recommended for the detection of occult peripheral arterial disease (PAD) in at-risk populations [1]. An ABI ≤0.9 is sensitive and specific for obstructive PAD and is associated with increased cardiovascular disease (CVD) risk and mortality independent of traditional risk factors and Framingham score [2–5]. It has also been recognized that individuals with a high ABI (≥1.4) have cardiovascular event and mortality rates that are comparably increased nearly 2-fold among healthy populations, and as much as 7-fold among males [6–10].

A high ABI represents poorly compressible infra-popliteal vessels and is histologically associated with medial arterial calcification in diabetics [11–13]. This process can mask the detection of PAD, and indeed a high ABI has been observed in tandem with lower extremity atherosclerosis in diabetics [14,15]. However, elevated ABI does not simply appear to be "atherosclerosis masked", as important differences in CVD risk factors and vascular outcomes exist between those with low and high ABI [8,16,17]. Moreover, increased coronary artery calcium (CAC) or carotid intima–media thickness (cIMT) has not been reliably detected in this subgroup [18,19].

The goal of the present study was to determine the relationships of high and low ABI with established and non-traditional CVD risk

Abbreviations: ABI, ankle–brachial index; CAC, coronary artery calcium; cIMT, carotid intima–media thickness; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; NCAD, non-compressible arterial disease; PAD, peripheral arterial disease; PDHS, Penn Diabetes Health Study.

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factors in a diabetic population without clinical atherosclerosis. Moreover, we sought to determine whether high ABI is associated with increased CAC. We defined an ABI ≥1.4 as a non-compressible arterial disease (NCAD) [9,17,20,21].

2. Materials and methods

The Penn Diabetes Heart Study (PDHS) is a cross-sectional observational cohort of patients aged 35–75 years with diabetes, enrolled between 2001 and 2011 [22,23]. Exclusions included evidence of clinical atherosclerotic cardiovascular disease (history of myocardial infarction, coronary revascularization or angiographic atherosclerosis, positive stress test, clinical peripheral arterial disease or peripheral arterial revascularization, stroke or transient ischemic attack by clinical records), advanced renal disease (Creatinine > 2.5 mg/dl) or type I diabetes (insulin use prior to age 35). Participants were recruited from the primary care and endocrinology practices affiliated with the Hospital of the University of Pennsylvania and the Philadelphia Veterans Affairs Medical Center. The University of Pennsylvania Institutional Review Board approved the study protocol, and all subjects gave written informed consent.

Subjects were interviewed, filled out medical questionnaire, and underwent standard anthropomorphic measurements, evaluated after a 12-h overnight fast. Hypercholesterolemia was defined as the use of lipid lowering medications or total serum cholesterol >200 mg/dl. Hypertension was defined as the use of antihypertensive medications or blood pressure >130/80 mmHg. Smoking status was derived from history and categorized as present, former, or never.

Total cholesterol, high-density lipoprotein cholesterol (HDL-c), and triglycerides were measured enzymatically (Hitachi 912 autoanalyzer, Roche Diagnostics, Basel, Switzerland) and LDL-c directly, after the lipoprotein fraction was obtained via ultracentrifugation (□-quantification technique). Lipoprotein(a) and high sensitivity C-reactive protein were measured by immunoturbidimetric assay (Wako Chemicals, U.S.A. Inc., Richmond, VA) on the Hitachi 912 autoanalyzer. All samples were assayed in duplicate, and pooled human plasma was included as a control across all assay plates to assess variability. Fasting chemistries and hemoglobin A1c were measured at clinical laboratories of the Hospital of the University of Pennsylvania by personnel blinded to the clinical characteristics and ABI status of the research subjects. Estimated glomerular filtration rate (eGFR) was calculated based on the abbreviated Modification of Diet in Renal disease Study equation [24]. Framingham risk scores were calculated as previously described [25].

