Factors Associated with Development of Large Abdominal Aortic Aneurysm in Middle-aged Men

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Objectives. To investigate whether any variables in a health-screened population study were associated with later development of large abdominal aortic aneurysms (AAA).


Material and methods. Within the Malmö Preventive Study 22,444 men and 10,982 women were investigated between 1974 and 1991. The mean age at the health screening was 43.7 years.

Results. After a median follow-up of 21 years, 126 men and six women (p < 0.001) had large AAA that were symptomatic or evaluated for operation (5 cm diameter or more) or had autopsy-verified ruptured AAA. The male group (mean age 47 years) was, because of difference in age (p < 0.001) also compared with an age-matched control group. The male patients with AAA showed increased diastolic blood pressure (p < 0.007) at the health screening. Smoking predicted the development of AAA (p < 0.0001). No difference in forced vital capacity or BMI was seen. Those who were physically inactive (e.g. not walking or cycling to work) had an increased risk of developing AAA (p < 0.001). Among the laboratory markers measured, the erythrocyte sedimentation rate did not differ (7.1 ± 5.9 vs. 6.4 ± 5.7), but cholesterol (6.3 ± 1.12 vs. 5.8 ± 1.0) (p < 0.0001) and triglycerides (1.9 ± 0.12 vs. 1.5 ± 0.07) (p < 0.001) were significantly elevated in these individuals who subsequently developing AAA. The inflammatory proteins alpha-1-antitrypsin, ceruloplasmin, orosomucoid, fibrinogen, and haptoglobin were increased (p < 0.001).

Conclusion. Male gender, smoking, physical inactivity and cholesterol are significant factors associated with the development of AAA.

Keywords: AAA; Associated risk factors; Atherosclerosis; Smoking; Hypercholesterolemia; Inflammatory markers.

Introduction

Abdominal aortic aneurysm (AAA) is relatively common in elderly men. Elastin and collagen degradation, increased activity of matrix metalloproteinases, inflammatory and immunologic activity, as well as altered wall shear stress, may be causative factors for the development of AAA.1 There are few studies on factors associated with the development of AAA during long-time follow-up in apparently healthy individuals.2,3 Most studies have analysed subpopulations or patients with confirmed AAA.4–10 Previous studies have shown age, male gender, smoking, hypertension and high cholesterol levels to be associated with the development of AAA.2–10

The evaluation of the incidence of AAA was previously based on autopsy findings, selected case studies, but also on population screening studies in which ultrasonography was used. In this study no initial screening for AAA was made and we included only those from our population cohort who had symptomatic AAA or AAA with a diameter larger than 5 cm and were evaluated for treatment or autopsy-proven ruptured AAA. The aim of this study was to determine the risk factors associated with development of large AAA in a population-based cohort.

Material and Methods

The Malmö Prevention Project11,12 is a health screening and intervention programme carried out during a 17-year period (1974–1991). A total of 22,444 men (mean age 43.7 ± 7 years) participated (participation rate 71%), of whom 126 were found to develop AAA. The
health screening programme also included a population of 10,982 women, but in this group only six individuals have been diagnosed with the development of AAA (p < 0.001).

**Health screening procedure**

The health screening and examination procedures have previously been described in detail.\(^\text{11,12}\) In brief; heart rate and blood pressure (BP) were measured in the right arm after 10 min’ rest. Body mass index (BMI) was calculated as kg/m\(^2\). Diabetes mellitus was considered to be present, if there was a history of treatment of diabetes or a fasting blood glucose level of more than 6.7 mmol/l or equal. Smoking was defined as current smoking at the time of participation in the health screening programme. Forced vital lung capacity (FVC), measured with a Spiroton apparatus (Drägerwerk AG, Lübeck, Germany), and activity assessed from a questionnaire decided the measure of physical fitness. The use of blood pressure-lowering drugs, heart glycosides, nitro vasodilators and analgesic drugs was recorded.

