Prevalence and risk factors for the development of abdominal aortic calcification among the US population: NHANES study

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Abstract

Introduction: Abdominal aortic calcification (AAC) is an important marker of subclinical cardiovascular disease and its prognosis. Advanced age, hypertension, smoking, dyslipidemia, diabetes mellitus, and higher truncal fat are known markers of AAC in studies conducted around the world. However, literature for these risk factors and their co-occurrence is limited in the US. Material and methods: We used data from dual energy X-ray absorptiometry (Hologic, v4.0) to detect the occurrence of AAC in a sample population (n = 3140) of the NHANES survey using a computer-assisted interviewing system to assess the risk factors for AAC.

Results: We found the national prevalence of AAC in the US to be 28.8%. After adjusting for confounders, persons with hypertension: OR = 1.66 (95% CI: 1.30–2.13) and smokers: OR = 1.63 (95% CI: 1.24–2.14) were more likely to have AAC compared to their respective counterparts. Increasing age was positively associated with AAC: OR = 1.06 (95% CI: 1.04–1.08). There was a statistically significant negative association between body mass index (BMI) and AAC, more so in smokers than in non-smokers: OR = 0.97 (95% CI: 0.94–0.97). We did not observe any statistically significant association between diabetes and AAC.

Conclusions: Advanced age, smoking, and hypertension were associated with increased occurrence of AAC. Paradoxically, increasing BMI was inversely associated with AAC and there was no statistically significant association between total body and trunk fat percentages and AAC. To the best of our knowledge, this is the first study to establish the nationwide prevalence and associated factors in the US.

Key words: abdominal aortic calcification, prevalence, risk factors, NHANES database.
Introduction

Abdominal aortic calcification (AAC), a marker of subclinical cardiovascular disease [1], is associated with the extent and severity of coronary artery disease [2], stroke and heart failure [3]. The absence of AAC has a high negative predictive value to rule out coronary artery disease [4]. Prevalence of AAC varies widely among different groups. Prior studies have reported a prevalence of 31% in postmenopausal women with primary hyperparathyroidism and 13% in age-matched controls [5] and 70.6% among patients with end-stage renal disease (ESRD) and chronic kidney disease (CKD) [6].

Advanced age [7], hypertension [2], dyslipidemia [2], diabetes mellitus [2], higher visceral and subcutaneous fat content [8, 9], and chronic smoking [2, 10] were highlighted as important risk factors for AAC. However, the pathophysiology of AAC is different from most vessel disorders and not thoroughly elucidated [1]. Factors like phosphate accumulation, inflammation, hormonal changes, metabolic disorders, and oxidative stress have been implicated in the differentiation of vascular smooth muscle cells from osteoblasts leading to mineral deposition in the vessel wall [11]. Also, genetic predisposition for the development of AAC is well known [12]. A multifactorial interplay of these factors contributes in the development and progression of AAC.

Though AAC is an important marker of subclinical cardiovascular disease (CVD) and predictor of adverse outcomes, there is little dedicated documentation on the risk factors in the general population in the US. Given the dearth of literature on this, we set out to evaluate the national prevalence and associated factors of AAC in persons 40 years of age and over in the US.

Material and methods

Survey design

The NHANES, conducted by the National Center for Health Statistics, collects nationally representative data on the health and nutritional status of the non-institutionalized US population. It utilizes a multistage probability sampling design and collects information from approximately 5,000 persons per year. Detail information on the survey design is available from the survey documentation [13]. Persons included in our analysis were 40 years and older with self-reported diagnosis of heart failure and valid entries for abdominal aortic calcifications.

Data collection

Survey participants were interviewed in their homes to ascertain demographic characteristics: age, gender, level of education, ethnicity, marital status, place of birth, health insurance, and smoking status using a Computer-Assisted Personal Interviewing system (i.e., interviewer-administered). Persons who reported having smoked at least 100 cigarettes in their lifetimes were classified as smokers. Body mass index (BMI) and waist circumference were obtained from trained health technicians using standardized protocols at mobile examination centers. Low-density lipoprotein (LDL) (md/dl) was obtained using standard laboratory protocols. The family poverty index was calculated by dividing the total family income by the poverty threshold, as defined by the US census bureau, with adjustment for family size at the time of the interview [14]. Family poverty index ratio of < 1 is considered “below poverty line” and ≥ 1 is considered “at or above poverty line”. Family PIR was grouped into three categories (PIR < 1.00, PIR 1.00–2.99 and PIR ≥ 3.00).

