Pathophysiology 26 (2019) 49–52

Contents lists available at ScienceDirect

Pathophysiology

journal homepage: www.elsevier.com/locate/pathophys

No association between the abdominal aorta diameter and cervicocephalic atherosclerosis—Potential non-atherosclerotic origins of abdominal aorta aneurysms?

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ARTICLE INFO

Article history:
Received 18 October 2018
Received in revised form
20 November 2018
Accepted 29 November 2018

Keywords:
Abdominal aorta
Carotid intima media thickness
Carotid siphon calcifications
Cervicocephalic atherosclerosis
Population-based study

ABSTRACT

The atherosclerotic origin of abdominal aorta (AA) aneurysms is controversial. Using the Atahualpa Project Cohort, we aimed to assess the relationship between the AA diameter and two surrogates of cervicocephalic atherosclerosis, including the carotid intima-media thickness (cIMT) and the presence of carotid siphon calcifications (CSC). Atahualpa residents aged ≥60 years undergoing ultrasound examinations of the abdominal aorta and the carotid arteries (to calculate the AA diameter and the cIMT), and head CT (to assess CSC severity) were included. Associations between AA diameter and cIMT and CSC severity were assessed by generalized linear models, after adjusting for relevant confounders. Of 256 participants, 64 (25%) had an increased cIMT and 85 (33%) had high calcium content in the carotid siphons. In univariate analysis, being male ($p < 0.001$) and having total cholesterol blood levels <240 mg/dL ($p = 0.022$) were associated with a higher AA diameter. Also in univariate analysis, the mean AA diameter was higher in individuals with an increased cIMT ($p = 0.021$), but such association disappeared in adjusted models. The AA diameter was not associated with high calcium content in the carotid siphons in either univariate or multivariate analyses. This population study shows no association between the AA diameter and cervicocephalic atherosclerosis in community-dwelling older adults, suggesting a non-atherosclerotic origin of AA aneurysms.

1. Introduction

Information on the association between the abdominal aorta (AA) diameter and cervicocephalic atherosclerosis is inconclusive. While some investigators have found no association, others maintain that the basic pathogenetic mechanisms of atherosclerosis – lipid deposition and inflammation of the intima-media complex – are also involved in dilatation of the AA [1–3]. The importance of assessing the association between AA diameter and the presence of cervicocephalic atherosclerosis comes from the fact that most individuals with cervicocephalic atherosclerosis are initially asymptomatic, and cerebrovascular complications related to these conditions may be catastrophic. Therefore, the finding of an AA of increased diameter during a routine abdominal sonogram might prompt the investigation of extra- and intracranial vascular beds in the search of subclinical cervicocephalic atherosclerosis. Using the Atahualpa Project Cohort, we aimed to assess the relationship between the AA diameter and two well-recognized surrogates of cervicocephalic atherosclerosis, including the carotid intima media thickness (cIMT) and the presence of carotid siphon calcifications (CSC) [4].

2. Methods

2.1. Study population

Atahualpa is a rural Ecuadorian village. As detailed elsewhere, the population is homogeneous regarding race/ethnicity, socio-economic status, and dietary habits; almost all men belong to the

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https://doi.org/10.1016/j.pathophys.2018.11.002
0928-4680/

blue-collar class and most women are homemakers [5]. These consistencies reduce the risk of unexpected confounders at the time of data analyses.

2.2. Inclusion criteria

Individuals enrolled in the Atahualpa Project meeting the following criteria were included in this study: 1) age ≥60 years, 2) having a complete set of baseline interviews assessing covariables of interest (see below), 3) having a non-enhanced CT of the head, and 4) having ultrasound examination of the extracranial carotid arteries and the abdominal AA. Those who did not fulfill all these criteria were not included. Participants had to sign a comprehensive written informed consent form to be considered eligible for the practice of the aforementioned interviews and procedures. The I.R.B. of Hospital-Clínica Kennedy, Guayaquil (FWA 00,006,867) approved the study.

