Plasma Fibrinogen and D-dimer Concentrations are Associated with the Presence of Abdominal Aortic Aneurysm: A Systematic Review and Meta-analysis

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Submitted 24 January 2009; accepted 21 May 2009
Available online 27 June 2009

Abstract

Objectives: To summarise the present evidence for an association between circulating fibrinogen or D-dimer and presence of abdominal aortic aneurysm (AAA) presence.

Design: MEDLINE database was searched to identify all case-control studies that compared plasma fibrinogen or D-dimer concentrations between patients with AAA and subjects without AAA. For each study, data regarding fibrinogen or D-dimer concentrations in both the AAA and control groups were used to generate mean differences (MDs) and 95% confidence intervals (CIs). Study-specific estimates were combined using inverse variance-weighted average of logarithmic MDs in both fixed- and random-effects models.

Results: Our search identified 10 eligible studies including 834 cases with AAA and 6971 controls without AAA for fibrinogen and six studies including 264 patients with AAA and 403 subjects without AAA for D-dimer. Pooled analysis demonstrated significantly higher fibrinogen (fixed-effects MD, 0.37 g l⁻¹; 95% CI: 0.30–0.44 g l⁻¹) and D-dimer (random-effects MD: 415.36 ng ml⁻¹; 95% CI: 128.97–701.76 ng ml⁻¹) concentrations in the AAA group than those in the control group.

Conclusions: We found that plasma fibrinogen and D-dimer concentrations are likely to be higher in cases with AAA than control subjects. Higher plasma fibrinogen and D-dimer concentrations may be associated with the presence of AAA.

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Circulating concentrations of many kinds of biomarkers have been measured and compared in patients with abdominal aortic aneurysm (AAA) and subjects without AAA to assess their possible role in the pathogenesis or progression of AAA. Circulating biomarkers could play a role in the diagnosis of AAA and may have a role in predicting subsequent progression of AAA. These biomarkers included extracellular matrix markers, matrix-degrading enzymes, proteins associated with thrombosis, lipids and markers of inflammation. Proteins involved in, stimulated by or...
associated with thrombosis, for example, fibrinogen and D-
dimer, have been the biomarkers most commonly assessed
in AAA.\textsuperscript{1} To summarise the present evidence for an associ-
ation between circulating fibrinogen or D-dimer and AAA
presence, we performed a systematic review and meta-
analysis of case-control studies that compared plasma
fibrinogen or D-dimer concentrations between patients
with AAA and subjects without AAA.

Materials and Methods

Search strategy

All case-control studies that compared plasma fibrinogen or
D-dimer concentrations between patients with AAA and
subjects without AAA were identified using a two-level
search strategy. First, a public domain database (MEDLINE)
was searched using a web-based search engine (PubMed).
Second, relevant studies were identified through a manual
search of secondary sources including references of initially
identified articles and a search of reviews and comment-
aries. All references were downloaded for consolidation,
elimination of duplicates and further analysis. The MEDLINE
database was searched from January 1966 to November
2008. MeSH keywords included fibrinogen; fibrin fragment
D; and aortic aneurysm, abdomen. Text keywords included
fibrinogen, fibrin fragment D, D-dimer and abdominal
aortic aneurysm.

Study selection and data abstraction

Studies considered for inclusion met the following criteria: the
design was a case-control study; the study population
was patients with AAA and subjects without AAA; and main
outcomes included means and standard deviations (SDs) of
plasma fibrinogen or D-dimer concentrations in the AAA
and control groups. Data regarding detailed inclusion criteria
and plasma fibrinogen or D-dimer concentrations were
abstracted (as available) from each individual study.

