

Atherosclerosis and Abdominal Aortic Aneurysm Cause, Response, or Common Risk Factors?

Jonathan Golledge, Paul E. Norman

Abdominal aortic aneurysm (AAA) rupture has been recognized as a significant cause of mortality for adults aged >60 years in the developed world for some time.¹ AAAs are usually asymptomatic until rupture occurs, and screening programs have been shown to reduce mortality in men aged >65 years.² Most AAAs detected by ultrasound are <50 mm in diameter, and there is currently no recognized treatment for these AAAs.^{3,4} Studies aimed at understanding the pathogenesis of AAA are important as they may identify targets for novel therapy.

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The mechanisms initiating and stimulating progression of AAA are still poorly understood, with most knowledge coming from cross-sectional association studies in humans and increasingly from investigations in animal models.⁴ Such studies suggest the importance of inflammatory pathways, matrix degradation, thrombosis, hemodynamic forces, and a host of associated signaling molecules in AAA pathogenesis.^{4,5} On the basis of the new insights from rodent models, a number of novel strategies are being investigated as potential treatments for small AAA.⁵ To date, there have been very few well-designed randomized controlled trials assessing the efficacy of medication in reducing AAA complications in patients.⁴

Patients with AAAs frequently have atherosclerosis, and numerous studies show the association of coronary heart disease and peripheral atherosclerosis with AAA.^{4,6} Whether this association between AAA and atherosclerosis is causal or simply due to common risk factors is unknown. One possibility is that an AAA develops as a pathological response to aortic atherosclerosis, a theory first suggested more than half a century ago, when the term “atherosclerotic aneurysms” was commonly used, but still prevalent today.^{7,8} The most compelling argument for a causative role of atherosclerosis in AAA has been centered on arterial remodeling.⁹ A large body of in vitro, animal, and histology data suggests that when an arterial luminal stenosis develops, compensatory changes occur in the media in response to shear stress alterations.⁹ The

extracellular matrix remodeling promotes expansion of the artery in an attempt to normalize lumen diameter and shear stresses.⁹ Excessive remodeling might explain the severe medial thinning but not, perhaps, the marked inflammation seen in biopsies of the walls of advanced AAA. Elastin breaks stimulated by medial proteolysis and the diffusion of proinflammatory cytokines from inflammatory cells present within atheroma or associated thrombosis could, however, provide the stimulation for the chronic inflammatory response seen (Figure).^{4,5,9} On the basis of the premise that atherosclerosis stimulates AAA development, all patients with AAA would necessarily have significant atherosclerosis and thus should be considered for indicated medical therapy, as currently advised by American Heart Association guidelines in which AAA is considered an atherosclerotic equivalent.¹⁰ An alternative theory suggests that the development of AAA and atherosclerosis are independent. Shared environmental and genetic risk factors may promote the development of both atherosclerosis and AAA in some patients, but the mechanisms involved are distinct. A third, perhaps “on the fence” view would be that either aortic atherosclerosis or AAA can develop first and both can subsequently stimulate the development of the other (Figure). Currently, evidence to support one of these theories over the other is largely limited to

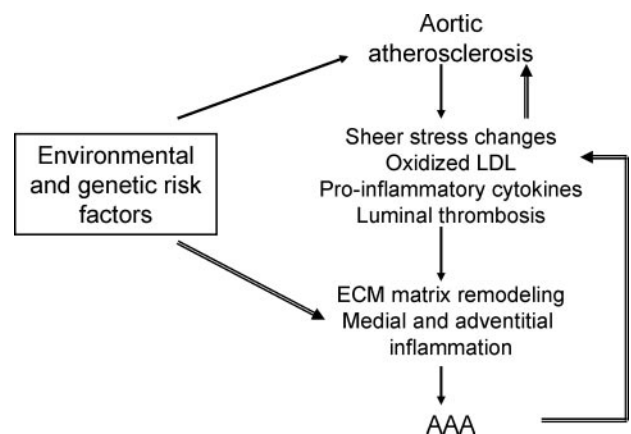


Figure. According to theory 1 (solid arrows), environmental and genetic risk factors lead to development of aortic atherosclerosis. Resultant positive remodeling, intimal thrombosis, and release of proinflammatory cytokines stimulate secondary matrix degradation and adventitial inflammation which promotes AAA development. According to theory 2 (double arrows), environmental and genetic risk factors directly stimulate aortic medial degradation and adventitial inflammation, leading to AAA formation, which secondarily stimulates intimal atherosclerosis. More likely, both pathways act to some extent, with the relative proportion varying from patient to patient depending on the risk profile. ECM indicates extracellular matrix; LDL, low-density lipoprotein.

