Peripheral Arterial Disease

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Objectives — Homeostatic glucose control may play an important role in the development of peripheral arterial disease among individuals without diabetes. We sought to evaluate the association between HbA1c (A1C) and peripheral arterial disease in a representative sample of the U.S. population with and without diabetes.

Research Design and Methods — A cross-sectional study was conducted among 4,526 National Health and Nutrition Examination Survey 1999–2002 participants ≥40 years of age. Peripheral arterial disease was defined as an ankle-brachial index < 0.9 (n = 327).

Results — Among nondiabetic subjects, the age-standardized prevalence of peripheral arterial disease was 3.1, 4.8, 4.7, and 6.4% for participants with an A1C < 5.3, 5.3–5.4, 5.5–5.6, and 5.7–6.0%, respectively (P trend < 0.001). The prevalence of peripheral arterial disease was 7.5 and 8.8% for diabetic participants with A1C < 7 and ≥7%, respectively. After multivariable adjustment and compared with nondiabetic participants with A1C < 5.3%, the odds ratio (95% CI) of peripheral arterial disease for nondiabetic participants with an A1C of 5.3–5.4, 5.5–5.6, and 5.7–6.0% was 1.41 (0.85–2.32), 1.39 (0.70–2.75), and 1.57 (1.02–2.47), respectively, and it was 2.33 (1.15–4.70) and 2.74 (1.25–6.02) for diabetic participants with A1C < 7 and ≥7%, respectively.

Conclusions — An association exists between higher levels of A1C and peripheral arterial disease, even among patients without diabetes. Individuals with A1C levels ≥ 5.3% should be targeted for aggressive risk factor reduction, which may reduce the burden of subclinical cardiovascular disease even among those without diabetes.


The risk for clinical cardiovascular disease among individuals with diabetes is two to four times higher compared with their counterparts without diabetes (1–4). Higher rates of subclinical cardiovascular disease among patients with diabetes have also been reported (5–7). Among the population of patients with diabetes, homeostatic glycemic control may be an important mediating factor in preventing cardiovascular disease (8).

More recently, some studies have noted elevated levels of glycemia to be associated with cardiovascular disease among the general population without diabetes (9–13). For example, after excluding individuals with diabetes (i.e., self-report of a previous diagnosis and/or fasting plasma glucose ≥140 mg/dl and/or a 2-h postchallenge plasma glucose ≥200 mg/dl), the multivariable adjusted relative hazard of cardiovascular disease mortality for women in the highest quintile (≥6.7%) versus the lowest four quintiles (<6.7%) of HbA1c (A1C) was 2.61 (95% CI 1.40–4.88) in the Rancho Bernardo Study (12). However, no association was present between A1C and cardiovascular mortality among men in this study.

Given the strong association between glycemic control and the development of clinical and subclinical cardiovascular disease among diabetic patients and mounting evidence that mild abnormalities of glucose metabolism may be associated with cardiovascular disease in nondiabetic individuals, we hypothesized that a strong association may exist between homeostatic glycemia and subclinical cardiovascular disease among patients without diabetes. Therefore, we examined the association between A1C and peripheral arterial disease among a nationally representative sample of U.S. adults participating in the National Health and Nutrition Examination Survey (NHANES) 1999–2002.

Research Design and Methods — NHANES 1999–2002 was a cross-sectional survey of the civilian noninstitutionalized population of the U.S. The procedures involved in NHANES 1999–2002 have been published in detail and are available online (14). In brief, this study included a stratified multistage probability sample based on selection of counties, blocks, households, and individuals within households.

Overall, 5,874 adults ≥40 years of age participated in the interview and examination components of NHANES 1999–2002. Of these participants, ankle-brachial index (ABI) was available for 4,930 participants (84%). After excluding 10 participants with an ABI ≥1.5, values usually related to noncompressible vessels in the legs, and 392 participants with missing covariable data (e.g., total cholesterol), 4,528 participants were included for all analyses.

NHANES consisted of an in-home in-
Peripheral arterial disease was defined as ABI < 0.9 (16,17). Detailed descriptions about blood collection and processing are provided in the NHANES Laboratory/Medical Technologists Procedures Manual. C-reactive protein was measured using latex-enhanced nephelometry, and total cholesterol was measured enzymatically. Serum creatinine was measured using the modified Jaffe reaction with glomerular filtration rate estimated by the abbreviated formula from the Modification of Diet in Renal Disease study after creatinine calibration (18,19). Chronic kidney disease was defined as an estimated glomerular filtration rate < 60 mL/min/1.73 m$^{-2}$ (2). Serum glucose was measured at the University of Missouri Diabetest Diagnostic Laboratory using a modified hexokinase enzymatic method. A1C was also measured at the University of Missouri using a boronate affinity high-performance liquid chromatography system. Diabetes was defined as a serum glucose ≥ 126 mg/dl after fasting for a minimum of 8 h, a serum glucose ≥ 200 mg/dl for those who fasted < 8 h before their NHANES visit, A1C ≥ 6.1%, and/or self-reported current use of antidiabetes medication.

