

Carotid Atherosclerosis and Relation to Growth of Infrarenal Aortic Diameter and Follow-up Diameter: The Tromsø Study CME

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WHAT THIS PAPER ADDS?

Even strongly cross-sectional associated the role of atherosclerosis in abdominal aortic dilatation and aneurysm formation has been questioned. Prospective data in this area are sparse. The new prospective data presented in this study demonstrate an independent linear dose–response relationship between carotid plaque growth and growth of abdominal aortic diameter. These observations suggest that atherosclerosis may explain some of the variance in dilatation of the abdominal aorta and aneurysm formation. Identification and aggressive treatment of risk factors for atherosclerosis are recommended in patients with dilatation of the abdominal aorta.

Objectives: This research aims to study how carotid atherosclerosis is related to growth of infrarenal aortic diameter and aneurysmal formation.

Design: Population-based follow-up study.

Materials and methods: At baseline, ultrasound examination of the carotid artery and the abdominal aorta was performed in 4241 persons from a general population with no evidence of abdominal aortic aneurysm (AAA). The burden of atherosclerosis was assessed as carotid total plaque area (TPA). After a mean follow-up of 6.3 years, a new ultrasound examination was performed and measurements of the aortic diameter and carotid TPA were repeated. The effects on aortic diameter progression, follow-up diameter and risk for AAA were assessed in multiple linear and logistic regression models according to carotid TPA, adjusted for known risk factors.

Results: When analysing AAA as a dichotomous variable, a borderline association between atherosclerosis and AAA could be demonstrated. When modelling aortic diameter as a continuous variable, a 1-SD increase in 5 years' carotid plaque area (Δ TPA) was associated with a 0.12-mm growth in infrarenal aortic diameter (standard error (SE) 0.04) and a 0.20-mm wider aorta at follow-up (SE 0.06). No independent relation was seen for baseline atherosclerosis.

Conclusions: Carotid plaque progression was positively related to growth in infrarenal aortic diameter and aortic diameter at follow-up. Whether this co-variation between plaque growth and aortic diameter growth is causally related or independent events is still an open question.

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The formation of an abdominal aortic aneurysm (AAA) has historically been considered to be a focal manifestation of advanced atherosclerosis as the presence of atherosclerosis

in the aneurysmal wall and in other circulatory beds is a common finding in AAA patients.^{1,2} However, the aetiological role of atherosclerosis in AAA has been questioned.^{3,4} The strong association between atherosclerosis and AAA may be confounded by several shared risk factors, smoking in particular, and also hypertension and hyperlipidaemia, although the strength of these associations differs between the two diseases.^{5–12}

Recent case–control studies did not find evidence for more carotid, coronary or peripheral atherosclerosis in AAA patients.^{13,14} In a previous cross-sectional population-based study, we could not find any consistent relationship between total carotid plaque area (TPA) and maximal

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infrarenal aortic diameter, in aortic diameter <27 mm. Neither were we able to demonstrate any correlation between TPA and aneurysmal diameter in those with AAA. However, an aortic diameter beyond 27 mm was associated with increased burden of both carotid atherosclerosis and coronary heart disease (CHD).¹⁵ Due to the cross-sectional design of that study, no inferences could be made whether atherosclerosis precedes aortic dilatation or vice versa. In the present study of 4241 persons without AAA, we prospectively examined how baseline carotid TPA and carotid plaque growth (Δ TPA) were related to increase in infrarenal aortic diameter, follow-up diameter and incident AAA.

MATERIALS AND METHODS

Study population

The Tromsø Study was initiated in 1974 and is a population-based, prospective study with six repeated health surveys including total birth cohorts and random samples of the inhabitants of the municipality of Tromsø, Norway.¹⁶ The study has been approved by The Regional Committee for Medical and Health Research Ethics and informed consent was obtained from all participants. As a part of the fourth survey in 1994/1995, a total of 6892 men and women, aged 25–84 years, underwent ultrasound scanning of the abdominal aorta in order to measure the maximal diameter of the infrarenal aorta. The attendance rate was 79%.¹⁷ Ultrasound of the carotid artery was also performed. In the fifth survey, conducted in 2001, 5087 (85%) of these subjects attended the part of the study that included ultrasound examination of the abdominal aorta. Persons with a Y-graft were excluded ($n = 37$). Baseline carotid TPA and baseline and follow-up maximal infrarenal transversal and anterior–posterior aortic diameters were available in 4326 persons. However, an AAA (defined as the maximal infrarenal aortic diameter ≥ 30 mm) was present at baseline in 85 persons. They were excluded from this follow-up. Thus, 4241 subjects (1995 men and 2246 women) aged 25–82 years in 1994 were included in the present study.