Although it is most commonly utilized to assess bone density, dual energy X-ray absorptiometry (DXA) imaging can also reliably establish the presence of AAC. DXA imaging has been found comparable to other popular diagnostic modalities in this regard. DXA scans were obtained by certified radiology technologists at mobile examination centers. Exclusion criteria for DXA imaging were self-reported pregnancy or positive urine pregnancy test; history of radiographic contrast use within seven days; body weight ≥ 450 lbs; or a history of scoliosis with surgical rod implantation. There was a rigorous continuous monitoring that ensured that scan analysis was accurate and consistent. These consisted of quality control phantoms scans according to a predetermined schedule and daily Hologic Anthropomorphic Spine Phantom to ensure accurate calibration of the densitometer at the beginning of every day. Persons included in our study were ≥ 40 years with complete data for AAC.

The AAC-24 scoring semi-quantitative technique was used for the evaluation of AAC according to previously published methods [15]. Persons with a score ≥ 1 on the 24-point AAC scale were considered to have AAC. Body composition was analyzed using the Hologic software, APEX v4.0 (Hologic) followed by expert review conducted by the University of California, San Francisco (UCSF), Department of Radiology on 100% of analyzed participants for accuracy and consistency of results. All study questionnaires, exact question wording and response are available at no cost to the public [13].

Statistical analysis

Relevant questionnaire data files with variables of interest were merged with demographic information. Appropriate survey weights for dataset were applied to ensure estimates are representa-
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Results

A total of 3140 participants underwent DXA imaging of which 28.8% had evidence of AAC. Table I shows the general characteristics of all study participants. In unadjusted models, older persons with a history of smoking, hypertension and diabetes were more likely to have AAC compared to their counterparts. AAC was also associated with the country of birth, race, marital status, poverty index ratio and health insurance status. Average BMI among persons with AAC was lower than among those without. There were no statistically significant associations between other variables and AAC status. Detailed results are shown in Table I.

After adjusting for confounders, persons with hypertension: OR = 1.66 (95% CI: 1.30–2.13) and ever smokers: OR = 1.63 (95% CI: 1.24–2.14) were more likely to have AAC compared to their respective counterparts. Increasing age was positively associated with AAC: OR = 1.06 (95% CI: 1.04–1.08). There was a statistically significant negative association between BMI and AAC, more so in smokers than in non-smokers (Figures 1, 5 and 6): OR = 0.97 (95% CI: 0.94–0.97). We did not observe any statistically significant association between diabetes and AAC. Detailed results are shown in Table II.

Figures 1–6 show probability of having AAC across various variables viz: BMI, age, total body fat, waist circumference, and smoking history after controlling for confounders.

Discussion

Using nationally representative data, the national prevalence of AAC among persons 40 years and older was 28.8%. Advanced age, smoking, hypertension and poverty were independently associated with AAC. Paradoxically, increasing BMI was inversely associated with AAC. There was no statistically significant association between total body and trunk fat percentages and AAC. To the best of our knowledge, this is the first study to establish the nationwide prevalence and associated factors in the US.

The strong association between advancing age and AAC was consistent with prior reports [5–7]. This could be attributed to the role of cumulative oxidative stress in the pathogenesis of AAC [17]. Oxidative stress in vascular smooth muscle cells leads to the activation of various signals such as Wnt, leading to osteogenic differentiation in the vascular walls [18]. Calcium deposition may further cause inflammation thus creating a vicious cycle leading to calcification of the vessel [19]. Also, increasing age is a risk factor in age-related diseases such as chronic kidney disease, cardiovascular diseases, neurodegenerative disorders, cancer etc., where the increased production of free radicals is known to play a major role in the pathogenesis and progression of AAC [20]. Unfortunately, we were unable to control for CKD which has been established as a significant risk factor for AAC.

Consistent with prior studies [21], hypertension was positively associated with AAC. However, debate remains on whether hypertension causes AAC or if AAC causes increased blood pressure due to arterial stiffness. An exact causal relationship cannot be drawn based on demographic studies alone. Smoking, which in itself is a risk factor for hypertension [22, 23], was also highly significantly correlated with the occurrence of AAC. This finding is consistent with various studies exploring the demographics of subjects with AAC [21, 24], dating as early as 1980 [25]. The mechanism of smoking with relation to AAC is, however, not completely understood.

