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Interaction between widening of diameter of abdominal aorta and cardiovascular risk factors and atherosclerosis burden

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Abstract The aim of this study was to investigate influence of traditional cardiovascular risk factors (CVRF) and subclinical atherosclerosis (ATS) burden on early stages of abdominal aortic diameter (AAD) widening among adults. 2,052 consecutive patients (P) (39 % women), mean age 52 ± 13 years, were prospectively screened for CVRF, ATS, and AAD. B-mode ultrasound was used to evaluate the largest AAD and to detect carotid and femoral atherosclerotic plaques. Mean AAD was 15.2 ± 2.8 mm. Atherosclerotic plaques were detected in 71 % of patients. Significant univariate correlation between AAD, traditional CVRF, and ABS was found. However, multiple regression analysis showed that only seven of them were significantly and weakly correlated with AAD ($R^2 = 0.27$, $p < 0.001$). On the other hand, a multivariate logistic analysis was used to evaluate CVRF impact on enlarged AAD ≥25 mm (EAAD) as compared to those with AAD <25 mm. These factors did not account for more than 30 % of interaction ($R^2 = 0.30$, $p = 0.001$). Furthermore, despite a large proportion of patients with high number of CVRF, and subclinical ATS, rate of patients with AAD ≥25 mm was low (1 %) and scattered regardless their CHD risk score or ATS burden. In conclusion, these results suggest that although some traditional CVRF and presence of ATS are associated with early stages of EAAD, other determinants still need to be identified for a better understanding of abdominal aortic aneurysm pathogenesis.

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Introduction

Relative role of contributors to abdominal aortic aneurysm (AAA) development is still a matter of debate. Atherosclerosis (ATS) and AAA share common risk factors, such as male sex, advanced age, and smoking habits [1]. In contrast, robust data indicate that diabetes, a major cardiovascular risk factor (CVRF), is inversely correlated with presence and progression of AAA [1, 2]. Contribution of hypertension [2, 3], obesity [4, 5], and hypercholesterolemia [6, 7] in AAA development remains at present unclear. ATS and AAA differ also with respect to histological findings. Media weakening involving chronic inflammation, and extensive protease-mediated degradation, is a main feature of AAA [8, 9]. Population-based studies have shown that the presence of peripheral vascular disease, or coronary heart disease (CHD), two well-known atherosclerosis-linked diseases, are strong predisposing factors for AAA development [10, 11]. Numerous epidemiological studies have evaluated the correlation between CVRF and AAA. In contrast, only few studies focused on the association between subclinical ATS and CVRF with abdominal aortic diameter (AAD) and enlarged AAD ≥25 mm (EAAD) which has been demonstrated to be related to AAA risk [12]. To better elucidate AAA pathogenesis, the purpose of this study was to evaluate the influence of traditional CVRF and subclinical ATS on early stages of AAD enlargement among a population of adult patients at high risk of cardiovascular diseases (CVD).

Methods

Study population and cardiovascular risk factors

Consecutive 2,052 patients, aged 20–80 years, referred to the Lipid Unit of a University Hospital for cardiovascular risk assessment (Framingham coronary heart disease Risk-Score), and/or therapeutic advice, were enrolled. All participants gave informed written consent, and study protocol was approved by the local ethics committee. CVRF were prospectively collected as indicated here: patients answered a detailed questionnaire collecting information on family history of premature CHD, personal history of CVD, diabetes, hypertension, blood lipids, and current medications. Blood pressure was measured with a digital blood pressure monitor. Body mass index (BMI) and the Framingham coronary heart disease risk score were calculated for all patients.

All patients underwent venous blood drawing following an overnight fast. Total cholesterol, HDL cholesterol (HDL-C), triglycerides, and glucose were determined on fresh plasma samples using an auto-analyser (Cobras-Mira Plus^{TM}, Roche, Basel, Switzerland).

