REVIEW ARTICLES

Richard P. Cambria, MD, Section Editor

Abdominal aortic aneurysm and abdominal wall hernia as manifestations of a connective tissue disorder

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Background: **Abdominal aortic aneurysms (AAAs) and abdominal wall hernias represent chronic degenerative conditions. Both aortic aneurysms and inguinal hernias share common epidemiologic features, and several investigators have found an increased propensity for hernia development in patients treated for aortic aneurysms. Chronic inflammation and dysregulation in connective tissue metabolism constitute underlying biological processes, whereas genetic influences appear to be independently associated with both disease states. A literature review was conducted to identify all published evidence correlating aneurysms and hernias to a common pathology.**

Methods: **PubMed/Medline was searched for studies investigating the clinical, biochemical, and genetic associations of AAAs and abdominal wall hernias. The literature was searched using the MeSH terms "aortic aneurysm, abdominal," "hernia, inguinal," "hernia, ventral," "collagen," "connective tissue," "matrix metalloproteinases," and "genetics" in all possible combinations. An evaluation, analysis, and critical overview of current clinical data and pathogenic mechanisms suggesting an association between aneurysms and hernias were undertaken.**

Results: **Ample evidence lending support to the clinical correlation between AAAs and abdominal wall hernias exists. Pooled analysis demonstrated that patients undergoing aortic aneurysm repair through a midline abdominal incision have a 2.9-fold increased risk of developing a postoperative incisional hernia compared with patients treated for aortoiliac occlusive disease (odds ratio, 2.86; 95% confidence interval, 1.97-4.16; $P < .00001$), whereas the risk of inguinal hernia was 2.3 (odds ratio, 2.30; 95% confidence interval, 1.52-3.48; $P < .0001$). Emerging evidence has identified inguinal hernia as an independent risk factor for aneurysm development. Although mechanisms of extracellular matrix remodeling and the imbalance between connective tissue degrading enzymes and their inhibitors instigating inflammatory responses have separately been described for both disease states, comparative studies investigating these biological processes in aneurysm and hernia populations are scarce. A genetic predisposition has been documented in familial and observational segregation studies; however, the pertinent literature lacks sufficient supporting evidence for a common genetic basis for aneurysm and hernia.**

Conclusions: **Insufficient data are currently available to support a systemic connective tissue defect affecting the structural integrity of the aortic and abdominal wall. Future investigations may elucidate obscure aspects of aneurysm and hernia pathophysiology and create novel targets for pharmaceutical and gene strategies for disease prevention and treatment. (J Vasc Surg 2011;54:1175-81.)**

Abdominal aortic aneurysms (AAAs) and abdominal wall hernias constitute significant health problems creating substantial social and financial burdens for health and surgical services in several countries. Similar epidemiologic features for AAAs and inguinal hernias have been described, with both conditions largely affecting males of increasing age with a history of smoking and/or chronic obstructive pulmonary disease.[1,2] Furthermore, the clinical correlation between aneurysms and hernias is well documented, and increasing evidence suggests that patients with AAAs have a great propensity for abdominal wall hernias.[3]

The pathogenesis of aneurysmal disease of the aorta and abdominal wall herniation is complex and multifactorial. Current concepts converge on the fact that a dysregulation in connective tissue metabolism is responsible for the clinical manifestation of aneurysm or hernia.[4-8] However, even though mechanisms of imbalance of collagen synthesis and degradation have been described for both clinical conditions, no unified biological theory to link aneurysms and hernias to a common