Venous blood was collected after an overnight fast in order to determine the erythrocyte sedimentation rate (ESR), hematocrit and haemoglobin (Hb) levels, total leukocyte count, platelet count, and serum total cholesterol, triglycerides, total calcium, albumin, creatinine, electrolytes, gamma glutamic acid transferase (GT), alanine amino transferase (ALAT), aspartate amino transferase (ASAT), alkaline phosphatases (ALP) and uric acid. The analyses were performed by routine methods at the Clinical Chemistry Laboratory of Malmö University Hospital. The fasting capillary blood glucose level was determined in all subjects.

Individuals who were health-screened and had hypertension, hyperlipidemia, diabetes mellitus or pathological glucose tolerance or high alcohol intake were offered intervention and referred to outpatient clinics. The Ethics Committee at Lund University approved the study. All participants gave informed consent.

**Patients and control groups**

During the 28 years between the start of this health screening programme and December 31, 2002, 126 men and six women of this cohort were documented to have symptomatic or large (5–5.5 cm in diameter) AAA. They either underwent operative reconstruction (n = 98), were evaluated for aneurysm exclusion, but treated conservatively (n = 19), or were found to have autopsy-verified ruptured AAA (n = 15). This documentation was based on hospital register data, SwedVasc quality control data and death certificates. Only those who had objectively documented treatment-requiring AAA were included in the analysed group.

Plasma protein analyses were performed in a subgroup of 6477 men of whom 63 developed AAA. Details have been separately reported,\(^\text{10}\) but are included to give as much information as possible on the factors associated with the development of AAA.

Male patient baseline values for the different variables at the time of health screening were compared with the corresponding values for the case control group established because of differences in age. The closest birth date case not having AAA was selected to the control group, but also to the entire screened male population cohort (n = 22,444 [6477 regarding plasma protein analyses]).

**Statistics**

Values are presented as mean \(\pm\) SD. The differences between groups were assessed with the Mann–Whitney U-test, or the chi-squared test as appropriate. Because of the multiple comparisons, a post-hoc adjustment using Bonferroni’s correction of \(p\) values was performed, revealing that only \(p\) values below 0.01 should be considered as truly significant. The relative risk of the development of AAA was estimated in terms of the odds ratio (OR) and the 95% confidence interval (CI) for a one standard deviation increase (for measurable variables) or in terms of the presence versus absence of a given factor as determined by a logistic regression analysis. The independent significance of each variable was assessed by a multiple logistic regression analysis after adjustment for other significant risk factors. In this analysis \(p\) values less than 0.05 were considered statistically significant.

**Results**

Six women and 126 men developed AAA during the observation period (\(p < 0.0001\)). The median time between the health screening and detection of AAA was 21 years (range 6–30 years), and the median age at the detection of AAA was 68 years (range 49–81 years). Male patients with AAA (n = 126) were further analysed. At the health screening, this group was significantly older (47 [37–60] years) than the entire screened male population (n = 22,444, 43.7 [26–61] years; \(p < 0.0001\)). Therefore, we established an age-
adjusted case control group with 126 patients. Demographic data at health screening are seen in Table 1. The male patients with AAA had higher diastolic blood pressure (134/90 vs. 131/86 mmHg; \( p < 0.007 \)).

A significantly higher proportion of the patients with AAA were smokers at the health screening (81 vs. 51%; \( p < 0.0001 \)). Those who had smoked daily for more than 10 years were even more frequent among the patients who developed AAA (\( p < 0.0001 \)). The subgroup of pipe smokers also seemed to have an increased risk (\( p < 0.08 \)).

Reported alcohol consumption was not a risk factor for the development of AAA. Neither were factors such as being busy, easily stressed or suffering from insomnia associated with later development of AAA.

The initial questionnaire from the health screening showed that the case control group and entire male population were more physically active (\( p < 0.001 \)) than those who developed AAA. Forced vital capacity did, however, not differ.

