

Assessment of plasma D-dimer as a diagnostic and prognostic aid for abdominal aortic aneurysm

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Abdominal aortic aneurysms (AAAs) are currently identified by incidental imaging or ultrasound screening.

The potential diagnostic and prognostic value of D-dimer for AAA was assessed in this study. 1260 men from a population-based ultrasound screening study were included, of which 299 had small AAAs monitored by repeat ultrasound for a median of 5 years. 132 patients referred to a vascular clinic were also recruited, of which 41 had an AAA. The potential diagnostic and prognostic value of D-dimer was analyzed.

Plasma D-dimer was independently associated with AAA with an incremental increase in AAA prevalence found in subjects with higher D-dimer values. D-dimer was also predictive of AAA expansion. This study suggests that D-dimer may usefully aid methods to focus screening for AAAs and also be useful in identifying patients with higher risk of AAA progression.

Introduction

The abdominal aorta is the main vessel supplying blood to the abdomen, pelvis and legs. Weakening and dilation of this artery is a condition known as abdominal aortic aneurysm (AAA). Screening studies suggest that AAA is present in 1-5 % of men aged >65 years [1].

AAA can lead to aortic rupture, which is usually fatal and responsible for a considerable number of deaths in the Western World, although recent reports suggest that incidence may be falling [2]. Patients with AAA are also at increased risk of other cardiovascular events, such as myocardial infarction and stroke [3].

Identification of AAAs is usually by incidental imaging since in most cases they are asymptomatic. Other means to identify patients with AAAs could facilitate early identification of at-risk individuals for cardiovascular risk management and treatment of their AAA as currently indicated [4].

Current guidelines for AAA advocate open or endovascular repair of AAAs measuring >55 mm in maximum diameter [5]. Smaller AAAs are monitored by repeat imaging at 3-24 months intervals, depending on the initial AAA diameter [5].

Most patients with AAA receive prolonged monitoring involving repeat imaging and physician consultation, with up to 70 % of patients eventually requiring AAA surgery [6].

Currently, initial AAA diameter is the only measure suggested to determine the frequency of monitoring interval for small AAAs. Additional predictors of outcome may provide a much more streamlined and individualized management pathway for patients with small AAAs [4].

Circulating biomarkers have been suggested as a potential means to aid both identification and monitoring of small AAAs. A number of previous small studies suggested that plasma D-dimer was elevated in patients with AAAs [7]. This manuscript provides a summary of a recent study which suggested that measurement of plasma D-dimer could be used to aid diagnosis and prognosis of AAA.

The work has been previously published in full [8].

The study

Study subjects were recruited from two sources [9, 10]:

- a) 1260 men from the Health in Men Study (HIMS). 337 of these were diagnosed as having AAA. 299 of the men with small AAAs were followed at 6-12 monthly intervals for a median of 5.5 years. Average yearly change in AAA diameter was calculated, taking into account all measurements [11]. AAA growth was also expressed as percentage increase in initial AAA diameter per year. The control persons in the HIMS group were generally healthy.
- b) 132 patients referred to the Vascular Department at The Townsville Hospital, Queensland. 41 of these were diagnosed as having AAA. The control persons in this

group had symptoms of intermittent claudication due to lower-limb athero-thrombosis.

In both groups AAA was defined by maximum infrarenal aortic diameter ≥ 30 mm.

Clinical risk factors were defined based on history or previous diagnosis of smoking, hypertension, diabetes, coronary heart disease (CHD) and dyslipidemia. Waist-hip ratio (WHR) was measured in the HIMS subjects.

The following variables were assessed: age, sex (referral group only), CHD, smoking, diabetes, hypertension, dyslipidemia, WHR, creatinine, C-reactive protein (CRP) and D-dimer. The effect of D-dimer on AAA prevalence adjusted for other risk factors was assessed. In cases where more than one cut-off of a single variable proved to be of relevance, the odds ratios (ORs) were expressed relative to the baseline of the lowest cut-off.

Diagnostic and prognostic value of D-dimer

In a multiple logistic regression model, where all risk factors were examined, plasma D-dimer proved to be dominant, see Table I and Table II.

Average yearly increase in AAA diameter was positively correlated with plasma D-dimer ($r=0.39$, $p<0.001$). Plasma D-dimer was independently associated with AAA progression after adjusting for other risk factors, including initial AAA diameter.

Plasma D-dimer plus initial AAA diameter were able to predict groups of patients with median yearly increase in AAA diameter as disparate as 0.2 and 2.5 mm/year [8].

Conclusions

Currently there are no circulating markers in clinical use for aiding diagnosis or prognosis for AAA [4]. Previous studies of AAA biomarkers have tended to concentrate on small groups of subjects and failed to employ tools to assess potential diagnostic and prognostic ability of markers [4].

Risk factor	Odds ratio (95 % conf. interval)
Age >80 years	2.1 (1.0-4.3)
CHD	2.3 (1.6-3.3)
Ever smoking	3.7 (2.5-5.4)
Dyslipidemia	1.5 (1.1-2.1)
Waist-hip ratio >1.0	2.7 (1.7-4.3)
CRP >1.9 mg/L	1.4 (1.1-1.9)
Creatinine >85 µmol/L	1.5 (1.1-2.0)
D-dimer >90 ng/mL	2.2 (1.4-3.5)
D-dimer >190 ng/mL	5.6 (3.4-9.1)
D-dimer >400 ng/mL	12.1 (7.1-20.5)
D-dimer >900 ng/mL	24.7 (13.7-44.6)

TABLE I: Risk factors for AAA in the population group [8]

Risk factor	Odds ratio (95 % conf. interval)
Age >70 years	4.9 (1.9-12.3)
Male sex	6.8 (1.9-24.1)
D-dimer >110 ng/mL	8.2 (2.9-23.0)

TABLE II: Risk factors for AAA in the referral group [8]

The current study suggests that plasma D-dimer may have potential to aid identification and management of AAA. The exact cut-off of D-dimer to employ for either of these uses will likely depend on which D-dimer assay is used and on what the aim of the assessment is and the population being analyzed.

Thus if the aim is to screen in order to identify any subjects with possible AAAs, a low cut-off, such as >90 ng/mL, may be required, accepting there will be a number of false positives, for example in patients with DVT and aortic dissection [12, 13].

However, if the most overall accurate and economic use is required, a higher cut-off will be needed. Using D-dimer plus the other risk factors, which made up our logistic regression model, a sensitivity of 85 % was achieved along with a specificity of 67 %. This equates

to 15 false negatives per 100 patients with AAA and 33 false positives per 100 patients without AAA.

Development of risk-stratification groups is probably a more useful use of D-dimer plus clinical risk factors as illustrated by our classification and regression tree analysis described in the full publication [8]. Here multiple D-dimer cut-offs were employed along with clinical risk factors and CRP to identify groups with disparate AAA risk.

The novel finding of the current study was the association of plasma D-dimer with AAA progression. This finding remained after the adjustment for AAA diameter. It has been suggested that AAA thrombus is involved in aneurysm progression as a result of promoting inflammation and aortic-wall degradation [14].

D-dimer concentrations could reflect the “activity” of thrombus and thus provide a measure of on-going aortic-wall destruction. Further evidence is required and it is likely that randomized trials will address the effect of anti-platelet agents in limited AAA progression in the future.

In conclusion this work suggests that D-dimer can add to both a diagnostic and prognostic algorithm for AAA. The exact level of D-dimer employed and its economic value need further assessment in other populations.

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