Serum triglyceride: a possible risk factor for ruptured abdominal aortic aneurysm

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Background We aimed to determine the relationship between ruptured abdominal aortic aneurysm (AAA) and serum concentrations of lipids and apolipoproteins.

Methods A cohort of 21 520 men, aged 35–64 years, was recruited from men attending the British United Provident Association (BUPA) clinic in London for a routine medical examination in 1975–1982. Smoking habits, weight, height and blood pressure were recorded at entry. Lipids and apolipoproteins were measured in stored serum samples from the 30 men who subsequently died of ruptured AAA and 150 matched controls.

Results Triglyceride was strongly related to risk of ruptured AAA. In univariate analyses the risk in men on the 90th centile of the distribution relative to the risk in men on the 10th (RO_{10-90}) was 12 (95% confidence interval [CI] : 3.8–37) for triglyceride, 5.5 (95% CI: 1.8–17) for apolipoprotein B (apoB) (the protein component of low density lipoprotein [LDL]), 0.15 (95% CI: 0.04–0.56) for apo A1 (the protein component of high density lipoprotein [HDL]), 3.7 (95% CI: 1.4–9.4) for body mass index and 3.0 (95% CI: 1.1–8.5) for systolic blood pressure. Lipoprotein (a) (Lp(a)) was not a significant risk factor (RO_{10-90}= 1.6, 95% CI: 0.6–3.0). In multivariate analysis triglyceride retained its strong association.

Conclusion Triglyceride appears to be a strong risk factor for ruptured AAA, although further studies are required to clarify this. If this and other associations are cause and effect, then changing the distribution of risk factors in the population (by many people stopping smoking and adopting a lower saturated fat diet and by lowering blood pressure) could achieve an important reduction in mortality from ruptured AAA.

Keywords Abdominal aortic aneurysm, triglyceride, cholesterol, apolipoprotein B

Accepted 9 April 1998

Ruptured abdominal aortic aneurysm (AAA) accounts for 2% of all deaths in men aged >60 in England and Wales. The aetiology of the condition is incompletely understood; atheromatous disease is usually a prerequisite, but the destruction of elastin within the aortic wall is also important. Both smoking and blood pressure are strongly related to the risk of AAA. The relationships of serum cholesterol, triglyceride and other lipids to risk are uncertain, because only limited data are available. We used data from a prospective epidemiological study (the British United Provident Association [BUPA] study) to examine the association of lipids and apolipoproteins as well as blood pressure and smoking with mortality from ruptured AAA.

Methods

The BUPA prospective study comprises 21 520 men aged 35–64 years, who attended the BUPA medical centre in London between 1975 and 1982 for a routine medical examination. The men were asked to fast before the visit. Medical history, smoking habits and blood pressure, weight and height were recorded at the initial examination. Serum samples were stored at −40°C. With the co-operation of the Office of National Statistics we were notified of all deaths from the National Health Service Central Register; we then sought further clinical details of each death from the certifying doctor. The present analysis is based on an analysis of mortality up to the end of October 1993 (average follow-up time 13 years) when 30 men had died of a ruptured AAA (ICD 9th revision codes 441.3 and 441.4). Five controls were matched to each case by age at entry (to same year of age), duration of storage of serum samples (to same calendar year), number of serum freeze-thaw cycles (about a third of...
serum samples had been thawed previously) and smoking status (non-smoker, ex-smoker, cigarette smoker smoking 1–14, 15–24, 25–34 and ≥35 per day). Serum cholesterol, triglyceride, apolipoproteins B and A1 (the protein components of low density [LDL] and high density [HDL] lipoprotein cholesterol respectively) and lipoprotein (a) (Lp(a)) were measured on the stored serum samples; details of the biochemical analyses are described elsewhere. We here used a different assay to the one previously used to measure Lp(a), namely the Macra Lp(a) ELISA from Terumo (Elkton, MD, USA). We previously referred to Lp(a) as apolipoprotein (a) or apo(a), which is the protein component of Lp(a). Most studies which use this assay or the one we used previously refer to Lp(a) and we here follow this convention.