**Statistical analysis**

The population was divided into six mutually exclusive groups based on diabetes status and A1C level. Individuals without diabetes were categorized into quartile of A1C (< 5.3, 5.3–5.4, 5.5–5.6, and 5.7–6.0%), and individuals with diabetes were categorized as having well-controlled diabetes or not (A1C < 7 or ≥ 7%, respectively). The age-standardized characteristics of the study population were calculated for each of these six categories, with trends across all six categories, and across quartile of A1C among nondiabetic subjects, determined using maximum likelihood estimation. For trend analyses, diabetes and A1C groups were ordered from lowest to highest as follows: no diabetes and lowest to highest quartile of A1C, diabetes and A1C < 7%, and diabetes and A1C ≥ 7%.

The age-standardized prevalence of peripheral arterial disease was calculated for each A1C category for individuals with and without diabetes. The odds ratio (OR) of peripheral arterial disease was calculated for each A1C level, with the lowest quartile of A1C among individuals without diabetes as the reference, using multivariable logistic regression models. Initially, ORs were adjusted for age, and then they were adjusted for age, race/ethnicity, sex, systolic blood pressure, current and former cigarette smoking, alcohol consumption, being physical active, waist circumference, chronic kidney disease, total cholesterol, and C-reactive protein. Trends in the OR of peripheral arterial disease across A1C category were determined for the full population and limited to nondiabetic participants modeling A1C category as a continuous variable, using logistic regression.

The age-adjusted; age-, race/ethnicity- and sex-adjusted; and multivariable-adjusted OR of peripheral arterial disease associated with 1-percentage point–higher A1C was calculated, using logistic regression models. These ORs were calculated for the full study population; individuals with A1C < 7 and < 6.1%, separately; and, finally, for individuals without diabetes. The consistency of the association between 1-percentage point–higher A1C and peripheral arterial disease across important subgroups was determined by logistic regression methods stratified by race/ethnicity, sex, and cigarette smoking status.

Sample weights that account for the unequal probabilities of selection, over-sampling, and nonresponse were applied for all analyses using SUDAAN (version 8.0; Research Triangle Institute, Research Triangle Park, NC). SEs were estimated using the Taylor series linearization method.

**RESULTS**

After age standardization, individuals with higher levels of A1C were, on average, older, less likely to be female, and more likely to be non-Hispanic black or Mexican American, versus non-Hispanic white (Table 1). Additionally, after age standardization, those with higher levels of A1C were more likely to be current smokers and had higher systolic blood pressure, larger waist circumference, and higher C-reactive protein. Additionally, age-standardized ABI was lower among individuals with higher levels of A1C.

Overall, 327 study participants (5.1%) in NHANES 1999–2002 had peripheral arterial disease. After age standardization, the prevalence of peripheral
CONCLUSIONS — In the current study, higher A1C levels were associated with a higher prevalence of peripheral arterial disease, as indicated by race/ethnicity, sex, and current/former smoking. The association was strongest among African Americans and among those with diabetes. A1C levels were lower in patients with diabetes and higher in those without diabetes. The association between A1C levels and peripheral arterial disease persisted even after adjustment for age, sex, race/ethnicity, smoking, and other cardiovascular risk factors. The results suggest that A1C levels may be a useful indicator of risk for peripheral arterial disease in clinical settings.
cholesterol, C-reactive protein, and chronic kidney disease. The definition of diabetes used in the current study reflects cut points from evidence-based guidelines (20). However, as noted in these guidelines, the risk of microvascular disease and target organ damage extends below these cut points (20). The results of the current study add to previously published evidence and suggest substantial benefits of tight glycemic control, even among patients without diabetes.

A meta-analysis of observational studies has documented an increased risk of cardiovascular disease associated with higher levels of A1C among patients with diabetes (7). Specifically, the pooled relative risk (RR) of cardiovascular disease for each 1–percentage point–higher A1C was 1.18 (95% CI 1.10–1.26) from 10 studies that included 7,435 patients with type 2 diabetes. Additionally, this study also investigated the impact of A1C on peripheral arterial disease among patients with type 2 diabetes. Three studies of A1C and peripheral arterial disease among type 2 diabetic patients were identified (21–23). Each of the identified studies reported A1C to be associated with a significant increased RR of peripheral arterial disease, after pooling together the results from the three studies, the RR of peripheral arterial disease associated with 1–percentage point–higher A1C was 1.28 (95% CI 1.18–1.39) among patients with type 2 diabetes (7). Our study extends these findings to a large nationally representative population sample of nondiabetic patients. Among nondiabetic patients in the current study, each 1–percentage point–higher A1C was associated with an age-, race/ethnicity-, and sex-adjusted OR of 2.00 (1.13–3.54) and a multivariable-adjusted OR of 1.77 (0.97–3.21) for peripheral arterial disease.