2.3. Ultrasound examinations

Carotid and abdominal ultrasounds were performed by the use of a Terason Smart 3300 NexGen ultrasound scanner (Teratech Corporation, Burlington, MA, USA). A 2–5 MHz convex probe was used for AA examinations, and a 4–15 MHz linear probe for carotid examinations. According to guidelines for assessment of the AA in adults [6], transverse images perpendicular to the long axis of the vessel were obtained near the celiac artery, at or near the level of the renal arteries, and above the iliac bifurcation. Measurements for analyses were taken at the greatest AA diameter (from the outer to outer edges) at any of these levels. Abdominal ultrasounds were performed by a single experienced sonographist. Exams were repeated in a random number of 50 individuals two weeks after the first exam by the same sonographist. Intra-rater reliability was good (k = 0.77).

Carotid ultrasounds focused on cIMT assessment by scanning the near and far walls of each carotid artery at the segment extending from 10 to 20 mm proximal to the tip of the flow divider into the common carotid artery, at the carotid bifurcation from the tip of the flow divider and extending 10 mm proximal to the flow divider tip, and at the proximal 10 mm of the internal carotid artery. The cIMT was calculated as the mean of the 12 measurements (six left and six right), and was considered increased if >1 mm [7]. Carotid ultrasounds were performed by two experienced sonographists. Then, exams performed by one sonographist were read by the other, and *vice versa*. When measurements of the total cIMT from the two readers differed by 0.2 mm or more (one standard deviation from the mean), images were again reviewed by the two readers for consensus. Both readers were blinded to clinical manifestations and CT findings.

2.4. Neuroimaging protocol

Head CTs were performed with a Philips Brilliance 64 CT scanner (Philips Medical Systems, The Netherlands). Slice thickness was 3 mm, with no gap between slices. Women of child-bearing age underwent a pregnancy test before the study, and those who were positive were rescheduled for a CT after delivery. CT digital images were viewed on the Osirix Medical Imaging software (Pixmeo, Geneva, Switzerland) using the bone window setting to identify and grade carotid siphon calcifications. Individuals were stratified into those with low and high arterial calcium content [8]. Low calcium content was defined as the absence or near-absence of calcification, or as the presence of tiny scattered calcifications. High calcium content was defined as the presence of uni- or bilateral thin confluent, or thick – interrupted or continuous – calcifications. Two independent readers, blinded to clinical and sonographic data, reviewed the studies (k = 0.78) and discrepancies were resolved by consensus.

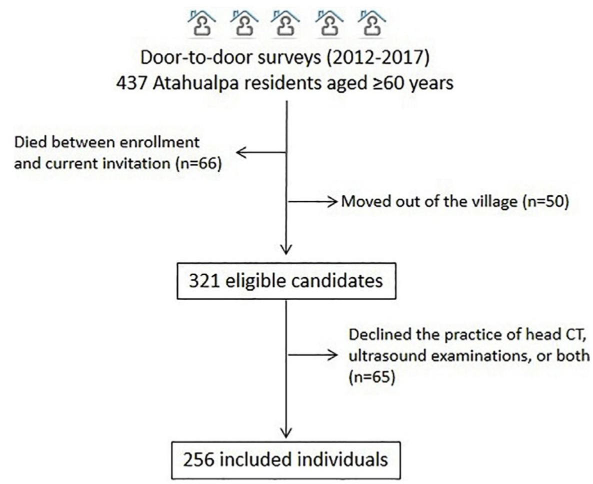

Fig. 1. Flow diagram depicting the process of enrollment and the reasons for not including potentially eligible individuals.

2.5. Clinical covariables

Confounders included demographics and cardiovascular risk factors (smoking status, physical activity, diet, the body mass index, blood pressure, fasting glucose, and total cholesterol blood levels), which were assessed by means of interviews and procedures previously described in the Atahualpa Project, using cutoffs and criteria proposed by the American Heart Association [9].

2.6. Statistical analysis

Data analyses are carried out by using STATA version 15 (College Station, TX, USA). In univariate analyses, continuous variables were compared by linear models and categorical variables by x^2 or Fisher exact test as appropriate. A multivariate generalized linear model was fitted to assess the association between the AA diameter (dependent variable) and each of the investigated covariables. Then, two different models were fitted to assess the independent association between AA diameter and cIMT and CSC (as dependent variables), after adjusting for covariables reaching $p < 0.1$ significance in the previous model.