Hypertension was defined as SBP >140 mmHg and/or DBP >90 mmHg, and/or current use of anti-hypertensive agents. Smoking status was defined as current, former, or never. Obesity was defined as BMI $\geq$30 kg/m^2. Hypercholesterolemia was defined as plasma total cholesterol >6.5 mmol/L and/or current use of lipid lowering therapy. Hypertriglyceridemia was defined as plasma triglyceride level $\geq$1.7 mmol/L. Low HDL-C was defined as an HDL-C <1 mmol/L. Diabetes was defined by the current use of physician-prescribed antiglycemic medications or a fasting serum glucose level $\geq$7 mmol/L. CHD was defined as a history of angina, acute coronary syndrome, or myocardial infarction. Cerebrovascular disease was defined as any history of transient ischemic attack or stroke. A positive family history of premature (men aged <55, and women <65 years) CHD was considered when there was a history of CHD in a first degree relative.

Abdominal aorta evaluation

B-mode ultrasound (US) imaging, using a 3.5-MHz real-time sector scanner, was used to measure AAD below renal arteries. Abdominal aorta (AA) was examined both in antero-posterior and lateral views. Maximum external diameter within the infrarenal segment was measured. AA was considered enlarged if diameter was $\geq$25 mm but <30 mm, presence of AAA was defined as an AAD $\geq$30 mm [13].

Subclinical atherosclerosis evaluation

Carotid and femoral arteries were analyzed by B-mode US imaging. The analysis was performed with a colour duplex scanner, using a high resolution 7 MHz linear array scan head. The duplex scan was coupled with the M'ATHS software performing semi-automatic on frame measures (Metris, Paris, France). Carotid arteries were examined from the lowest visible part, in the supraclavicular fossa, to the submandibular angle. Femoral arteries were scanned from 4 cm above, and 4 cm below, the inguinal bifurcation. Plaque was defined as a focal encroaching of $\geq$1.2 mm into the arterial lumen measured from media-adventitia to intima-lumen interface. Plaque thickness was measured in its largest portion. Whenever more than one plaque were present within the same arterial segment, only the thickest one, measured in the longitudinal view, was recorded. To quantify ATS burden an "Atherosclerosis Burden Score" (ABS) ranging from 0 to 4, reflecting the number of arterial bifurcations with plaques, was used.

Statistical analyses

All statistical analyses were performed using STATA 11.0 software (Stata corp., College station, TX, USA). The results were expressed as mean $\pm$ standard deviation (SD), categorical data as percentages, or interquartile ranges. Comparison between categories was based on the *t* test for continuous variables, and χ^2 test for categorical variables. Association between aortic diameter, CVRF, and ABS were assessed with univariate (Pearson's and Spearman's rank) correlation, and multivariable linear modeling regression analysis. Finally, interaction between EAAD, CVRF, and other potential determinants, was assessed with logistic multivariate regression analysis.

Results

Consecutive 2,052 patients were included in the study. At the time of abdominal ultrasound, mean participants age was 52 $\pm$ 13 years (range from 20 to 80 years old). Sixty percent (1,245) of included patients were men. General characteristics of studied population are summarized in Table 1. There were significant statistical differences between men and women concerning CVRF distribution. Hypertension, current and past smokers, hypertriglyceridemia, low HDL-C, personal history of CVD ($p < 0.001$), and diabetes ($p < 0.01$) were more frequent in men than in women. In contrast, there were more women with hypercholesterolemia and familial history of CHD than men ($p < 0.001$). The presence of subclinical ATS (ABS $\geq$ 1) was high in our study population (71 %).