Laboratory data (Table 2) showed increased serum total cholesterol (6.3 ± 1.1 vs. 5.9 ± 1.0 mmol/l; \( p < 0.0001 \)), triglyceride (1.9 ± 1.2 vs. 1.5 ± 0.7 mmol/l; \( p < 0.0001 \)), and plasma fibrinogen levels (3.95 ± 0.65 vs. 3.50 ± 0.80 mmol/l; \( p < 0.001 \), Table 3) in subjects later developing AAA.

We did not find any differences regarding the recorded use of medication between the patients with AAA and the control group or the background health-screened population.

Furthermore, a logistic regression analysis was performed to evaluate the variables that differed as independent associated factors (Table 4). Since fibrinogen inactivity, and serum cholesterol remained as independent factors associated with development of AAA such as male gender, smoking and high cholesterol. In the highest quartile, we saw an absolute risk of 1.2% compared with 0.1% in the lowest quartile of serum total cholesterol values.

### Discussion

In recent years, we have learned much about the pathology of AAA. Some of the more important factors are elastolysis, impaired collagen production and increased degradation, increased levels of matrix proteinases, inflammatory reactions with increased CRP levels, leukocyte and macrophage accumulation in the aneurysmal wall, and increased immunological activity.1

This study verifies earlier population-based studies showing several factors associated with the development of AAA such as male gender, smoking and high cholesterol levels.2–10 A large number of case control studies on patients with AAA have focused on these risk factors.

Table 1. Baseline characteristics at the time of the health screening programme of male individuals with detected AAA compared with a case control series (age-adjusted)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>AAA-group (( n = 126 ))</th>
<th>Case-control group (( n = 126 ))</th>
<th>Screened males, (( n = 22,244 ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>47 ± 6.1</td>
<td>47 ± 6.1</td>
<td>43.7 ± 6.6</td>
</tr>
<tr>
<td>Length (cm)</td>
<td>178 ± 7</td>
<td>176 ± 8</td>
<td>177 ± 7</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.4 ± 3.2</td>
<td>24.9 ± 3.3</td>
<td>24.7 ± 3.3</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>134 ± 19</td>
<td>131 ± 11</td>
<td>127 ± 15</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>90 ± 11**</td>
<td>86 ± 11</td>
<td>85 ± 10</td>
</tr>
<tr>
<td>COHb (%)</td>
<td>4.0 ± 3.0</td>
<td>3.1 ± 2.8</td>
<td>2.3 ± 2.8</td>
</tr>
<tr>
<td>FVC (l/min)</td>
<td>4.2 ± 0.9</td>
<td>4.2 ± 0.8</td>
<td>4.5 ± 0.9</td>
</tr>
<tr>
<td>FEV1.0 (l/s)</td>
<td>3.3 ± 0.7</td>
<td>3.2 ± 0.7</td>
<td>3.5 ± 0.8</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>81***</td>
<td>51</td>
<td>51</td>
</tr>
<tr>
<td>Physical active (%)</td>
<td>20***</td>
<td>58</td>
<td>48</td>
</tr>
</tbody>
</table>

Results (but no statistical comparison) on the total screened male population are also shown. Values presented as mean ± SD. * \( p < 0.05 \); ** \( p < 0.01 \); *** \( p < 0.001 \) for comparison between AAA-group and case controls. BMI, body mass index; BP, blood pressure; COHb, carbon monoxide; FVC, forced vital capacity; FEV1.0, forced expiratory volume in 1 s.

Eur J Vasc Endovasc Surg Vol 30, October 2005
factors, and an association has been further verified between AAA and age, male gender, smoking, total cholesterol, triglycerides, fibrinogen, C-reactive protein, CRP, interleukin-6, IL-6, tumor necrosis factor-α, TNF-α, and homocysteine. A correlation has also been suggested by several studies for hypertension, arteriosclerosis, high-density lipoprotein cholesterol, HDL-cholesterol, and fibrinogen levels. In some case-control studies, an association has been demonstrated between AAA and triglycerides, cytokines, IL-6, TNF-α, acute phase reactants, oxidative stress, and shear stress.