Cardiovascular risk factors

Information about smoking habits, angina pectoris, myocardial infarction and use of anti-hypertensive drug was collected from self-administered questionnaires. Information about the use of lipid-lowering drugs (mainly statins) was collected at the screening examination. The participants were asked the following questions: “Do you have or did you ever have angina pectoris (heart cramp)?” and “Do you have or did you ever have a heart attack (myocardial infarction)?” If the answer to either question was yes, the participant was classified to have CHD. Standardised measurements of height, weight, blood pressure and non-fasting serum total cholesterol, high-density lipoprotein (HDL)-cholesterol and triglycerides were performed as described previously.¹¹

Ultrasonography of the abdominal aorta and carotid artery

The ultrasonographic measurements of the abdominal aorta have been described in detail previously.^{11,17} The maximal infrarenal aortic diameter was in the present analyses defined as the mean of the maximal transversal and anterior–posterior diameters. The difference between inter- and intra-observer variability of the maximal aortic diameter in the ultrasound examination at baseline was ≤ 4 mm in 95% of the pairs.¹⁷ At follow-up in 2001, the corresponding figures were 87% and 96%.¹² An incident AAA was defined as follow-up maximal infrarenal aortic diameter ≥ 30 mm or as gone through surgery on the abdominal aorta due to aneurysm between baseline and follow-up screening.

The carotid ultrasound examination was carried out as detailed elsewhere.^{18,19} A plaque was defined as a localised protrusion of the vessel wall into the lumen of at least 50% compared to the adjacent intima–media thickness. In each subject, a maximum of six plaques were registered in the near and far walls of the common carotid artery (CCA), bifurcation and internal carotid artery (ICA), respectively. Digitalised longitudinal plaque images were transferred to and standardised in Adobe Photoshop, to calculate the plaque area.²⁰ In subjects with more than one plaque, the areas of all plaques were summarised to give the TPA.

Statistical analyses

As the follow-up differed somewhat between the individuals, we calculated the estimated change per 5 years and included this variable in the analysis instead of the change without adjustment for follow-up period. The maximal infrarenal aortic diameter at follow-up, the estimated change per 5 years in aortic diameter and incident AAA were the dependent variables in the regression models. Carotid TPA and the estimated change in this variable per 5 years (Δ TPA) were the main explanatory variables. Change was assessed as 2001 readings – 1994 readings. Known risk factors for atherosclerosis and AAA were introduced as covariates. We assessed the effect of atherosclerosis and risk factors using a general linear model and logistic regression (the GLM and LOGISTIC procedures in the SAS statistical software). First, the age- and sex-adjusted mean levels of cardiovascular risk factors and measures of atherosclerosis at baseline were calculated in six categories of maximal infrarenal aortic diameter at follow-up: <18, 18–20, 21–23, 24–26, 27–29 and ≥ 30 mm (see Table 2). Linear trends across strata were tested by logistic regression for categorical variables and by linear regression for continuous variables (Tables 2 and 4). Linear and logistic regression models were used to model the independent relation between carotid atherosclerosis and aortic diameter and AAA (Tables 3 and 5). In these models, baseline TPA and Δ TPA were the main explanatory variables. Other vascular risk factors were introduced as continuous or binary variables in the model in order to adjust for confounding. We used the SAS statistical software package

Table 1. Characteristics of the study population.