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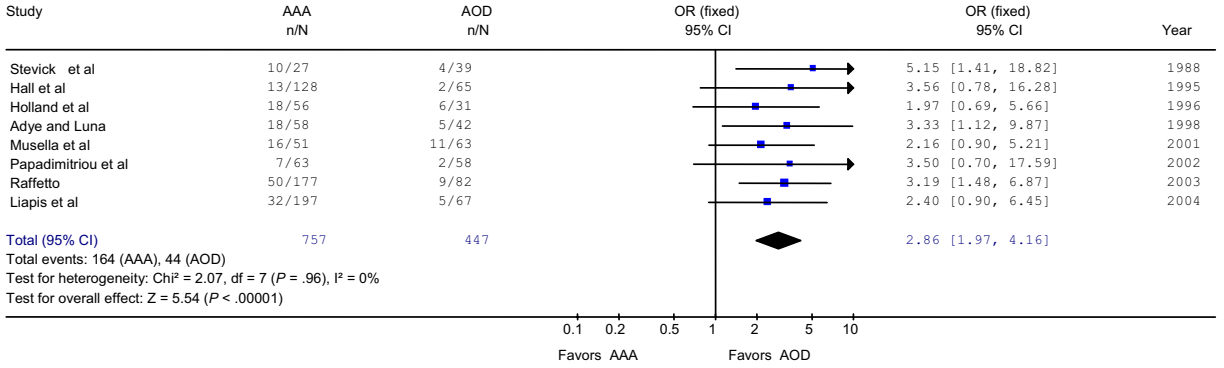


Fig 1. Meta-analysis of studies comparing the incidence of incisional hernias in patients with abdominal aortic aneurysms (*AAAs*) and aortoiliac occlusive disease (*AOD*). *CI*, Confidence interval; *OR*, odds ratio.

pathology has been proposed. Identification of common underlying pathogenic mechanisms may give further insight into the biological processes of disease development and have implications in clinical practice such as selective aneurysm screening in high-risk hernia populations and a pharmacotherapeutic potential.

The objective of this article was to identify all published evidence correlating AAAs and abdominal wall hernias at the clinical, biochemical, and genetic level. An evaluation, analysis, and critical overview of current supporting data linking these conditions to common pathogenic biological processes is being undertaken.

METHODS

PubMed/Medline was searched for studies investigating the clinical, biochemical, and genetic associations of AAAs and abdominal wall hernias. The literature was searched using the MeSH terms "aortic aneurysm, abdominal," "hernia, inguinal," "hernia, ventral," "collagen," "connective tissue," "matrix metalloproteinases," and "genetics" in all possible combinations. Search of the electronic databases was conducted from 1966 to the present day, and the reference lists of related articles were also manually extracted and collected as part of a second-level search. Retrieved articles were categorized as those correlating aneurysm and hernia at the clinical, biochemical, and genetic level. Eighty-eight relevant English language articles were identified, of which 17 were specifically investigating the association of AAAs and abdominal wall hernias. An evaluation, analysis, and critical overview of current clinical data and pathogenic mechanisms suggesting an association between aneurysms and hernias are being undertaken. A meta-analysis of studies comparing the incidence of postoperative incisional hernias and inguinal hernias in patients undergoing AAA repair and aortoiliac occlusive disease reconstruction through a midline incision was conducted. Study-specific estimates were combined using random-effects models or fixed-effects models as appropriate. The presence of between-study heterogeneity was assessed using the Cochrane I^2 test. The statistical package used was the free version of RevMan 4.2, The Cochrane Collaboration.