Statistical analysis

We conducted a meta-analysis of summary statistics from
the individual studies because detailed, patient-level data
were not available for all studies. For each study, data
regarding plasma fibrinogen or D-dimer concentrations in
both the AAA and control groups were used to generate
mean differences (MDs) and 95% confidence intervals (CIs).
In articles reporting the median and the interquartile range
(IQR), we took the median to be representative of the mean
and converted the IQR into an SD by divided it by 1.35.\textsuperscript{2}
When the concentrations were stated separately in
subgroups of the AAA or control group, we combined them
as values of the AAA or control group by the use of standard
formulae.\textsuperscript{2} Study-specific estimates were combined using
inverse variance-weighted average of logarithmic MDs in
both fixed- and random-effects models. Between-study
heterogeneity was analysed by means of standard $\chi^2$
tests. Where no significant statistical heterogeneity was
identified, the fixed-effect estimate was used preferen-
tially as the summary measure. Sensitivity analyses were
performed to assess the contribution of each study to the
pooled estimate by excluding individual studies one at
a time and recalculating the pooled MD estimates for the
remaining studies. To assess the impact of differential
control selection on the pooled estimate, the association of
plasma fibrinogen or D-dimer and AAA presence was
explored separately in studies with healthy controls.
Publication bias was assessed graphically using a funnel plot
and mathematically using an adjusted rank-correlation
test, according to the method of Begg and Mazumdar.\textsuperscript{3} All
analyses were conducted using Review Manager (RevMan)\textsuperscript{4}
and Microsoft Excel (Version 11.5.0).

Results

Our search identified 12 case-control studies\textsuperscript{5–16} that
compared plasma fibrinogen concentrations and seven
studies\textsuperscript{7,12,13,15,17–19} that compared plasma D-
dimer concentrations between patients with AAA and subjects
without AAA. Of these studies, we excluded two studies\textsuperscript{15,16}
in which the mean and SD of fibrinogen or D-dimer
concentrations could not be abstracted. In total, our meta-
analysis included 10 studies\textsuperscript{5–14} and data on 834 cases with
AAA and 6,971 controls without AAA for fibrinogen, and six
studies\textsuperscript{7,12,13,15,17–19} and data on 264 patients with AAA and
403 subjects without AAA for D-dimer.

Plasma fibrinogen concentrations and AAA
presence

Eight\textsuperscript{5,7,8,10–14} of the 10 studies reported plasma fibrinogen
concentrations in men and women combined, whereas the study
by Al-Barjas et al.\textsuperscript{6} stated those in men exclusively and
the study by Singh et al.\textsuperscript{9} reported those separately in
men and women. Four\textsuperscript{5,9,11,12} of the 10 studies stated the
means and SDs of fibrinogen concentrations, whereas the
other six studies\textsuperscript{6–8,10,13,14} stated the medians and IQRs.
In the latter six studies, we obtained the means and SDs by
means of the standard formulae.\textsuperscript{2} Eight\textsuperscript{7–9,10,12–14} of the
10 studies reported plasma fibrinogen concentrations in
healthy controls, whereas the other two studies stated
those separately in healthy controls and controls with
atherosclerosis (peripheral arterial disease\textsuperscript{8} or ilio-femoral
stenosis\textsuperscript{11}). In the latter two studies, we combined the
separately reported concentrations as values in the control
group by the use of the standard formulae.\textsuperscript{2}

Six\textsuperscript{6–10,13} of the 10 individual studies demonstrated
significantly higher plasma fibrinogen concentrations, and
three studies\textsuperscript{5,12,14} showed non-significantly higher ones in
the AAA group than those in the control group. Pooled
analysis of the 10 studies (representing 834 cases with AAA
and 6,971 controls without AAA) demonstrated significantly
higher fibrinogen concentrations in the AAA group than
those in the control group in fixed-effect models (MD,
$0.37$ g l$^{-1}$; 95% CI: $0.30–0.44$ g l$^{-1}$; $p < 0.00001$ (Fig. 1)).
There was no significant study heterogeneity of results
($p = 0.44$) and accordingly no difference in the pooled
result from random-effects modelling. To assess the impact
of qualitative heterogeneity in study design and control
selection on the pooled effect estimate, we performed several sensitivity analyses. In general, exclusion of any single study from the analysis did not substantively alter the overall result of our analysis. Additionally, combining MDs between plasma fibrinogen concentrations in the AAA group and those in the healthy control group (representing 834 patients with AAA and 6898 healthy controls) did not substantially change the pooled point estimate (random-effects MD, 0.42 g dl⁻¹; 95% CI: 0.34–0.53 g dl⁻¹; \( p < 0.00001 \)) (heterogeneity, \( p < 0.00001 \)).