Baseline (1994)	
Age, y	59.4 (9.5)
Male sex, %	47.0
Systolic blood pressure, mmHg	143.3 (21.5)
Smoking, pack-years	11.0 (13.8)
Total cholesterol, mmol/L	6.69 (1.26)
HDL cholesterol, mmol/L	1.53 (0.44)
Diabetes, %	2.2
Lipid-lowering drugs, %	2.0
Anti-hypertensive drugs, %	11.1
Maximal infrarenal aortic diameter, mm	20.6 (2.7)
CHD present at baseline, %	9.5
Measures of atherosclerosis	
Baseline TPA, mm ²	8.4 (14.5)
ΔTPA estimated per 5 years, mm ²	4.7 (11.7)

Values are unadjusted means (SD) or percentages.

(SAS, version 9.2; SAS Institute; Cary, NC, USA). Two-sided *p*-values were used throughout, and 95% confidence intervals computed.

RESULTS

Mean (range) follow-up time was 6.3 (5.4–7.2) years. Table 1 displays characteristics for the study population. The mean carotid plaque growth (ΔTPA) per 5 years was 4.7 mm² and the growth in maximal infrarenal abdominal aortic diameter was 0.12 mm.

Table 2 shows the risk factor level at baseline stratified by maximal infrarenal aortic diameter at follow-up. For age, male sex, smoking and HDL-cholesterol, there were linear dose–response relations with increasing aortic diameter. There was also a linear increase in ΔTPA by increasing abdominal diameter. Baseline TPA and CHD demonstrated a J-shaped correlation to aortic diameter at follow-up (Fig. 1). Baseline TPA was inversely correlated with aortic diameter up to 27 mm; beyond this diameter TPA increased, particularly in those with an AAA (maximal

infrarenal aortic diameter ≥30 mm). When stratifying the 5-year aortic diameter growth into quintiles (not tabulated), no dose–response relation was found for baseline TPA, whereas for ΔTPA, male sex, smoking, HDL (inverse) and diabetes (inverse) there appeared significant trends.

Table 3 shows multivariable adjusted estimates of carotid atherosclerosis for 5-year progression of aortic diameter and aortic diameter at follow-up. Whereas no correlation was found for baseline TPA, a 1-SD increase in 5-year ΔTPA was correlated to a 0.12-mm (standard error, SE = 0.04) growth in aortic diameter in the multivariable model. The multivariable analyses demonstrated no relationship with baseline TPA, but a 1-SD increase in 5-year ΔTPA was associated with a 0.20-mm (SE 0.06) larger aortic diameter at follow-up. Thus, ΔTPA was independently related to growth in aortic diameter as well as follow-up diameter.

The relationship between ΔTPA and change in aortic diameter in the 2019 persons who had plaque progression during follow-up is given in Fig. 2. In accordance with the results from linear regression (Table 3), there was a strong positive relationship between plaque growth and growth in infrarenal aortic diameter (*p* < 0.0001).

During follow-up there were 130 incident cases of AAA, defined as maximal infrarenal aortic diameter ≥30 mm. Table 4 shows quintiles of 5-year change in aortic diameter in these 130 individuals. Both for ΔTPA (but not baseline TPA) and baseline CHD prevalence there were positive dose–response trends with increasing aneurysmal diameter. However, in multivariable linear regression models, ΔTPA was associated neither with 5-year growth in aortic diameter nor aortic diameter at follow-up (results are not shown in the tables). Another two participants had undergone surgery between the two screenings because of an incident AAA. Their maximal infrarenal aortic (graft) diameter at follow-up was 19.5 and 29.5 mm, respectively. In a multivariable logistic model including all 132 persons with AAA, a 1-SD increase in baseline TPA and a 5-year ΔTPA was associated with 15% (odds ratio 1.15, 95% confidence

Table 2. Risk factor level at baseline stratified by maximal infrarenal aortic diameter at follow-up.