Table 1 Clinical characteristics of patients

Parameters	Women	Men	All
Number (%)	807 (39)	1,245 (61)	2,052
Age (mean ± SD)	53.2 ± 14	51.5 ± 12[†]	52.2 ± 12.9
Familial history of premature CVD (%)	23.8	18.4[†]	20.5
Personal history of CVD (%)	4.3	10.9[‡]	8.3
Current smokers (%)	21.3	28.1[‡]	25.4
Past smokers (%)	15.9	29.6[‡]	24.2
Hypertension (%)	39	47.1[‡]	43.9
Hypercholesterolemia (%)	57.9	51.7[†]	54.1
Hypertriglyceridemia (%)	22.5	40.2[‡]	33.2
Low HDL cholesterolemia (%)	9.4	26.3[‡]	19.6
Obesity (%)	13.4	15.3	14.4
Diabetes mellitus (%)	7.2	11.2[†]	9.7
Number of patients with ABS ≥1 %)	64.6	74.5[‡]	70.6

Statistical differences: women versus men [†] $p < 0.01$, [‡] $p < 0.001$

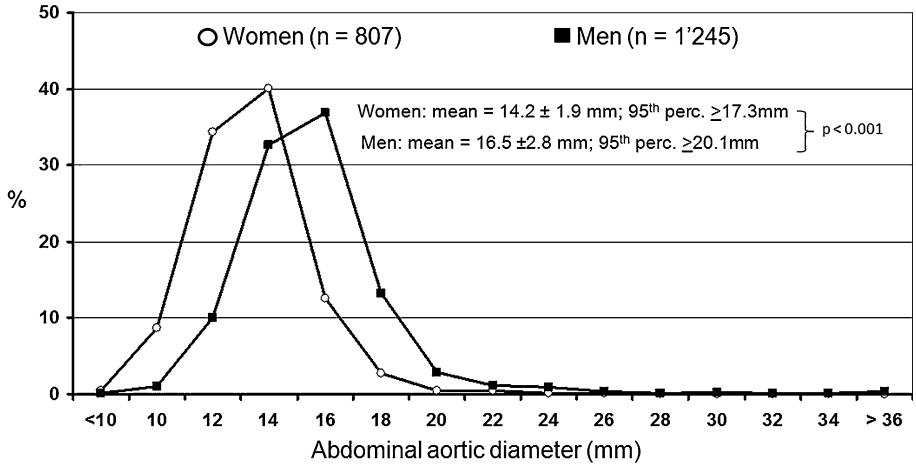

Fig. 1 Distribution of abdominal aortic diameter by gender

Mean AAD increased with age ranging from 12.3 ± 2.3 mm, in 20–29 years old men, to 15.3 ± 2.9 mm among those 70–80 years old. Among women, AAD increased from 14.0 ± 1.7 mm, in the 20–29 years old, to 18.4 ± 4.5 mm among those aged 70–80 years. Thus, men showed significantly larger AAD than women (mean AAD of 16.4 ± 2.9 mm vs. 14.2 ± 1.9 mm, respectively; $p < 0.001$) (Fig. 1).

Prevalence of patients with either an EAAD ≥20 mm, ≥25 mm, or AAA was respectively 4.0, 0.97, and 0.44 %. Among subjects >65 years old, this prevalence was respectively 3.9, 1.1, and 0.0 % among women and 17.2, 5.2, and 2.3 % among men.

As illustrated in Fig. 2, all parameters significantly correlated with AAD. However, this figure indicates that patients with EAAD are unequally far from regression line. When performing analysis using the univariate linear regression (Spearman's correlation) a significant correlation was observed between AAD and 12 of the 14 studied parameters. Vice versa, when multivariate analysis was performed, a correlation was found only for 6 of the parameters ($R^2 = 0.27$, $p < 0.001$) (Table 2). However, this correlation was no more significant for AAD ≥20 mm ($R^2 = 0.14$, $p < 0.54$).

Probability to observe an EAAD ≥25 mm in association with all these same parameters was also analyzed (Fig. 3). Only gender, hypertriglyceridemia, current smoking, ABS, and age were found to be significantly associated with EAAD. However, these factors accounted for no more than 30 % of interaction ($R^2 = 0.30$, $p < 0.001$).

Discussion

The results presented herein indicate that ATS burden, and some CVRF are positively correlated with AAD increase. However, in our population of middle-aged patients with increased cardiovascular risk, a subgroup of patients with an EAAD ≥20 or 25 mm are unequally far from the regression line regardless of CVRF and CHD risk score.