Interestingly, we found that increased BMI is negatively correlated with the occurrence of AAC, indicating that a higher BMI may be protective from AAC. This is in agreement to previous studies which reported similar negative correlation [26, 27]. Though smokers were found to have a significantly higher odds of development of AAC, there was a rather protective association among smokers with increasing BMI and AAC. This runs in contrary to the observation that obesity associated with chronic smoking is known to significantly enhance cardiovascular mortality [28]. To the best of our knowledge, there are no studies examining this synergistic effect of obesity and chronic smoking for protection from AAC or vascular calcification. Therefore, future studies focusing on this synergistic effect may shed light on the pathophysiology of AAC in general.
Table I. Participant characteristics

| Variable                      | Percentage (%) | AAC+ (28.83% of all subjects) | AAC– (71.17% of all subjects) | P-value |
|-------------------------------|----------------|-------------------------------|-------------------------------|---------|
| Age                           |                | 57.38 (56.75–58.01) 63.53 (61.82–65.25) 54.89 (54.36–55.41) | < 0.001 |
| BMI                           | 28.53 (28.48–28.90) | 27.79 (27.33–28.25) 28.84 (28.33–29.20) | < 0.001 |
| Waist circumference           | 39.29 (39.00–39.59) | 39.13 (38.67–39.59) 39.54 (39.07–39.64) | 0.276 |
| LDL                           | 115.58 (113.68–117.47) | 115.30 (113.17–117.44) 115.70 (112.93–118.46) | 0.833 |
| Total fat percentage          | 33.63 (33.02–34.24) | 32.86 (31.76–33.95) 33.81(33.25–34.37) | 0.055 |
| Trunk fat percentage          | 32.86 (32.22–33.50) | 32.39 (31.23–33.55) 32.97 (32.38–33.56) | 0.226 |
| Sex                           |                | 48.08 48.61 47.86 | 0.742 |
| Female                        | 51.92 51.39 52.14 | 0.024 |
| Race                          |                | 11.63 8.64 12.84 | < 0.001 |
| Hispanic                      | 10.94 8.11 10.94 | 0.024 |
| Non-Hispanic black            | 68.94 76.10 68.94 | 0.276 |
| Non-Hispanic white            | 7.28 7.15 7.28 | 0.226 |
| Hypertension                  |                | 36.19 49.98 30.60 | < 0.001 |
| Yes                           | 68.31 50.02 69.40 | 0.003 |
| No                            | 88.50 83.36 87.02 | 0.001 |
| Diabetes mellitus             |                | 11.50 16.64 12.98 | 0.001 |
| Yes                           | 9.94 11.12 9.94 | 0.665 |
| No                            | 85.11 83.39 85.11 | 0.003 |
| Smoking history               |                | 46.00 55.35 42.22 | < 0.001 |
| Yes                           | 54.00 44.65 57.78 | 0.015 |
| No                            | 87.06 90.46 85.68 | 0.008 |
| Educational attainment        |                | 6.97 5.22 7.68 | 0.002 |
| High school diploma           | 9.94 11.12 9.94 | 0.002 |
| No high school diploma        | 85.11 83.39 85.11 | 0.002 |
| High school degree or equivalent | 5.11 5.49 4.95 | 0.665 |
| College degree                | 17.37 13.32 17.37 | 0.008 |
| Marital status                |                | 6.97 5.22 7.68 | < 0.001 |
| Never married                 | 68.51 62.88 70.80 | 0.015 |
| Married/living together       | 24.52 31.90 21.53 | 0.002 |
| Divorced/widowed/separated    | 82.63 86.68 82.63 | 0.002 |
| Birthplace                    |                | 17.37 13.32 17.37 | 0.002 |
| United States                 | 17.37 13.32 17.37 | 0.008 |
| Outside the United States     | 87.06 90.46 85.68 | 0.002 |
| Insurance status              |                | 12.94 9.54 14.32 | 0.002 |
| Insured                       | 11.05 11.42 10.90 | 0.002 |
| Uninsured                     | 29.82 36.78 26.99 | 0.002 |
| Poverty index ratio           |                | 59.14 51.80 62.11 | 0.002 |
| < 1                           | 11.05 11.42 10.90 | 0.002 |
| ≥ 1 and < 3                   | 29.82 36.78 26.99 | 0.002 |
| ≥ 3                           | 59.14 51.80 62.11 | 0.002 |