Despite consistent results among diabetic patients, studies of glucose metabolism abnormalities and cardiovascular disease among nondiabetic patients have provided inconsistent results (10, 12, 24, 25). In men without diagnosed diabetes participating in the European Prospective Investigation of Cancer and Nutrition (EPIC-Norfolk) study, the RR of all-cause mortality associated with A1C of 5.0–5.4, 5.5–6.9, and >7%, compared with their counterparts with A1C <5%, was 1.41, 2.07, and 2.64, respectively (P trend <0.001) (10). Additionally, in a nested case-control study of the Women’s Health Study, the crude RR of cardiovascular disease among participants in the highest versus lowest quartile of A1C was 2.25 (95% CI 1.59–3.18) (24). However, after adjustment for additional factors, including blood pressure and C-reactive protein, this association was no longer present (RR 1.00). Among women in the Rancho Bernardo study, higher A1C was not associated with a significant increase in all-cause mortality, but it was associated with a significant increased relative hazard of cardiovascular disease and ischemic heart disease mortality (12). How-

**Figure 1**—Age-standardized prevalence of peripheral arterial disease by level of A1C among individuals with and without diabetes. PAD, peripheral arterial disease.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>ORs of peripheral arterial disease by level of A1C for participants with and without diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Quartile of A1C among nondiabetic subjects (range, %)</strong></td>
<td>No Diabetes</td>
</tr>
<tr>
<td><strong>Quartile 1 (3.5–5.5)</strong></td>
<td>1.00 (ref.)</td>
</tr>
<tr>
<td><strong>Quartile 2 (5.5–7.0)</strong></td>
<td>1.48 (0.96–2.29)</td>
</tr>
<tr>
<td><strong>Quartile 3 (7.0–7.5)</strong></td>
<td>1.43 (0.93–2.23)</td>
</tr>
<tr>
<td><strong>Quartile 4 (7.5–7)</strong></td>
<td>1.41 (0.85–2.32)</td>
</tr>
<tr>
<td><strong>Adjusted for Age, race, and sex</strong></td>
<td>1.00 (ref.)</td>
</tr>
<tr>
<td><strong>Adjusted for Multivariable</strong></td>
<td>1.00 (ref.)</td>
</tr>
</tbody>
</table>

Data are OR or OR (95% CI). *P* for the full population were calculated across all six A1C and diabetic groups ordered from lowest to highest as follows: no diabetes and lowest to highest quartile of A1C, diabetes and A1C <7%, and diabetes and A1C >7%. Adjusted for age, race, ethnicity, sex, systolic blood pressure, current and former cigarette smoking, alcohol consumption, physical activity, waist circumference, chronic kidney disease, total cholesterol, and C-reactive protein.
ever, no association was present between A1C and all-cause or cause-specific mortality among men.

Studies of A1C with subclinical cardiovascular disease have produced conflicting evidence (26–29). In a nested case-control study within the Atherosclerosis Risk in Communities (ARIC) study, the mean A1C level was 5.18 and 5.07%, respectively (P = 0.004), among case subjects (carotid artery far-wall thickness >2.5 mm or bilateral thickening exceeding the 90th percentile of the cohort distribution) and control subjects matched for age, race, sex, and Atherosclerosis Risk in Communities field center (far- and near-wall thickness lower than the 75th percentile of intima-media thickness on all carotid artery segments) (28). However, no association between A1C and intima media thickness was present after multivariable adjustment. Additionally, among 582 individuals at risk for diabetes, a significant age- and sex-adjusted association between A1C and intima-media thickness was no longer significant, with an OR of 1.24 (95% CI 0.82–1.89), after multivariable adjustment (35). Among older Caucasian adults without known diabetes in the Hoorn study population, each 1-percentage point–higher A1C was associated with a multivariable-adjusted OR of peripheral arterial disease of 1.35 (1.10–1.65) (26). Other studies have also found associations of higher rates of subclinical cardiovascular disease at higher levels of glycemia (29). These latter studies are consistent with the results from the current analysis; the multivariable-adjusted OR of peripheral arterial disease associated with an A1C of 5.7–6.0%, compared with an A1C <5.3%, was 1.57 (1.02–2.47). Additionally, previously published data from the Diabetes Control and Complications Trial have shown that the risk of retinopathy progression, microalbuminuria, and neuropathy increased continuously with higher levels of A1C over its entire range.