### Plasma D-dimer concentrations and AAA presence

All of the six studies reported plasma D-dimer concentrations in men and women combined. Three of the six studies stated the means and SDs of D-dimer concentrations, whereas the other three studies reported the medians and IQRs. In the latter three studies, the means and SDs were obtained by means of the standard formulae.

Five of the six studies stated plasma D-dimer concentrations in healthy controls, whereas only the study by Aramoto et al. reported those in controls with arteriosclerosis obliterans.

Five of the six individual studies demonstrated significantly higher plasma D-dimer concentrations, whereas only the study by Serino et al. showed nonsignificantly higher ones in the AAA group than those in the control group. Pooled analysis of the six studies (representing 264 cases with AAA and 403 control subjects) demonstrated significantly higher D-dimer concentrations in the AAA group than those in the control group in random-effect models (MD, 415.36 ng ml⁻¹; 95% CI: 128.97–701.76 ng ml⁻¹; \( p = 0.004 \) (Fig. 2)). There was significant study heterogeneity of results (\( p < 0.00001 \)). In general, exclusion of any single study from the analysis did not substantively alter the overall result of our analysis. Combining five studies with healthy control group (representing 223 patients with AAA and 373 healthy controls) did not substantially change the pooled point estimate (random-effects MD, 364.00 ng ml⁻¹; 95% CI: 93.32–634.68 ng ml⁻¹; \( p = 0.008 \)) (heterogeneity, \( p < 0.00001 \)).

### Publication bias

To assess publication bias we generated a funnel plot of the logarithm of effect size versus the standard error for each study. There was no evidence of significant publication bias (\( p = 0.6767 \) for fibrinogen; \( p = 0.8510 \) for D-dimer; by Begg adjusted rank-correlation test).

### Discussion

The results of our analysis suggest that plasma fibrinogen and D-dimer concentrations may be higher in patients with AAA than those in subjects without AAA. Our analysis, however, must be viewed in the context of its limitations. First, there was qualitative heterogeneity in participant selection among included studies. Although eight of the 10 studies for fibrinogen reported the concentrations in men and women combined, one study stated those in men exclusively and another study reported those separately in men and women. Second, heterogeneity in control selection was present. Eight of the 10 studies for

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**Figure 1** Plasma fibrinogen concentrations among cases with abdominal aortic aneurysm (AAA) and controls without AAA. SD = standard deviation; CI = confidence interval.

**Figure 2** Plasma D-dimer concentrations among cases with abdominal aortic aneurysm (AAA) and controls without AAA. SD = standard deviation; CI = confidence interval.
fibrinogen stated the concentrations in healthy control, whereas the other two studies reported those separately in healthy controls and controls with atherosclerosis. In the sensitivity analysis, we combined MDs between the concentrations in the AAA group and those in the healthy control group, and the pooled point estimate was not substantively changed. Although five of the six studies for D-dimer stated the concentration in healthy controls, the other study reported those in controls with arteriosclerosis. Combining the five studies with healthy controls did not substantially change the pooled estimate. Despite these acknowledged limitations, we found that, based on a systematic review and meta-analysis, plasma fibrinogen and D-dimer concentrations are likely to be higher in cases with AAA than control subjects. Higher plasma fibrinogen and D-dimer concentrations may be associated with AAA presence. High fibrinogen levels in patients with AAA may reflect an underlying inflammatory process. Aortic aneurysms appear to be an important source of circulating interleukin-6, which has a pivotal role in stimulating the acute-phase response and elevates the circulating concentrations of several plasma proteins, including fibrinogen and C-reactive protein. An AAA may not develop because of elevated levels of fibrinogen but may cause elevated levels of fibrinogen. It has been shown in previous articles that the measured plasma levels of fibrinogen seem to correlate more much to the amount of parietal thrombus than to the size of the aneurysm. Al-Barjas et al. demonstrated that fibrinogen was positively correlated with the percentage of intraluminal thrombi occupying the lumen \( r = 0.358; \ p < 0.05 \), and the correlation could be explained by the effect of fibrinogen on clot structure. Raised fibrinogen levels increase fibrinopeptide cleavage, causing activation and the formation of a tight rigid fibril gel with thicker fibres and reduced permeation.