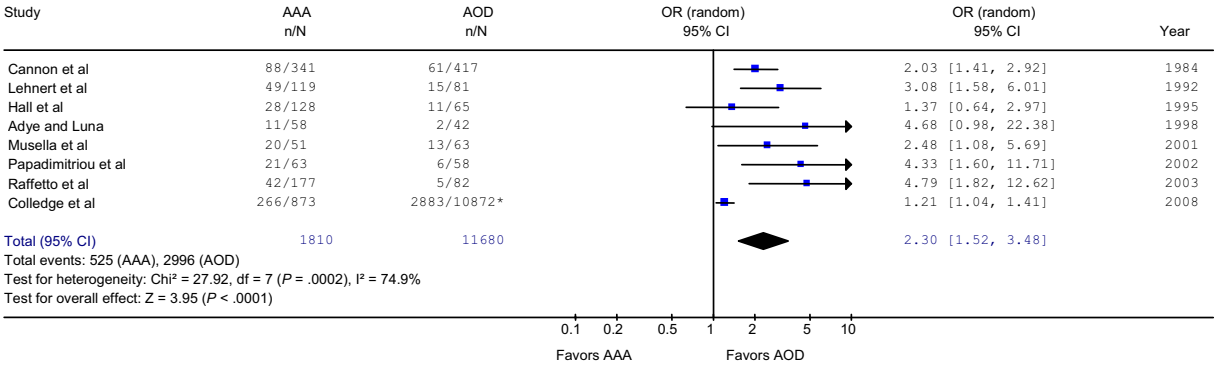
RESULTS

Clinical correlation between aneurysm and hernia

Aneurysm and incisional hernia. The initial presumption that an independent relationship exists between AAAs and incisional hernias formation has been documented by several reports.[9-18] Comparative studies evaluating the incidence of postoperative incisional hernias report values ranging between 10% and 37% for patients treated for AAAs, and 3% and 19% for those having aortoiliac reconstruction for occlusive disease. An updated meta-analysis of published reports found that patients who had a midline laparotomy for AAA repair had a 2.9-fold increased risk of developing postoperative incisional hernia compared with those with aortoiliac occlusive disease (odds ratio [OR], 2.86; 95% confidence interval [CI], 1.97-4.16; $P < .00001$; Fig 1). This difference persisted even after adjusting for confounding variables, which could potentially affect the outcome.[3]

Some authors have proposed prophylactic mesh wound closure to reduce the risk of ventral hernias.[19] A randomized clinical trial confirmed the significant effect of routine mesh placement after open aortic aneurysm reconstruction on the incidence of incisional hernia compared with sutured wound closure.[20] Conclusions drawn from previous studies have raised the hypothesis that a structural defect in aortic and abdominal wall connective tissue might exist, accounting for aneurysmal degeneration of the aorta and postoperative incisional hernia formation.

Aneurysm and inguinal hernia. Reported prevalences of inguinal hernias range between 19% and 41% for patients with a history of AAA repair, whereas values for nonaneurysm patients range between 5% and 27%.[11,13-16,21-23] Pooled analysis of these studies demonstrated that patients treated for AAAs have a 2.3-fold increased risk of inguinal hernia development compared with aortoiliac occlusive disease reconstruction (OR, 2.30; 95% CI, 1.52-3.48; $P < .0001$; Fig 2). A reverse link has also been identified,



*Subjects from AAA screening program.

Fig 2. Meta-analysis of studies reporting on the risk of inguinal hernia in patients with abdominal aortic aneurysms (*AAAs*) and controls. *AOD*, Aortoiliac occlusive disease; *CI*, confidence interval; *OR*, odds ratio.

constituting inguinal hernia as an independent risk factor for AAAs.[24,25] Research conducted in our institution has found that male patients with inguinal hernia have a fourfold increased prevalence of AAAs compared with control subjects without hernias.[26]