Peripheral arterial disease is a particularly strong prognostic indicator of future clinical cardiovascular disease events, and the importance of its recognition has been highlighted in several guidelines (30–33). Furthermore, it is easily diagnosed in clinical practice at minimal cost. It should be recognized that in the late stages of diabetes, calcification and increased arterial wall stiffness may lead to false elevations in ankle blood pressure. It is not clear whether such changes occur early in the disease process, but, if so, our findings may be more robust than indicated by the data.

Despite the potential benefits of lowering A1C noted in the current study, to our knowledge there is no clinical trial data showing that the risk of cardiovascular and peripheral arterial diseases is reduced by the continued reduction of A1C below 6.1%. However, one of the primary aims of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial is to assess whether a therapeutic strategy targeting an A1C of <6.0% will reduce the rate of cardiovascular disease events compared with a target of 7.0–7.9% (34). Recruitment for Action to Control Cardiovascular Risk in Diabetes began in 2003, with follow-up expected to last through 2009, and study results are anticipated to be available in 2010.

The results presented for the current study need to be interpreted in the context of the study’s limitations. Most notably, the cross-sectional nature of the present study limits assessment of the causal nature of the association between A1C and peripheral arterial disease. Additionally, although the sample size was large, the power to detect associations and effect modification was limited because of the low prevalence of peripheral arterial disease. For example, although elevated ORs of peripheral arterial disease were present when comparing nondiabetic patients with an A1C of 5.3–5.4 and 5.5–5.6% vs. <5.3%, the 95% CIs were wide and included the null. Given the graded nature of the association detected, with a larger sample size, these ORs most likely would have been statistically significant. Additionally, although we analyzed patients with diabetes separately, NHANES 1999–2002 procedures did not include the oral glucose tolerance test. Therefore, some patients classified as not having diabetes in the current study, based on serum glucose <126 mg/dl (<200 for those not fasting for >8 h) and A1C <6.1%, may have impaired glucose tolerance. Previous studies indicate the association with subclinical cardiovascular disease may be stronger for elevated postchallenge glucose levels and spikes, compared with higher A1C (35). An additional limitation is that because of time constraints during the NHANES visit, ABI was measured only in the posterior tibial artery, and the dorsalis pedis artery pressure was not measured. Finally, only a subsample of NHANES 1999–2002 participants were asked to fast overnight before their study visit. An association between higher fasting serum glucose and peripheral arterial disease appeared to be present (data not shown). However, the CIs were wide because of the limited number of cases in the fasting NHANES subsample.

Despite these limitations, there are several strengths involved in the current study. This study involved a nationally representative sample of the U.S. population >40 years of age. Additionally, all data were collected following rigorous methodology, including a study protocol with quality control checks.

In conclusion, higher levels of A1C among nondiabetic patients may be an indicator of increased risk of subclinical cardiovascular disease. A significant increased risk of peripheral arterial disease was noted at A1C levels between 5.7 and 6.0% among nondiabetic patients. Furthermore, nonsignificant increased risks of peripheral arterial disease were noted at A1C levels of 5.3–5.4 and 5.5–5.6%.

**Table 3—ORs of peripheral arterial disease associated with 1-percentage point–higher A1C**

<table>
<thead>
<tr>
<th></th>
<th>Full population</th>
<th>A1C &lt;7%</th>
<th>A1C &lt;6.1%</th>
<th>No diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjusted for age</td>
<td>1.24 (1.09–1.42)</td>
<td>1.83 (1.28–2.62)</td>
<td>2.25 (1.29–3.91)</td>
<td>2.14 (1.21–3.78)</td>
</tr>
<tr>
<td>Adjusted for age, race, and sex</td>
<td>1.27 (1.09–1.47)</td>
<td>1.81 (1.23–2.66)</td>
<td>2.19 (1.29–3.71)</td>
<td>2.08 (1.22–3.55)</td>
</tr>
<tr>
<td>Multivariable*</td>
<td>1.24 (1.05–1.47)</td>
<td>1.65 (1.07–2.55)</td>
<td>1.87 (1.02–3.43)</td>
<td>1.77 (0.97–3.21)</td>
</tr>
</tbody>
</table>

Data are OR (95% CI). *Adjusted for age, race/ethnicity, sex, systolic blood pressure, current and former cigarette smoking, alcohol consumption, physical activity, waist circumference, chronic kidney disease, total cholesterol, and C-reactive protein.
Measurement of A1C or other indicators of mild glucose abnormalities in clinical practice may be valuable in identifying patients with an increased risk of subclinical cardiovascular disease.

References