Baseline characteristics	Maximal infrarenal aortic diameter at follow-up, mm						<i>p</i> -Trend
	<18 <i>n</i> = 956	18–20 <i>n</i> = 1433	21–23 <i>n</i> = 1129	24–26 <i>n</i> = 461	27–29 <i>n</i> = 132	≥30 <i>n</i> = 130	
Age, ^a y	58.2	58.6	59.7	61.2	62.8	63.5	<0.01
Male sex, ^b %	20.6	38.2	59.5	78.5	83.0	79.3	<0.01
Systolic blood pressure, mmHg	143.8	142.9	143.9	141.8	142.6	145.4	0.8
Smoking, pack-years	10.3	10.7	10.4	11.6	14.9	18.7	<0.01
Total cholesterol, mmol/L	6.78	6.68	6.65	6.57	6.83	6.94	0.7
HDL cholesterol, mmol/L	1.54	1.55	1.54	1.49	1.47	1.39	0.0002
Diabetes, %	2.6	2.0	1.6	1.8	1.1	2.3	0.2
Lipid-lowering drugs, %	4.2	2.0	1.4	1.4	3.1	7.2	0.8
Anti-hypertensive drugs, %	8.6	8.9	9.4	10.3	7.2	10.5	0.4
CHD present at baseline, %	12.8	10.8	9.2	7.6	12.7	17.6	0.9
Measures of atherosclerosis							
Baseline TPA, mm ²	9.1	8.6	7.7	6.9	9.3	12.5	0.9
ΔTPA estimated per 5 years, mm ²	4.3	4.3	4.9	5.1	6.7	7.9	0.0006

All values are age- and sex-adjusted. Percentages were adjusted by logistic regression. Means were adjusted by ANOVA.

^a Adjusted for sex only.

^b Adjusted for age only.

Table 3. Carotid atherosclerosis in relation to 5-years change in maximal infrarenal aortic diameter and maximal infrarenal aortic diameter at follow-up.

Dependent variable	Main explanatory variable	β^a	SE	<i>p</i>
5-years change in maximal infrarenal aortic diameter	Baseline TPA, mm ²	0.01	0.05	0.74
5-years change in maximal infrarenal aortic diameter	Δ TPA estimated per 5 years, mm ²	0.12	0.04	0.0062
Maximal infrarenal aortic diameter at follow-up	Baseline TPA, mm ²	-0.08	0.06	0.18
Maximal infrarenal aortic diameter at follow-up	Δ TPA estimated per 5 years, mm ²	0.20	0.06	0.0008

The models were adjusted for age, sex, systolic blood pressure, total cholesterol, HDL-cholesterol, pack-years of smoking, diabetes mellitus, anti-hypertensive- and lipid-lowering medication.

^a Values are regression coefficients (SE) expressed in mm for 1-SD change in baseline TPA and Δ TPA.

interval (CI): 1.01, 1.32) and 14% (odds ratio 1.14, 95% CI: 0.99, 1.32), respectively, increased odds for having AAA at follow-up. The relationships were both of borderline statistical significance, however (Table 5). When additionally adjusted for baseline infrarenal aortic diameter, a strong and independent predictor of AAA,²¹ the estimates were reduced somewhat and did not reach statistical significance.

DISCUSSION

When modelling aortic diameter as a continuous variable, we found that progression of carotid atherosclerosis (Δ TPA) was related to growth in infrarenal abdominal aortic diameter as well as follow-up diameter both in those with and without incident AAA. However, for baseline atherosclerosis the relationship was more complex with no linear correlation to aortic growth, but an increased plaque burden was seen in persons with the widest aortic diameters at follow-up (≥ 27 mm). In the fully adjusted models, however, no independent relation was found between baseline atherosclerosis and aortic diameter. An explanation for this discordance between baseline TPA and Δ TPA could

be that atherosclerosis in its initial stages has less impact on abdominal aortic dilatation, but as the dilatation process proceeds, atherosclerosis becomes more important. However, neither in those with the highest aortic growth rate, the 130 subjects who developed an AAA during follow-up, could we demonstrate any linear relationship between baseline atherosclerosis and aortic diameter.

There is an ongoing discussion whether atherosclerosis is causally related to AAA formation.