3. Results

Fig. 1 is a flow diagram depicting the process of enrollment and the reasons for not including potentially eligible individuals. Of 437 individuals aged ≥60 years enrolled in the Atahualpa Project (2012–2017), 256 (59%) fulfilled inclusion criteria. The remaining 181 subjects had either died (n = 66) or moved out of the village (n = 50) between enrollment and the current invitation, or declined consent for the practice of one or more of the aforementioned studies (n = 65). Individuals enrolled in this study were younger ($p = 0.002$) and more often women ($p = 0.002$) than those who did not participate.

Characteristics of participants are depicted in Table 1. As noticed, the mean age was 71.2 ± 7.7 years (median age: 70 years; age range: 62–95 years), and 154 (60%) were women. A body mass index ≥30 kg/m^2 was present in 54 (21%) persons, blood pressure ≥140/90 mmHg in 109 (43%), fasting glucose ≥126 mg/dL in 81 (32%), and total cholesterol levels ≥240 mg/dL in 34 (13%). Four (2%) participants were current smokers, 11 (4%) had a poor diet, and 17 (7%) had poor physical activity. The mean AA diameter

Table 1
Characteristics of 256 Atahualpa residents aged ≥60 years included in the present study.

Age, years (mean ± SD)	71.2 ± 7.7
Women, n (%)	154 (60)
Current smokers, n (%)	4 (2%)
Poor physical activity, n (%)	17 (7%)
Poor diet, n (%)	11 (4%)
Body mass index ≥ 30 kg/m^2, n (%)	54 (21%)
Blood pressure ≥140/90 mmHg, n (%)	109 (43%)
Fasting glucose levels ≥126 mg/dL, n (%)	81 (32%)
Total cholesterol levels ≥240 mg/dL, n (%)	34 (13%)
Abdominal aorta diameter, mm (mean ± SD)	19.8 ± 3.3
Increased carotid intima-media thickness, n (%)	64 (25%)
High calcium content in the carotid siphons, n (%)	85 (33%)

was 19.8 ± 3.3 mm, whereas 64 individuals (25%) had a mean cIMT >1 mm (increased), and 85 (33%) had high calcium content in the carotid siphons.

In univariate analysis, the AA diameter was not associated with age (p = 0.444), smoking status (p = 0.587), the body mass index (p = 0.999), physical activity (p = 0.469), diet (p = 0.057), blood pressure (p = 0.998), and fasting glucose (p = 0.822). In contrast, male sex (p < 0.001) and having lower total cholesterol blood levels (p = 0.022) were significantly associated with a higher AA diameter. Also in univariate analysis, the mean AA diameter was higher in individuals with an increased cIMT than in those with a normal cIMT (20.6±4.2 *versus* 19.5 ± 2.9, p = 0.021), but there were no differences in the mean AA diameter across individuals with high or low calcium content in the carotid siphons (19.8±3.7 *versus* 19.9 ± 3.1, p = 0.982).

Risk factors associated with an increased cIMT in univariate analysis included increasing age (p < 0.001), male sex (p < 0.001), and blood pressure ≥140/90 mmHg (p = 0.007). Likewise, subjects with high content in the carotid siphons were older (p = 0.001), had worse physical activity (p = 0.002), blood pressure ≥140/90 mmHg (p = 0.026), and fasting glucose levels ≥126 mg/dL (p = 0.006). As noticed, risk factors associated with increased AA diameter on one side, and increased cIMT and CSC severity on the other, were different.

A multivariate generalized linear model, fitted to assess the association between the AA diameter (dependent variable) and each of the investigated covariables, showed statistically significance with sex (being male), and borderline significances with the body mass index and total cholesterol blood levels in the poor range. Consecutive additions of cIMT and calcium content to the model (as independent variables), did not show any association of these surrogates of cervicocephalic atherosclerosis with the AA diameter (Table 2).