Mechanisms of connective tissue metabolism for aneurysm and hernia formation

Pathogenesis and biology of AAAs. Aneurysms result from a chronic degenerative process that evolves over a long period of time. The National Heart, Lung, and Blood Institute defined current areas of research focusing on proteolytic degradation of the aortic wall connective tissue as well as inflammatory and immunologic responses as the main culprits of the pathogenic mechanisms of AAA formation.[4,5] Important structural elements of the aortic wall are elastin and collagen, found in the arterial media and adventitia providing passive strength to the wall, whereas medial smooth muscle cells define its active properties. Elastin is the main component of the media and provides and distributes tensile strength along the arterial wall. It is synthesized during the early stages of aortic wall development and has an estimated half-life of 60 years. Solid evidence exists supporting that elastin degradation occurs in the early stages of the pathogenic process of aneurysm development.[26-28] Collagen is the primary structural element of the adventitia, and unlike elastin, is under a continuous process of synthesis and degradation through life. It provides stiffness to the arterial wall. A report found increased collagen and a prominent inflammatory cell infiltration in the aneurysm wall compared with nonaneurysmal aortas.[29] Increased collagenolytic activity in the aneurysmal aorta being correlated with aneurysm size has been demonstrated in another report.[30] It seems that collagen synthesis increases during the early stage of aneurysm formation; however, at later stages, degradation exceeds synthesis, resulting in continuing aneurysm expansion and, ultimately, rupture.[29-31] The aortic wall extracellular matrix is a complex structure, which apart from its scaffold properties to the aortic wall, exerts a number of biological activities and regulates elastin and collagen synthesis and degradation, smooth muscle cell apoptosis, chemotaxis and cell migration, inflammation and immune responses, and angiogenesis.

There is ample evidence that matrix degradation by a variety of proteolytic enzymes, mainly matrix metalloproteinases (MMPs), is integral to aneurysm development, and that an imbalance between MMPs and their inhibitors (TIMPs) impairs normal physiological aortic wall remodeling.[32] Elastolysis is an early event in aneurysm formation. Freestone et al demonstrated that MMP-2 was the dominant gelatinase in small aneurysms, suggesting that it is the inciting enzyme in aneurysm genesis.[33] As opposed to MMP-2, McMillan et al found higher MMP-9 mRNA expression in moderate-diameter (5-6.9 cm) than small-diameter (<4 cm) aneurysms.[34] Evidence suggests that MMP-9 is the dominant proteolytic enzyme promoting continued expansion and rupture.[34,35] Several other MMPs have been demonstrated to play a role in the aneurysm degrading and inflammatory process (Table). Regulation of MMP activity is achieved at different levels, with TIMPs having been suggested as an important regulator of extracellular matrix degradation. The balance of aortic wall remodeling between MMPs and their inhibitors favors collagen and elastin degradation. However, the initiating events and the mechanisms for propagating these proteolytic enzymes in the aortic wall remain to be identified.

Investigations have also demonstrated a significant immunologic contribution to the pathogenesis of the disease. It seems that exogenous and/or endogenous factors disrupting the intima/adventitia and exposing elastin and interstitial collagen instigate an immune response resulting in a cascade of inflammatory events.[36,37] Immune cells, including macrophages and lymphocytes, along with smooth muscle cells and fibroblasts promote a strong inflammatory reaction, which activates proteolytic enzymes and extracellular matrix degradation. Elastin and collagen degradation products, in turn, propagate a sequestered inflammatory reaction, leading to further degeneration of the aortic wall, aneurysm expansion, and rupture. Oxidative