This study is based on the Malmo Preventive Study. Since we only noted six AAAs in women in the follow-up until now, we focused our analysis on the male population. Most studies do have selection bias. The majority included in this health screening analysis were men and the acceptable attendance rate was 71%. Undetected aneurysms at the health screening or during the follow-up cannot be ruled out, because patients were not routinely imaged. These factors need to be taken into account when analysing our data. Furthermore, some individuals in the screened population have moved to other areas, which also may have influenced our results. Another limitation with our study is the suboptimal autopsy rates. In Malmo, the autopsy rate remained until 1990, and was acceptable until 2000, but it is currently as low as in most western countries with an autopsy rate of 10–15%. However, we consider that the fairly large cohort of screened patients, followed for a median of over 20 years, still makes our results valuable, and the majority of clinically important aneurysms should have been recognized in our population.

Table 2. Laboratory data at the time of the health screening programme of male individuals with detected AAA compared with a case control series (age-adjusted)

<table>
<thead>
<tr>
<th></th>
<th>AAA-group (n = 126)</th>
<th>Case-control group (n = 126)</th>
<th>Screened males (n = 22,244)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESR (mm/h)</td>
<td>7.1 ± 5.9</td>
<td>6.4 ± 5.7</td>
<td>5.8 ± 6.0</td>
</tr>
<tr>
<td>WBC (×10^9/l)</td>
<td>6.3 ± 3.0</td>
<td>6.2 ± 1.9</td>
<td>6.1 ± 2.1</td>
</tr>
<tr>
<td>Hb (g/l)</td>
<td>146 ± 9.7</td>
<td>147 ± 9.3</td>
<td>148 ± 9.7</td>
</tr>
<tr>
<td>Creatinine (µmol/l)</td>
<td>94 ± 16</td>
<td>92 ± 12</td>
<td>93 ± 19</td>
</tr>
<tr>
<td>S-uric acid (µmol/l)</td>
<td>336 ± 65**</td>
<td>318 ± 67</td>
<td>324 ± 64</td>
</tr>
<tr>
<td>S-total cholesterol (mmol/l)</td>
<td>6.3 ± 1.1**</td>
<td>5.8 ± 1.0</td>
<td>5.6 ± 1.1</td>
</tr>
<tr>
<td>S-triglycerides (mmol/l)</td>
<td>1.9 ± 1.2**</td>
<td>1.5 ± 0.7</td>
<td>1.5 ± 1.1</td>
</tr>
<tr>
<td>F-b-glucose (mmol/l)</td>
<td>4.9 ± 0.8</td>
<td>4.8 ± 0.7</td>
<td>5.0 ± 1.0</td>
</tr>
<tr>
<td>S-GT (µkat/l)</td>
<td>0.73 ± 0.50</td>
<td>0.90 ± 0.48</td>
<td>0.69 ± 0.96</td>
</tr>
</tbody>
</table>

Results, but without statistical comparison for the screened male population, also shown. Values presented as mean ± SD. *p < 0.05; **p < 0.01; ***p < 0.001; S, serum; P, plasma; F, fasting; b, blood; ESR, erythrocyte sedimentation rate; WBC, white blood cell count; Hb, haemoglobin; GT, glutamic acid transferase.

Table 3. Inflammatory-related proteins in 6477 men (previously reported) of whom 63 later (median 19 years) developed AAA

<table>
<thead>
<tr>
<th></th>
<th>AAA-patients, (n = 63)</th>
<th>Male screening group (n = 6414)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinogen (g/l)</td>
<td>3.95 ± 0.65</td>
<td>3.50 ± 0.80</td>
</tr>
<tr>
<td>Alfa1-antitrypsin</td>
<td>1.40 ± 0.28</td>
<td>1.27 ± 0.27</td>
</tr>
<tr>
<td>Ceruloplasmin (g/l)</td>
<td>0.36 ± 0.07</td>
<td>0.32 ± 0.07</td>
</tr>
<tr>
<td>Orosomucoid (g/l)</td>
<td>0.91 ± 0.23</td>
<td>0.82 ± 0.20</td>
</tr>
<tr>
<td>Haptoglobin (g/l)</td>
<td>1.69 ± 0.79</td>
<td>1.38 ± 0.68</td>
</tr>
</tbody>
</table>