Brachial and ankle pressures were obtained with a hand-held Doppler (5 MHz, Nicolete Elite Vascular Model no. 100; Madison, WI). The ABI was calculated as the average of the ankle pressures (posterior tibial and dorsalis pedis) divided by the highest brachial pressure. Subjects were stratified into three groups [1]: PAD: any limb with an ABI ≤ 0.9 [2]; NCAD: any limb with an ABI ≥ 1.4; and [3] normal: those with both limbs ABI 0.91–1.39 [9,17,20,21]. One individual with an ABI ≤ 0.9 and an ABI ≥ 1.4 in opposing limb was excluded. We employed this strategy, rather than accepting the lower limb ABI, to enable the representation of any patient with abnormal limb into the respective PAD or NCAD group [9]. Global CAC was assessed in 40 continuous 3-mm thick computed tomograms collected on an EBT scanner (Imatron, San Francisco, CA) and scored by a single experienced and blinded technologist as previously described [26].

Categorical variables were compared with the chi-square test unless the expected number of observations per cell was less than 10, in which case the Fisher exact test was employed. For continuous variables, between group differences were analyzed with univariate analysis of variance, unless there was unequal variance (Bartlett's test < 0.05) in which case groups were compared with the Kruskal–Wallis test. Tobit linear regression was used to look at differences between ABI groups in adjusted multivariable models with log transformed CAC + 1 was used as the dependent variable, which collectively permits censoring of the high frequency 0 CAC scores and the application of linear regression of transformed values. This has been previously demonstrated to consistently detect associations with CVD risk factors and CAC in asymptomatic populations [26]. Due to the presumed non-linear association of ABI and CAC we also created cubic-spline functions with prespecified interior knots at ABI of 0.9 and 1.4 and employed these in regression models. All p values presented are 2-tailed, ≤0.05 was considered statistically significant. Analyses were performed with Stata 12.0 software (Stata Corp, College Station, TX).

3. Experimental results

Characteristics of the study sample are provided in Supplementary Table 1. Briefly, there were 1863 eligible participants in PDHS and the mean age was 58.9 years (range 35–78), with 36% women, 61% Caucasian, and 34% African–American. Hypertension and hyperlipidemia were frequent (65% and 71%, respectively), mean hemoglobin A1c was 7.1 ± 1.5% and the frequency of insulin use was 21%. The majority of patients were former or current smokers (59.2%). Among the entire cohort there were 187 (10.0%) subjects with PAD (ABI ≤ 0.9), and 75 (4.0%) with NCAD (ABI ≥ 1.4). Twelve subjects (0.6%) had at least one ankle vessel that was not compressible, and these comprised 16% of NCAD subgroup (Supplementary Fig. 1).

Demographic and clinical variables differed among ABI subgroups as depicted in Table 1. Individuals with PAD were older and more frequently African–American, while those with NCAD were more likely male and Caucasian. Compared to those with normal ABI, PAD was accompanied by a greater frequency of current smoking and a longer history of tobacco use, whereas individuals with NCAD had a longer duration of diabetes and a greater incidence of chronic kidney disease (eGFR < 60 ml/min/1.73 m^2). Ten-year Framingham risk was numerically higher in those with PAD or NCAD compared to normal ABI (Table 1).

Given significant differences in baseline demographics among the ABI subgroups, a multivariate logistic regression model was employed to identify independent predictors of PAD or NCAD among the PDHS cohort (Table 2). In the fully adjusted model increasing age, African–American race, current smoking, lower HDL-c, and obesity (BMI > 30 kg/mm^2) were all significant predictors of PAD. With respect to NCAD, younger age, male gender and Caucasian race all significantly predicted NCAD. There was also a small but significant relationship between diabetes duration and NCAD. Moreover, the presence of chronic kidney disease also significantly predicted NCAD (OR 2.33). In contrast to the relationship between current smoking and PAD, the absence of current smoking was nearly associated with NCAD in the adjusted model.

To clarify the significance of PAD and NCAD with respect to coronary subclinical atherosclerosis, we compared CAC scores across ABI subclasses. Overall CAC was prevalent across the cohort (64.8%; CAC > 0) and on unadjusted analysis differed between those with NCAD (78.4%), but not PAD (69.4%) compared to those with normal ABI (63.6%; $p = 0.01$ and 0.12, respectively). Similarly, when analyzed in fully adjusted models (see Fig. 1 legend for included variables) there was a significant relationship between NCAD and the presence of any CAC (OR 2.04; $p = 0.04$), but not between PAD and CAC (OR 1.29; $p = 0.24$). Total coronary calcium scores were higher among those with PAD or NCAD compared to those with normal ABI, though this effect was attenuated by age-

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