*Statistical significance. AAC – abdominal aortic calcification. Poverty index ratio defined as total household income divided by poverty threshold. Values represent within column percentages.
We also noted that there is no effect of increased waist circumference or trunk fat on occurrence of AAC, while there was a marginally inverse effect of total fat percentage, albeit not statistically significant. Dyslipidemia, which is an established consequence of obesity, has often been considered as a risk factor for vascular calcification and as its accelerant, especially in AAC [5, 18, 29]. Although the exact mechanism is not well known, oxidation of lipids may play a role in the pathogenesis of vascular calcification [17]. Also, different fat compartments have their own effect on development and progression of vasculopathy. This was highlighted by the findings in the Framingham heart study where it was found that increased peri-aortic fat mass was associated with both coronary and abdominal aortic calcification [30]. Also, subcutaneous and visceral fat mass have different effects in various metabolic disorders and this has been demonstrated in abdominal aortic calcification as well [8, 26, 31]. Diabetes, an established risk factor for atherosclerosis in many other vascular beds was not associated with AAC. This is contrary to findings by Echouffo-Tcheugui et al. [32] who reported a positive association between AAC and diabetes. However, their study was limited to African Americans only. Whether this is a spurious finding or another paradoxical observation as it is the case with obesity remains an unanswered question. This may
also suggest that while all vascular beds are prone to calcifications, the exact mechanisms as well as risk factors leading to their development.

Being a cross-sectional study, causal inferences cannot be deduced. Also, AAC has not been consistently evaluated over many survey cycles to have allowed for data pooling to increase sample size and statistical power for stable and reliable estimates. Furthermore, we were unable to adjust for CKD status, a condition with prevalent AAC. Notwithstanding these limitations, we are the first, to our knowledge, to report nationwide prevalence and associated factors of AAC in the US.

In conclusion, in the present study, we found that various factors that increased or decreased the probability for occurrence of AAC. Examining the complex pathogenesis involved in the development and progression of AAC was beyond the scope of this paper. However, further studies are needed to understand the synergistic effect of obesity and smoking along with the functions of different adipose tissue compartments in the pathophysiology of AAC.

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Table II. Factors independently associated with AAC prevalence (multivariate logistic regression comprising all variables with p < 0.10 in univariate models with AAC)

| Variable       | Categories                  | Odds ratio   | P-value |
|----------------|-----------------------------|--------------|---------|
| Body mass index|                              | 0.97 (0.94–0.97) | < 0.001 |
| Age            |                              | 1.06 (1.04–1.08) | < 0.001 |
| Race:          | NH Whites                   | 1            |         |
|                | Hispanics                   | 1.05 (0.65–1.67) | 0.84    |
|                | Blacks                      | 0.73 (0.42–1.28) | 0.25    |
|                | Others                      | 1.34 (0.95–1.89) | 0.09    |
| Marital status:| Married                     | 1            |         |
|                | Divorce/separated           | 1.18 (0.89–1.57) | 0.221   |
|                | Never married               | 0.82 (0.54–1.26) | 0.341   |
| Country of birth: | US                        | 0.70 (0.46–1.08) | 0.097   |
|                | Non-US                      |              |         |
| Insurance:     | Yes                         | 1.00 (0.68–1.48) | 1       |
|                | No                          |              |         |
| Poverty index ratio: | < 1          | 1            |         |
|                | 1 to 3                      | 1.10 (0.80–1.52) | 0.537   |
|                | > 3                         | 0.79 (0.51–1.23) | 0.272   |
| HTN:           | No                          | 1            |         |
|                | Yes                         | 1.66 (1.30–2.13) | 0.001   |
| Diabetes:      | No                          | 1            |         |
|                | Yes                         | 1.14 (0.89–1.45) | 0.279   |
| Smoking:       | No                          | 1            |         |
|                | Yes                         | 1.63 (1.24–2.14) | 0.002   |

Conflict of interest
The authors declare no conflict of interest.

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