There exist plausible hypotheses for how aortic dilatation is linked to atherosclerosis. Both aneurysmal dilatation and atherosclerotic plaque formation are complex remodelling processes with disturbances in synthesis and degradation of matrix proteins. Initially, atherosclerosis is an intimal disease, but the tunica media and adventitia may secondarily either dilate to preserve the lumen (expansive remodelling) or shrink and thus aggravate the obstruction caused by plaque formation (restrictive remodelling).^{22,23} In the severe forms of atherosclerosis, either progressive dilation (aneurysmal formation) due to expansive remodelling,²⁴⁻²⁶ or diffuse narrowing of the aortic lumen associated with chronic ischaemia of the lower limbs,²⁷ may

Table 4. Measures of atherosclerosis and risk factor levels in strata of 5-years change in infrarenal aortic diameter in incident AAA (*n* = 130).

	I <i>n</i> = 26	II <i>n</i> = 26	III <i>n</i> = 26	IV <i>n</i> = 26	V <i>n</i> = 26	<i>p</i> -Trend
5-years change in maximal infrarenal aortic diameter, mm	3.09	4.78	5.94	7.75	11.88	
Maximal infrarenal aortic diameter at follow-up, mm	30.91	31.95	31.76	34.05	39.15	<0.0001
Baseline TPA, mm ²	22.3	14.2	11.3	14.4	14.1	0.2
Δ TPA estimated per 5 years, mm ²	4.7	8.0	8.2	7.7	15.5	0.03
Baseline femoral lumen diameter, mm	6.75	8.23	7.86	7.45	7.60	0.5
Δ Femoral lumen diameter estimated per 5 years, mm	1.18	0.31	0.78	0.46	0.72	0.4
Baseline CHD, %	9.0	16.6	26.1	19.8	36.2	0.03
Age, years	64.8	61.8	64.2	62.8	60.3	0.06
Male sex, %	98.0	68.2	79.5	70.0	72.7	0.058
Baseline smoking, pack-years	17.3	19.1	19.9	27.2	21.7	0.09
Baseline total cholesterol, mmol/L	6.84	6.99	6.95	7.00	7.10	0.5
Baseline HDL cholesterol, mmol/L	1.28	1.42	1.32	1.32	1.30	0.8
Baseline systolic blood pressure, mmHg	149.7	145.8	151.2	150.2	146.1	0.9
Baseline diabetes, %	1.2	3.3	4.7	3.9	2.3	0.7
Baseline lipid-lowering drugs, %	11.2	7.8	4.8	8.4	2.3	0.3
Baseline anti-hypertensive drugs, %	11.4	19.4	6.6	14.8	21.0	0.5

All values, except for age and sex, are age- and sex-adjusted. Age was adjusted for sex and sex was adjusted for age.

Table 5. Carotid atherosclerosis as predictors and risk for incident AAA.^a

Dependent variable	Model I OR ^b	<i>p</i>	Model II OR ^b	<i>p</i>
Baseline TPA, mm ²	1.15 (1.01–1.32)	0.04	1.12 (0.97–1.29)	0.1
ΔTPA estimated per 5 years, mm ²	1.14 (0.99–1.32)	0.08	1.08 (0.92–1.26)	0.3

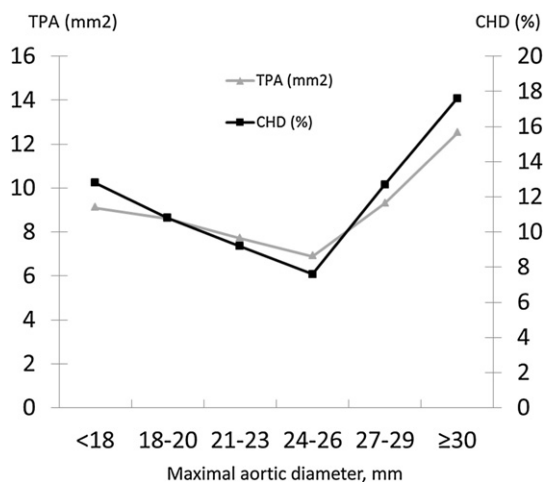
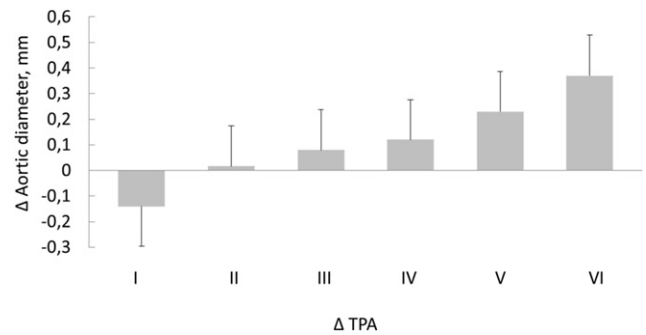
Model I was adjusted for age, sex, systolic blood pressure, total cholesterol, HDL-cholesterol, pack-years of smoking, diabetes mellitus, and anti-hypertensive- and lipid-lowering medication. Model II was additionally adjusted for baseline maximal infrarenal aortic diameter.