Logistic regression was used to estimate the associations of the risk factors with mortality from ruptured AAA. Blood pressure, serum triglyceride and Lp(a) data were logarithmically transformed to correct for skewness in the distributions; the distributions of the other variables were already close to Gaussian. As in our previous analysis on ischaemic heart disease, we expressed the gradient of risk across the population as the relative odds of death from ruptured AAA at the 90th centile compared to the 10th centile of the distribution of the risk factor—the RO<sub>10-90</sub>. This was derived by multiplying the logistic regression coefficient by the standard deviation of the risk factor and by 2.5632, and taking the exponential.

**Results**

Table 1 shows the mean ages at entry and levels of the risk factors in men who died from a ruptured AAA (cases) and in men who did not (controls). Serum triglyceride, apo B, systolic blood pressure and body mass index (weight/height<sup>2</sup>) were significantly higher in cases than in controls; apo A1 levels were significantly lower. There was no significant difference in total cholesterol, height or Lp(a) between the two groups. One case and one control were diabetic.

Table 2 shows the results of univariate analyses as the relative odds of dying from ruptured AAA between the 10th and 90th centiles of the distributions of the variables (RO<sub>10-90</sub>). The strongest association was with serum triglyceride (RO<sub>10-90</sub> = 12). The lower boundary of the 95% confidence interval (CI) was 3.8, so this result is consistent with a more modest risk attributable to triglyceride. Triglyceride was >2.43 mmol/l (the 90th centile point in the controls) in 13 (43%) of cases. The RO<sub>10-90</sub> estimates for serum apo B, serum apo A1, blood pressure and body mass index with a ruptured AAA are about 3–6, similar to the corresponding estimates for ischaemic heart disease reported previously (also shown, with some expansion, in Table 2). Serum triglyceride was, however, more strongly related to ruptured AAA than to heart disease.

On multivariate analysis (adjusting for all the factors in Table 2), serum triglyceride retained its strong association with ruptured AAA. The other factors (apo B, apo A1, Lp(a), systolic blood pressure, body mass index, and weight) were directionally related to ruptured AAA (with an inverse risk for apo A1) but the associations were no longer statistically significant after...
adjustment for triglyceride. However, there were important correlations between the variables, and our analysis is based on too few deaths (30) to be certain which of the associations are direct and indirect. In the controls triglyceride was correlated with apo B (r = +0.52), with body mass index (r = +0.25) and inversely with apo A1 (r = −0.37); body mass index was correlated with systolic blood pressure (r = +0.19) and apo B was inversely correlated with apo A1 (r = −0.26).

The association between death from ruptured AAA and smoking was determined from analysis of the entire cohort of 21 520 men (it could not be determined from our nested case-control set because we matched cases and controls by smoking status). Of the 30 men who died of a ruptured AAA, 18 (60%) were current smokers and the remaining 12 were ex-smokers; none had never smoked. In the entire cohort, adjusted to the age distribution of the cases, there were 39% current smokers, 37% ex-smokers and 24% lifelong non-smokers. With no cases in non-smokers the estimated relative risk of smoking is infinite; the lower 95% confidence limit is 2.7.

Discussion

The risk of death from a ruptured AAA was strongly related to serum triglyceride; the risk gradient from the 10th to the 90th centiles of the triglyceride distribution was 12 (95% CI: 3.8–37). This can also be expressed as relative odds of 1.16 (95% CI: 1.08–1.25) for an increase in triglyceride of 0.14 mmol/l (10% of the mean value in controls). The only other study of AAA in which triglyceride was measured in fasting blood samples was a retrospective case-control study (cases were those treated for AAA) with a result corresponding to a relative odds of 1.15 (95% CI: 1.03–1.27) for the same increase, which is very similar to our result. The same study reported a strong relationship with serum Lp(a) but our study did not confirm this result (Table 2).