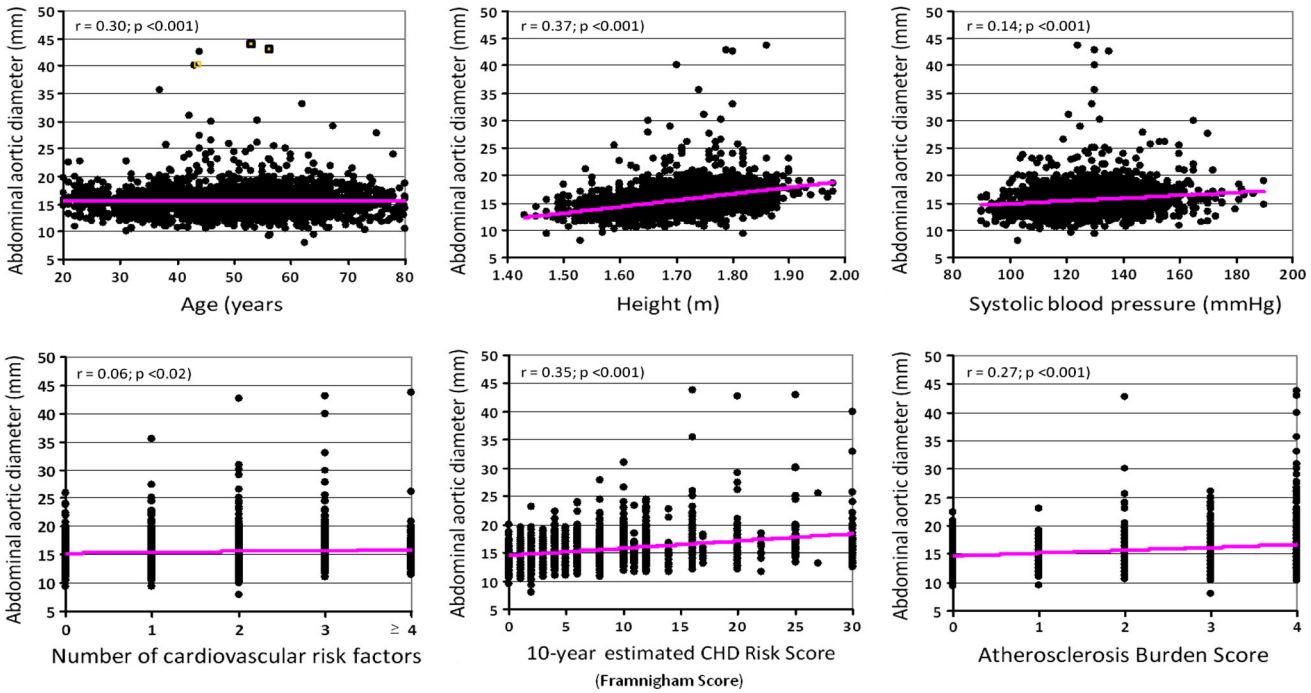

Fig. 2 Correlation (Pearson's) between the aortic abdominal diameter and cardiovascular risk factors and subclinical atherosclerosis

Table 2 Correlation between abdominal aortic diameter and traditional cardiovascular risk factors by univariate and multivariate regression analysis

Variables	Univariate regression analysis Coefficient ρ	Multivariate analysis p	Coefficient β	p
Gender (M vs. F)	0.474	0.000	0.371	0.000
Age (decades)	0.273	0.000	0.299	0.000
Familial history of premature CVD (yes vs. no)	0.058	0.009	−0.252	0.175
Personal history of CVD (yes vs. no)	−0.086	0.000	0.009	0.738
Atherosclerosis burden score (0–4 units)	0.257	0.000	0.049	0.039
Current smoking (yes vs. no)	−0.001	0.984	0.042	0.054
Past smoking (yes vs. no)	0.147	0.000	0.038	0.083
Diabetes mellitus (yes vs. no)	0.034	0.127	−0.028	0.183
Systolic blood pressure (mmHg)	0.148	0.000	−0.750	0.004
Diastolic blood pressure (mmHg)	0.0145	0.000	0.081	0.009
Total cholesterol (mmol/L)	−0.134	0.000	−0.006	0.801
HDL-cholesterol (mmol/L)	−0.168	0.000	−0.012	0.561
Triglycerides (mmol/L)	0.118	0.000	0.003	0.877
BMI (kg/m^2)	0.259	0.000	0.078	0.000