Table 4. Logistic regression analysis of variables found to significantly differ between the AAA group and the case control group (Odds ratio for 1 SD or yes/no questions, 95% confidence intervals)

<table>
<thead>
<tr>
<th></th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>S-triglycerides</td>
<td>1.28</td>
<td>0.92–1.79</td>
<td>0.1453</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>1.29</td>
<td>0.99–1.67</td>
<td>0.0692</td>
</tr>
<tr>
<td>S-cholesterol</td>
<td>1.45</td>
<td>1.05–1.99</td>
<td>0.0227</td>
</tr>
<tr>
<td>Physical inactivity</td>
<td>2.67</td>
<td>1.42–5.01</td>
<td>0.0022</td>
</tr>
<tr>
<td>Smoking</td>
<td>3.51</td>
<td>1.92–6.44</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Fig. 1. The absolute risk of the development of AAA depending on the level of cholesterol (divided in four quartiles, with small differences due to the fact that many had equal values).

Homocysteine, cysteine-C, plasmin–antiplasmin complexes, elastin peptides and its inhibition, MMP-2, PAF, connective tissue defects, and shear stress.

This study is based on the Malmö Preventive Study. Since we only noted six AAAs in women in the follow-up until now, we focused our analysis on the male population. Most studies do have selection bias. The majority included in this health screening analysis were men and the acceptable attendance rate was 71%. Undetected aneurysms at the health screening or during the follow-up cannot be ruled out, because patients were not routinely imaged. These factors need to be taken into account when analysing our data. Furthermore, some individuals in the screened population have moved to other areas, which also may have influenced our results. Another limitation with our study is the suboptimal autopsy rates. In Malmö, a high autopsy rate remained until 1990, and was acceptable until 2000, but it is currently as low as in most western countries with an autopsy rate of 10–15%. However, we consider that the fairly large cohort of screened patients, followed for a median of over 20 years, still makes our results valuable, and the majority of clinically important aneurysms should have been recognized in our population.
Genetic studies have shown alterations in several genes exhibiting a pattern of chronic inflammation, matrix degradation, arteriosclerosis and smooth muscle cell depletion,\textsuperscript{49–54} but this knowledge is currently based on a limited screening of less than 1\% of the genome. A familial history regarding AAA among relatives was not taken at the health screening in our population cohorts. An association between familial incidence and AAA has been strongly documented.\textsuperscript{55,56}

How predictive are the associated factors—male gender, smoking, physical inactivity and hypercholesterolemia—that we found? The presence of male gender, smoking or high cholesterol value increased the risk of the development of AAA many times, but the majority of male, smoking, inactive patients with hypercholesterolemia, will not develop AAA. In the future, maybe pharmacological treatment can prevent aneurysm formation? Genetical studies have localised some of the factors contributing to the development of aneurysm.\textsuperscript{49–54} Studies using beta-blockers, statins, anti-inflammatory drugs, or matrix proteinase-inhibition have found some effects on aneurysm growth.\textsuperscript{57–59}

Screening for AAA is currently under debate. Inactive, smoking men with hypercholesterolemia are a subgroup likely to benefit from screening. In the group having these factors, the absolute risk of developing AAA was 5–10 times higher than in active, non-smoking, normocholesterolemic male patients. We know that screening programmes for AAA are cost-effective, but the mortality from AAA is only moderately reduced.\textsuperscript{60,61}

In conclusion, we have confirmed male gender, smoking and hypercholesterolemia to be associated with the development of AAA. The fact that physically inactive patients were more prone to develop AAA was not previously established. It is an interesting finding, but only based on a questionnaire 21 years before AAA was diagnosed and therefore it needs to be further confirmed. So far, 126 documented AAAs have been seen in males with 21-years of follow-up after the initial health screening.

Acknowledgements

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Eur J Vasc Endovasc Surg Vol 30, October 2005
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