Table 3 shows our results (on univariate analyses) for the other risk factors, expressed as the relative odds associated with increases of 10% of the mean value in the controls (using a linear-logistic model in all cases), and for comparison the results obtained in other prospective studies. Two of the studies include thoracic aortic aneurysms. The study by Pleumeekers et al. is based on prevalence of AAA as determined by ultrasound examination. Despite the lack of a statistically significant association with serum cholesterol in two of the studies, the results are all consistent with an increase in risk of aortic aneurysm of about 10% for a 10% increase in cholesterol. The highly significant relationship with apo B in our data confirms this. We also found a significant inverse association with apo A1. From the results in their case-control study with respect to LDL and HDL cholesterol (of which apo B and apo A1 are the corresponding protein components). However, in the only other cohort study in which HDL cholesterol was measured, no association was apparent. All the studies are consistent with moderate relationships between blood pressure and aortic aneurysms, and between height and aortic aneurysms.

The strong association with triglyceride and the lipoproteins and with blood pressure are of etiological importance, but strong as they are, they are not strong enough for use as screening tests. For example, our case-control difference in triglyceride levels predicts that only 40% of deaths occur in men at the top 10% of the distribution of triglyceride. Ultrasound is, however, highly effective as a screening test for future ruptured AAA.

In view of the correlation (r = +0.52) between triglyceride and apo B, multivariate analysis could not determine which of the two may be causally associated. Further studies are needed to clarify the importance of the association with triglyceride in particular. However, since lowering dietary fat intake lowers serum total cholesterol, apo B and triglyceride levels, this approach is likely to lower risk. If the relationship with lipids, blood pressure, and smoking are cause and effect, the lifestyle changes advocated to reduce the risk of ischaemic heart disease (stopping smoking, eating less saturated fat, and lowering blood pressure) could substantially reduce mortality from ruptured AAA.

Table 3 Relative odds of aortic aneurysm for increase in specified risk factors by 10% of the mean value in controls (which are specified below) for published prospective studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Cholesterol 0.6 mmol/l</th>
<th>HDL cholesterol 0.12 mmol/l (15 mg/dl apo A1)</th>
<th>Systolic blood pressure 14 mmHg</th>
<th>Diastolic blood pressure 8.5 mmHg</th>
<th>Height 0.17 m</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strachan</td>
<td>0.98 (0.86–1.10)</td>
<td></td>
<td></td>
<td>1.14 (1.20–1.73)</td>
<td>1.65 (1.00–2.69)</td>
</tr>
<tr>
<td>Reed</td>
<td>1.30 (1.05–1.62)</td>
<td></td>
<td></td>
<td>1.38 (1.04–1.82)</td>
<td>2.55 (1.18–5.49)</td>
</tr>
<tr>
<td>Goldberg</td>
<td>1.28 (1.05–1.57)</td>
<td></td>
<td></td>
<td>1.32 (1.02–1.72)</td>
<td></td>
</tr>
<tr>
<td>Pleumeekers</td>
<td>1.16 (1.03–1.30)</td>
<td>1.00 (0.92–1.09)</td>
<td></td>
<td>1.11 (0.97–1.27)</td>
<td></td>
</tr>
<tr>
<td>Present study</td>
<td>1.10 (0.88–1.36)</td>
<td>0.64 (0.47–0.87)</td>
<td></td>
<td>1.28 (1.00–1.64)</td>
<td>1.25 (0.98–1.61)</td>
</tr>
</tbody>
</table>

Relative odds derived from linear-logistic model in all cases.

* Relative odds derived from case-control differences by multiplying this by the specified increase in risk factor, dividing by variance and taking the exponential.


9 Norrgård Ö, Angquist KA, Dahlen G. High concentrations of lpa lipoprotein in serum are common among patients with abdominal aortic aneurysms. Int Angiol 1988;7:46-49.