ρ Spearman's rank correlation coefficient, β standardized regression coefficient

Few studies have been published assessing AAD epidemiology and particularly concerning the role of traditional CVRF on aortic diameter variability and early stages of AAA [14–18].

The present study is in agreement with the previous ones showing a link between AAD enlargement with aging and male gender [19, 20]. With age, arteries undergo changes in their structural and functional capacities. Arterial wall collagen-to-elastin ratio increases, as a result of decreased elastic elements, leading to arterial dilation. In parallel, arterial wall stiffness tends to increase [19]. Gender differences in AAD are probably explained by higher height and stiffness in AA of men [21, 22].

When concerning the other CVRF, a positive correlation between BMI and AAD increment was observed in our patients similarly to what reported by others [14–16]. This

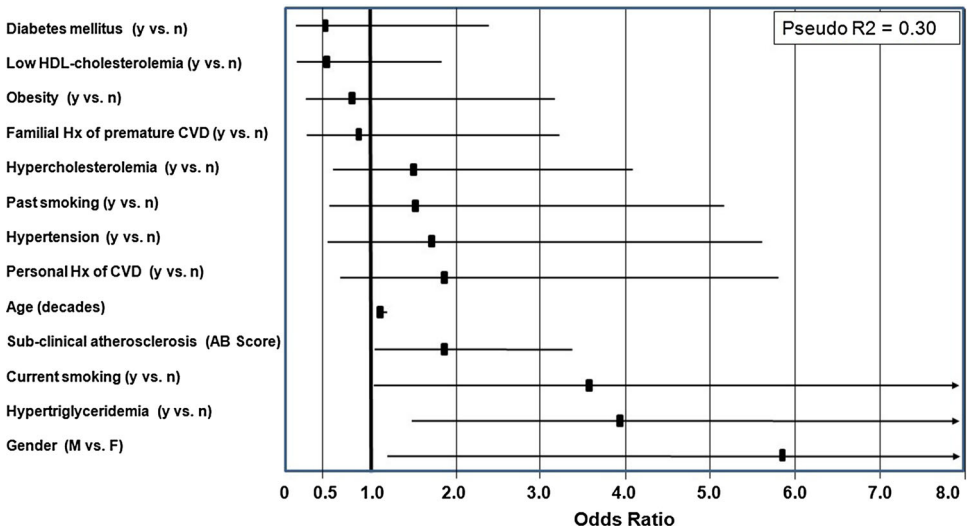

Fig. 3 Interaction between enlarged abdominal aortic diameter (≥25 mm) and cardiovascular risk factors and subclinical atherosclerosis, by multivariate regression analysis

association may be explained by the ability of adipose tissue to release adipokines. Indeed, it has been shown that adipokines, including resistin, adiponectin, and leptin, can play a paramount role in AAA pathogenesis [4].

Hypertension has limited effect on arterial diameter. In contrast to Paivansalo et al. [16], we and others observed a correlation between hypertension and weak AAD increment [14, 18, 19]. Increase in arteries diameter has been advocated as a possible increase of fluid volume secondary to sodium retention [23].

Although smoking constitutes a significant risk for aneurysm development, two previous studies [14, 15], evaluating impact of CVRF on AAD, have shown lack of association between smoking and AAD. Paivansalo et al. [16]. describe a significant correlation in smoking women only ($p < 0.005$). In our study, correlation was nearly significant ($p = 0.054$). More recently, Johnsen et al. [17] have shown that AAD increases markedly, between 18 and 29 mm, with current smoking ($p < 0.0001$). Finally, in the MESA study [18], the current smoking was independently and significantly associated with increasing AAD ($p < 0.01$).