Two case-control studies, in which we could not abstract the mean and SD of fibrinogen or D-dimer concentrations, were excluded from the present meta-analysis. These studies including very small number of participants showed no association between plasma fibrinogen or D-dimer concentrations and AAA presence. In the study by Milne et al. including 23 patients with AAA and 16 control patients with symptomatic carotid artery stenoses, all patients had plasma fibrinogen levels within normal range although these tended to be at the upper end of the range, whereas one patient had a minimally elevated level of D-dimer. Fligelstone et al. compared 20 patients with claudication, 20 patients with critical limb ischaemia and 20 patients prior to elective AAA surgery to 20 general surgical controls. The fibrinogen level was normal for all patients in the claudication and AAA groups but was significantly elevated in seven patients in the critical ischaemia group.

Plasma fibrinogen is increased by smoking; thus, the association of fibrinogen with AAA could simply reflect the well-established link between smoking and AAA. Singh et al. in the multivariate model including smoking demonstrated that a high plasma fibrinogen level increased the risk of AAA significantly and independently in men (adjusted odds ratio [OR], 1.42; 95% CI: 1.22–1.67; \( p < 0.001 \)) but not women (adjusted OR, 1.23; 95% CI: 0.91–1.66; \( p = 0.18 \)). After adjustment for age, sex, pack years, a history of cardiovascular disease and the ankle brachial pressure index, Lee et al. showed that a SD increase \((+0.76 \text{ g l}^{-1})\) in fibrinogen was associated with a significant increase in risk of AAA (OR, 1.51; 95% CI: 1.05–2.16; \( p < 0.05 \)) and that the OR of AAA was 3.75 (95% CI, 1.80–7.82; \( p < 0.001 \)) for every unit increase \((+1 \text{ in ng ml}^{-1})\). The association of fibrinogen with AAA even after adjustment for other risk factors in these two studies supports the independent link between fibrinogen and AAA.

It is unlikely that fibrinogen and D-dimer assessments will replace ultrasonography as first-line diagnostic modality to rule in or rule out the presence of AAA. It is postulated, however, that biomarkers measured at diagnosis or during follow-up might provide important prognostic information about subsequent aortic behaviour, allowing more patient-specific management compared with relying on aortic diameter alone. Al-Barjas et al. demonstrated that fibrinogen level was positively correlated with the size of AAA \((r = 0.323; \ p < 0.01)\). Yamazumi et al. showed that the largest diameter of AAA correlated with the levels of D-dimer \((r = 0.644, \ p = 0.0001)\). Engström et al. measured plasma fibrinogen in 6075 healthy men (mean age: 46.8 ± 3.7 years), and 63 men had a fatal or surgically/endovascularly repaired AAA after a mean time of 19 years. Fibrinogen was significantly associated with future AAA after adjustments for age, screening year and potential confounders (OR, 2.1; \( p < 0.01 \), when comparing the risk in the top quartile vs. quartile 1–3). These findings, however, are inconclusive, and further studies are needed to confirm whether plasma fibrinogen and D-dimer concentrations have a role in predicting subsequent progression or rupture of AAA.

Conflict of Interest

No conflicts of interest, no study sponsors.

Acknowledgements

No conflicts of interest declared.

References


