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The associated risk factors for coronary artery calcium in asymptomatic individuals with and without diabetes in rural Central Appalachia

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ABSTRACT

Aim: To examine the risk factor of coronary artery calcium (CAC) in individuals with diabetes and those without diabetes in Central Appalachia.
Methods: Study population included 2479 asymptomatic participants who underwent CAC screening between August 2012 and November 2016. CAC score was classified into four categories [0 (no plaque), 1–99 (mild plaque), 100–399 (moderate plaque), and ≥400 (severe plaque)]. Multinomial logistic regression analyses were conducted to test the association between CAC and cardiovascular disease (CVD) risk factors among participants with diabetes, age and gender matched controls, and randomly selected controls.
Results: 13.6% of total participants had diabetes. Around 69%, 59.8%, and 57.7% of the participants with diabetes, matched controls, and randomly selected controls had CAC score ≥1, respectively. Participants with diabetes had higher prevalence of all CVD risk factors than controls. Among participants with diabetes, hypertension and physical inactivity increased the odds of CAC = 100–399, while among those without diabetes, hypertension and hypercholesteremia increased the odds of having CAC = 1–99 and CAC ≥ 400.
Conclusion: Half of study participants had subclinical atherosclerosis (i.e., CAC), and individuals with diabetes had higher CAC scores. This study suggests that individuals with diabetes in Central Appalachia might benefit from screening for CAC.

1. Introduction

In 2015, 30.3 million (9.4%) and 84.1 million individuals in the United States (U.S.) had diagnosed diabetes or pre-diabetes, respectively.[1] It has been projected that the prevalence of diabetes in the U.S. will increase by 64% from 2010 to 2025.[2] The negative health outcomes for patients with diabetes such as increased risk of cardiovascular diseases (CVDs)[3–5] have been well reported. Evidence indicates that individuals with diabetes are at a high risk for developing atherosclerotic CVD such as coronary heart disease (CHD), which has historically led to diabetes being considered as a CVD risk equivalent.[6–11] Adults diagnosed with diabetes have a nearly two-fold increased risk of CVD related mortality, compared to those without diabetes.[4,6] Thus, controlling and managing diabetes is expected to reduce the risk for complications of CVD and related deaths. The prevalence of diabetes in the U.S., however, is not uniform, with geographic regions such as Central Appalachia, referred to as the "Diabetes Belt", which exhibits a disproportionately high burden relative to the rest of the nation.[12] This highlights the critical need to identify those at risk for developing CVD early in high-risk geographic areas with a disproportionate share of diabetes and the need to target interventions in these regions with the goal of reducing long-term health outcomes. However, research

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about the early detection of CVD in individuals with diabetes in the Central Appalachian region is sparse. This situation provides the basis for this study, which leverages mechanisms to overcome poor health literacy and patient understanding, with the goal of providing earlier and more appropriate risk stratification and resource utilization.

Individuals with diabetes have increased risk of clinical and subclinical atherosclerosis,[4,13] a marker of coronary artery disease (CAD) that be detected by coronary artery calcium (CAC) scoring.[14,15] Research suggests that CAC has a high predictive value in classifying CVD risk among asymptomatic individuals,[16,17] including those with diabetes who are more likely to have atypical CAD symptoms,[18,19] Studies have found that CAC is a significant predictor of CVD events even among individuals characterized as having low risk for future CVD events[16] and CVD outcomes, compared to traditional risk factors and other novel risk assessment tools.[4,17] Additionally, studies have shown that CAC score is even more sensitive in predicting future CVD events among individuals with diabetes.[20,21] Individuals with diabetes tend to have both higher CAC scores[22] and more rapid CAC accumulation over time.[23] Moreover, higher mortality was observed for a similar increase in CAC scores among individuals with diabetes, compared to those without diabetes. As a contribution to this research, this study seeks to investigate CAC scores in asymptomatic individuals with diabetes in the high-risk region of Central Appalachia. Research on CAC in individuals living with diabetes in this region is sparse, which undermines national efforts under *Healthy People 2020* to address health disparities in the U.S.[24]

The goal of this study was to address this health disparity by examining the association between modifiable and non-modifiable risk factors of CVD and CAC in asymptomatic individuals with diabetes and those without diabetes in Central Appalachia. The aims were to 1) assess the differential characteristics of individuals with and without diabetes in terms of demographics and CVD risk factors; 2) evaluate the prevalence and extent of CAC in individuals with and without diabetes; and 3) examine the modifiable and non-modifiable CVD risk factors of CAC among individuals with diabetes and those without diabetes. The results of this analysis should inform clinicians and public health practitioners in high-risk rural environments in the use of CAC screening for the early detection of CAD in asymptomatic patients with diabetes as recommended by clinical guideline,[25,26] with an ultimate goal to improve primary prevention interventions to reduce cardiovascular events. Additionally, these data could direct implementation of policies/programs that simultaneously address the disproportionately high burden of CVD and diabetes in regions such as Central Appalachia to reduce health disparities in the U.S.