Lastly, we did not find any correlation between AAD and diabetes. This result is in accordance with the previous studies demonstrating inverse or no association between AAD and diabetes [8, 14].

Statistical multivariate regression analysis revealed a significant association between subclinical ATS burden score (ABS) and AAD increment. This result is in agreement with others demonstrating similar association using different tools or techniques to quantify subclinical ATS burden. Two studies [14, 18], demonstrated a significant association between increasing AAD and presence and extent of calcified ATS in AA and iliac arteries, or coronary calcium using EBCT and calcium score. Patel et al. [15] found similar association using ultrasounds to measure AAD and IMT at several AA locations. AAD increase in the presence of ATS may be explained by arterial remodelling: preservation of arterial lumen cross-sectional area in spite of advancing ATS within the arterial wall (Glagov's phenomenon) [24]. Labropoulus et al. studied vessel diameters throughout the vascular system in 67 ± 12-year-old subjects with and without ATS and found that all arteries dilate during early ATS plaque formation confirming the Glagov's phenomenon throughout the vascular tree [25]. Finally, Mohiaddin et al. [26] confirmed the presence of Glagov remodeling in AA by cardiovascular magnetic resonance, with an increment of 1 mm over 2 years in patients with arterial plaques.

An association between some CVRF and AAD does not necessarily imply a link of causality. Multivariate regression analysis showed that CVRF and ABS accounted for only 27 % ($R^2 = 0.27$) of AAD variability in our study.

When concerning the subgroup of 20 patients with EAAD ≥25 mm, only age, gender, current smoking, hypertriglyceridemia, and ABS appeared to be significant positive predictors. These risk factors are similar to those known for AAA [27, 28].

Interestingly, despite a large proportion of patients with diffuse ATS lesions (71 %) and ≥3 CVRF (37 %), prevalence of EAAD and AAA was low in our study population, 0.97 and 0.44 %, respectively. Among men older than 65 years of age, the 5.2 % EADD and the 2.3 % AAA prevalence were lower than those found in other studies. Indeed, screening studies show that AAA occurs in 4–9 % of individuals over the age of 60 [1, 3].

If ATS was the dominant feature of aortic enlargement, the proportion of subjects with an aortic dilation should be widely superior. In our study, the dilation of aortic diameter was observed only in 2.4 % of patients with an ABS

score ≥3, and in 2.9 % of those with a history of coronary artery disease. In the subgroup of patients with AAD ≥20 mm ($n = 83$), these rates were 9.3 and 12.9 %, respectively. Moreover, the subpopulation of patients with AAD ≥25 mm was scattered regardless of CVRF number, CHD risk score, or ATS burden. Herein, these traditional CVRF accounted for a role in AAD enlargement for no more than 30 % as expressed by the pseudo-R^2. Similarly, in the Tromsø Study, no consistent dose–response relationship between ATS and AAD was found [18]. These observations strongly suggest that other factors than CVRF and ATS are implicated in EAAD and ultimately AAA formation. Thus, ATS may not be a causal but rather a predisposing contributor for AAA. Indeed, recent studies demonstrated the paramount role played by inflammation, proteolysis, apoptosis, and oxidative stress in AAA development and progression underlying the systemic nature of the aneurysmal process [8, 29, 30].

The cross-sectional nature of the present study and the lack of direct atheroma measurement within the aorta have to be considered as limitations that possibly interfere on the causal relationship between ATS, CVRF, and AAD increment. Nevertheless, this study provides additional evidence suggesting that pathophysiology of EAAD and AAA is complex and multifactorial.

Our results demonstrate that traditional CVRF and ATS only modestly contribute to AAD increase and are poor predictors of EAAD, supporting the view that other key factors need to be searched to further improve knowledge of pathophysiology and AAA prediction.

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Conflict of interest None declared.

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