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Table. Some Similarities and Differences Between Atherosclerosis and AAA

Characteristic	Similarities	Differences
Clinical risk factors	Smoking, hypertension, and obesity are common risk factors for AAA and aortic atherosclerosis. ⁴	Diabetes is a negative or neutral risk factors for AAA but an important risk factor for atherosclerosis. ⁴ Male gender and smoking are much more dominant risk factors for AAA than atherosclerosis. ⁴
Circulating risk factors	AAA and atherosclerosis have many similar biomarkers, eg, fibrinogen, CRP, and HDL (negative). ¹¹	There are a number of disparate markers for AAA and atherosclerosis, eg, LDL has no clear association with AAA but is an important risk factor for atherosclerosis. ¹²
Genetic risk factors	Family history is an important risk factor for both AAA and atherosclerosis. ⁴ A locus on chromosome 9p21 is associated with CHD, stroke, and AAA. ¹³	Some recognized genetic determinants of atherosclerosis have no consistent association with AAA, eg, apolipoprotein E single-nucleotide polymorphisms. ¹⁴
Histology	Intimal atheroma and thrombosis are usually present in both AAA and atherosclerosis. ⁴	Marked elastin fragmentation and adventitial chronic inflammation are mainly restricted to AAA. ⁴
Rodent models	Some mice (e.g. apolipoprotein E-deficient) prone to atherosclerosis are also more sensitive to AAA induction. ¹⁵ Interventions protective from AAA frequently also reduce atherosclerosis. ¹⁶	There are examples of differential effects of interventions on AAA and atherosclerosis progression, eg, TNF and MMP-12 deficiency and PPAR ligation. ¹⁷⁻¹⁹

CRP indicates C-reactive protein; HDL, high-density lipoprotein; LDL, low-density lipoprotein; CHD, coronary heart disease; TNF, tumor necrosis factor; MMP, matrix metalloproteinase; PPAR, peroxisome proliferator-activated receptor.

documenting similarities and differences in risk factors and findings within rodent models for atherosclerosis and AAA (Table).^{4,11-19}

In the current issue of *Arteriosclerosis, Thrombosis, and Vascular Biology*, Johnsen et al examine data from the well-respected Tromso study in an attempt to better elucidate the relationship between atherosclerosis and AAA.²⁰ The investigators examine the relationship between intimal atherosclerosis and aortic dilatation in a large group of 3282 women and 3164 men aged between 25 and 74 years. Atheroma was assessed primarily by estimating the total plaque area of the right common and internal carotid arteries on ultrasound. The luminal diameter of the common femoral artery was also used as a surrogate marker of atherosclerosis severity. The authors report a significant association between carotid artery total plaque area and history of coronary heart disease with AAA prevalence. There was no association between carotid artery total plaque area and aortic diameter within the AAA range; ie, there was no consistent correlation between atheroma extent and AAA severity. The authors suggest that their findings fit better with atherosclerosis and AAA developing in parallel, rather than atherosclerosis directly leading to AAA. The authors are to be commended for tackling this difficult area, which has been relatively little studied. They do acknowledge several limitations of their study that make it impossible to make any definitive conclusions on the relationship between atheroma and AAA. The latter particularly includes the cross-sectional nature of the study and the lack of direct atheroma assessment within the aorta. The authors also did not appear to include diabetes in the clinical variables for which they adjusted in their analyses. Diabetes is positively associated with atherosclerosis but, in contrast, has been negatively associated with AAA and therefore is an important risk factor for which to adjust.⁴ It would indeed be a surprise if the extent of carotid atherosclerosis and AAA size were closely correlated in a cross-sectional study. If atherosclerosis is playing a role in AAA development, it is to be expected that its severity within the aorta would be most relevant. Although there appears to

be a systemic component to atherosclerosis development, many regional factors, such as hemodynamic stresses, determine the distribution of atherosclerosis. Thus, it would be expected that carotid and aorta atheroma severity would vary. Thus, the findings from the current study are not able to convincingly refute a role for atherosclerosis in AAA.

In our opinion, it is likely that multiple mechanisms are responsible for both AAA and atherosclerosis development (including some of those illustrated in the Figure). The relative importance of these different mechanisms is likely to vary from patient to patient and is one of the reasons that standardized therapies for all patients with the same condition are only partially successful. Prospective imaging, and particularly interventional studies, are required to address the value of therapies selectively targeting mechanisms implicated in aortic dilatation and atherosclerosis, respectively, in patients with AAA. Recent human association studies have shown conflicting results on whether drugs that are effective for atherosclerosis, such as statins, inhibit AAA progression.^{21,22} Unfortunately, randomized controlled trials to assess these types of drugs are unlikely to be feasible. Two current randomized trials, however, are examining the efficacy of doxycycline and exercise therapy in limited AAA progression. Studies of this type and further carefully designed animal experiments are required to shed further light on the relationship between atherosclerosis and AAA, and, in particular, its therapeutic implications.

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Disclosures

None.

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