^a 132 Persons with AAA were included in analyses.

^b OR for having AAA for 1-SD increase in baseline TPA or ΔTPA.

occur. The J-shaped correlation between baseline TPA and maximal infrarenal aortic diameter at follow-up (Table 2) may indicate that atherosclerosis in its initial stages has little impact on abdominal aortic dilatation, but as the atherosclerotic process progresses, it becomes more important as also suggested by the results displayed in Fig. 1. However, if the hypothesis was true, one should expect plaque burden in 1994 to predict aortic diameter in 2001, but in this study this is not the case. Even if many AAA researches consider atherosclerosis as a needed initiating factor, our findings could simply indicate that atherosclerosis and aortic growth progress in parallel but through different and partly independent processes due to shared risk factors.

Other studies looking into the qualitative aspects of atherosclerosis reported lipid laden (soft) plaques to be associated with expansive remodelling of the vessel and arterial dilation, which could be related to the formation of an aneurysm.²⁶ Conversely, in cases with more fibrous and calcified plaques, the increased rigidity of the aortic wall would prevent compensatory dilation, thus facilitating the obliterative form of the disease.²⁶ These

**Figure 1.** Age- and sex-adjusted baseline total carotid plaque area (TPA) and prevalence of CHD in strata of aortic diameter at follow-up ($n = 4241$).**Figure 2.** Age- and sex-adjusted 5-years change (SE) in infrarenal aortic diameter by strata of 5-year total carotid plaque growth (ΔTPA) ($n = 2019$).

findings may imply that the qualitative aspects of atherosclerosis (plaque morphology), more than the extent of atherosclerosis, play a role in aortic dilatation and aneurysmal formation.

The main limitation of our study is the inter- and intra-observation variability. In studies on progression, the measurement errors of at least two measurements are accumulated, giving substantially lower statistical power compared to baseline measurements only. We have presented the aortic diameter estimates without adjustments for baseline aortic diameter. Adjustments for baseline values of the dependent variable without correction for measurement error may introduce bias that leads to an overestimation of the risk estimates.²⁸ The possibility of regression towards the mean must also be considered in this study.²⁹ In fact, those having the largest aortic diameter and plaque burden at baseline had the lowest growth rate and vice versa.

The strength of the study is that atherosclerosis was assessed directly by ultrasound in the carotid artery, which is a representative measure of the global burden of atherosclerosis,³⁰ and that it is population based and prospective over a time period of 6 years. The attendance rate at baseline was high (79% of the eligible population). Furthermore, 78% of the individuals who had their aortas examined in 1994 and were alive and living in Tromsø in 2001 had a follow-up ultrasound examination. Carotid and abdominal ultrasonography were performed in 75% of the eligible population, where the majority of subjects were aged 55–74 years. The attendance rate in those older than 74 years was only 58%, and this is of some concern as this age group has the highest prevalence of AAA and atherosclerosis. However, given that the association between atherosclerosis and aortic diameter does not differ between the not examined and the scanned group, this will not influence the strength of the associations.

In summary, when analysing aortic diameter as a continuous variable, carotid plaque growth, but not baseline atherosclerosis, was independently related to growth in abdominal aortic diameter and follow-up diameter. Whether the co-variation between plaque growth and aortic diameter growth is causally related or independent events is still an open question.

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CONFLICT OF INTEREST

There are no conflicts of interest in connection with this paper.

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