2. Study participants

This study is a collaboration between the investigators and the largest cardiovascular center in the Central Appalachian region, and involves asymptomatic individuals from Kentucky, North Carolina, Tennessee, and Virginia. The recruitment, enrollment, and data collection processes have been published in previous studies.[27–30] Briefly, 3000 asymptomatic individuals from the region participated in CAC screening through self- or physician-referral from August 2012 and November 2016. Prior to the screening, each individual had to sign an informed consent stating voluntary agreement to participate, and they could withdraw their consent at any time during the screening process without retribution. Based on a standard protocol, only individuals aged ≥45 years for males, ≥55 years for females, or ≥18 years and referred by a healthcare provider were eligible to participate in the screening. Seventy-nine participants were excluded from the analysis because they were non-whites ($n = 34$), missing information on race ($n = 33$), and had extreme body mass index (BMI) >70 or < 14 ($n = 12$). One participant was excluded for an erroneous CAC score to reduce the effect of outliers. Additionally, participants with missing information in any one of the variables included in the study were excluded from the analysis ($n = 441$). The final analytic sample comprised of 2479 individuals.

3. Materials and methods

Since this study focused on subclinical atherosclerosis, as evaluated by CAC screening, in asymptomatic individuals with diabetes, each particpant was asked if they had been informed by a physician or healthcare professional that they had diabetes and/or whether the participant was currently taking any medication to control diabetes (yes/no). Using this question, 336 participants were found to have diabetes. For each participant who reported having diabetes, age and gender matched individual without diabetes was selected and included in the matched control group. If more than one individual without diabetes could be matched based on age and gender, one out of all the eligible participants was selected randomly. Further, to create the random control group, all the participants without diabetes were listed and random numbers were generated to pick the participants without diabetes.

The study protocol was approved by the Institutional Review Board (IRB) of the collaborating health system and of the authors' institution [Blinded for review].

3.1. Study outcome: coronary artery calcium (CAC)

The CAC score was ascertained by the collaborating health system in Central Appalachia. The entire process to ascertain the CAC score, including recruitment of participants, the CAC screening, generating the CAC scores, and reporting the results to the participant, was controlled by physicians and radiologists of the health system. Consistent with study procedure and standard protocol,[31] participants in the CAC screening were required to remove all metal objects from the chest area and three stick-on electrode leads were placed on the chest. The person was asked to lie still on a 64-slice Computed Tomography (CT) scanner as it advanced through the gantry. Three passes were completed with the individual holding their breath for ≥10 s each time. After the procedure, a CAC score based on the Agatston algorithm[32] was computed to quantify the volume of calcification or plaque, an indicator of atherosclerosis burden. The score was calculated as the product of the area of calcification per coronary tomographic segment and a factor rated 1 through 4 depending on the maximal X-ray density in that segment.[32] The result was numerically coded on an ordinal scale as 0 (No plaque), 1–99 (Mild plaque), 100–399 (Moderate plaque), and 400 or greater (Severe plaque).

3.2. Independent variables

A self-administered questionnaire was used to collect additional information on demographics (age and sex), medical conditions, health behavior, and history of CVD. Age was recorded as a continuous variable and sex was assessed as male or female. Information on clinical status of hypertension and hypocholesteremia were collected by asking participants if they had been informed by a physician or any healthcare provider about whether or not they had such conditions and/or if they were using any antihypertensive or anti-cholesterol medications. For smoking status, self-reported former or current smoker was classified as 'ever smoker' and those who had never smoked were classified as 'never smoker'. Additionally, participants were asked if they had a history of CAD or family history of coronary heart disease (CHD). Further, physical inactivity was ascertained by asking if the participants classified their lifestyle as primarily sedentary or not, with responses recorded in bivariate format (yes/no). Height and weight were self-reported by the participants and used to calculate BMI of each participant. All participants with a BMI ≥ 30 were classified as being obese.[33]

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