4. Discussion

This population-based study, conducted in community-dwelling older adults living in a rural setting, shows no association between the AA diameter and increased cIMT and CSC severity. On the premise that the latter two variables are related to atherosclerosis, these results suggest that atherosclerosis is not in the path of the AA diameter (or in the further development of AA aneurysms). Results from univariate analysis are in line with this assumption, since risk factors for increased AA diameter were completely different than those associated with the two surrogates of cervicocephalic atherosclerosis.

As previously mentioned, information on the relationship between the AA diameter and surrogates of atherosclerosis is limited. In a large preliminary study, the AA diameter was not associated with the cIMT, despite a positive association with coronary artery calcium burden [2]. In such study, the lack of association between the AA diameter and the cIMT was not confined to subjects with AA aneurysms, but also to those with an AA diameter <30 mm. These results cast doubts about the atherosclerosis origin of AA aneurysms, and suggests the existence of potential alternative pathways to explain their occurrence, like the presence of a dilative arteriopathy. Yet, in another study designed to assess the association between cardiovascular risk factors, the AA diameter, and atherosclerotic plaques in both carotid and femoral arteries, the authors found that the presence of atherosclerotic plaques in the aforementioned arteries were a poor predictor of enlarged AA [1]. The association between the AA diameter and CSC severity was not investigated in those studies.

The relationship between AA diameter and coronary atherosclerosis, but not with atherosclerosis in other vascular beds is not fully understood, particularly on the light that atherosclerosis is a systemic process. However, the same has been reported for the so-called Frank's sign (earlobe crease), which has been associated

Table 2
Upper panel: fully-adjusted generalized linear model, with abdominal aorta diameter as the dependent variable, showing independently statistically significant association with sex (being men), and borderline significances with the body mass index and total cholesterol blood levels in the poor range. *Middle and lower panels:* most parsimonious generalized linear model (with variables reaching p < 0.1 significance in the fully-adjusted model), showing no significant associations between abdominal aorta diameter and increased carotid intima media thickness or high calcium content in the carotid siphons (added as independent variables).

Abdominal aorta	β coefficient	95% confidence interval	*p* value
Age	0.006	−0.045 to 0.057	0.815
Sex	−3.371	−4.138 to -2.604	<0.001
Smoking status	0.853	−2.078 to 3.783	0.567
Body mass index	−0.896	−1.823 to 0.030	0.058
Physical activity	0.063	−1.449 to 1.573	0.935
Diet	−0.991	−2.770 to 0.788	0.274
Blood pressure	0.107	−0.651 to 0.865	0.782
Fasting glucose	0.107	−0.681 to 0.894	0.790
Total cholesterol	0.955	−0.107 to 2.017	0.078
Age	0.001	−0.049 to 0.049	0.990
Sex	−3.305	−4.074 to -2.536	<0.001
Body mass index	−0.882	−1.787 to 0.023	0.056
Total cholesterol	1.006	−0.034 to 2.050	0.059
Carotid intima-media thickness	−0.333	−1.211 to 0.545	0.456
Age	0.006	−0.419 to 0.053	0.810
Sex	−3.376	−4.123 to -2.629	<0.001
Body mass index	−0.895	−1.802 to 0.013	0.053
Total cholesterol	1.007	−0.047 to 2.061	0.061
High calcium in carotid siphons	−0.023	−0.798 to 0.751	0.952

with coronary artery atherosclerosis but not with atherosclerosis in other vascular beds [10–12].

The present study has limitations. The sonographic assessment of the AA might underestimate its diameter when compared with CT angiography [13]. In addition, the cross-sectional design – precluding the assessment of causation – is another potential limitation. On the other hand, major strengths of our study include the population-based design as well the unbiased inclusion of participants at the community level.

5. Conclusions

The lack of association between the abdominal aorta diameter and cervicocephalic atherosclerosis suggests a non-atherosclerotic origin of abdominal aorta aneurysms. Further longitudinal studies are needed to better understand the relationship between the AA diameter and cervicocephalic atherosclerosis. Such studies should also include interaction models to assess the effect-modification of age and sex in the relationship between the AA diameter and cervicocephalic atherosclerosis, since demographics have shown to play a role in these variables [14].

Funding

This study was partially supported by Universidad Espiritu Santo – Ecuador, Guayaquil, Ecuador.

Disclosure statement

The authors have no conflicts of interest to disclose.

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