Table. Role of MMPs in the pathogenesis of aneurysm and hernia

MMP	*Enzyme*	*Genetic location*	*Main extracellular matrix substrates*	*Role in aortic aneurysm*	*Role in abdominal wall hernia*
MMP-1	Collagenase 1	11q22-q23	Collagens (I, II, III, VII, VIII, X), gelatin, fibronectin, vitronectin, laminin, aggrecan	Collagenolysis, associated with risk of rupture	Increased activity in recurrent inguinal hernia
MMP-2	Gelatinase A	16q13	Collagens (I, II, III, IV, V, VII, X, XI), gelatin, elastin, fibronectin, vitronectin, laminin	Elastolysis, dominant role in early stages of aneurysm formation	Dominant role in direct inguinal hernia
MMP-3	Stromelysin 1	11q23	Collagens (III, IV, V, VII, IX, X, XI), gelatin, elastin, fibronectin, vitronectin, laminin	Elastin and collagen degradation, activates other pro-MMPs, angiogenesis	—
MMP-8	Collagenase 2	11q21-q22	Collagens (I, II, III), aggrecan	Collagen degradation, aneurysm rupture	—
MMP-9	Gelatinase B	20q11.2-q13.1	Collagens (IV, V, XI, XIV), gelatin, elastin, vitronectin, laminin, aggrecan	Elastolysis, collagenolysis, dominant role in later stages of aneurysm formation and rupture	Overexpression in inguinal hernia
MMP-12	Macrophage elastase	11q22.2-q22.3	Collagens (I, IV, V), gelatin, elastin, fibronectin, vitronectin, laminin	Elastolytic activity	—
MMP-13	Collagenase 3	11q22.3	Collagens (I, II, III, IV, VI, IX, X, XIV), gelatin, fibronectin, aggrecan	Collagenolysis, associated with risk of rupture	Role in recurrent inguinal hernia
MMP-14	MT1-MMP	14q11-q12	Collagens (I, II, III), gelatin, fibronectin, tenascin, vitronectin, laminin	Activates pro-MMP-2	Activates pro-MMP-2, increased expression in direct/indirect inguinal hernia

MMP, Matrix metalloproteinase.

stress significantly contributes to the pathophysiology of inflammation. Zhang et al demonstrated increased expression of inducible nitric oxide synthase in the aneurysm wall tissues as compared with normal aorta.[38] The integral part of the whole process is a reduction in medial smooth muscle cells (apoptosis), which are the principal cell type producing extracellular matrix components.[39] It seems however, that during life, as oxidative stress increases and more and more assaults occur at the endothelial and smooth muscle levels, there is a natural biological anti-inflammatory process that counteracts the tendency toward inflammatory degradation.

Understanding of the significance of MMPs in biology and pathology has led to the development of numerous potent synthetic inhibitors of MMPs. Such agents may be of great therapeutic value, and some of them are in clinical trials for the treatment of cancer and inflammatory conditions.[40] Tetracyclins nonselectively inhibit MMPs via mechanisms similar to those of endogenous inhibitors and have been shown to effectively prevent elastin and collagen destruction and aneurysmal dilatation.[41]

Pathogenesis and biology of abdominal wall hernias. Hernia has historically been considered to be caused by structural defects in the integrity of the abdominal wall, which may result from various intrinsic or exogenous triggering factors.[2] Current concepts put forward the premise that hernia development is a biological process.[6-8] There is sufficient evidence to suggest that the underlying etiologies are associated with disturbances in connective tissue metabolism and impaired extracellular matrix turnover.

Collagen is the predominant structural protein of the abdominal fascial layers and the main component of the extracellular matrix. Type I and Type III are those collagen types implicated in abdominal wall hernia formation. Type I collagen represents highly cross-linked mature collagen that confers mechanical strength to fascial tissues, whereas Type III collagen is less cross-linked, consists of thinner fibers, and provides less strength to the tissues. In healthy tissues, extracellular matrix is under a dynamic process of synthesis and degradation. An imbalance in collagen homeostasis expressed as either delayed or abnormal collagen synthesis or increased proteolytic collagen breakdown has been found to have a causal effect on herniogenesis.[8]

An altered collagen structure and disordered collagen Type I/Type III ratio have been demonstrated by several investigators in fascia connective tissue of both patients with inguinal and incisional hernias.[42-47] The decreased Type I/Type III collagen ratio in the connective tissue of patients with abdominal wall hernias may be attributed to either a primary defect in collagen synthesis or altered collagen degradation caused by inordinate extracellular matrix activity. The degrading limb of the dynamic homeostatic process of collagen metabolism has been evaluated by measuring the levels of MMPs in abdominal wall fascial

layers.[48] Several studies have demonstrated an MMP-2 overexpression in both transversalis fascia and skin fibroblasts from patients with direct inguinal hernias compared with controls.[43,49,50] Research conducted in our institution demonstrated an imbalance of MMP/TIMP activity at both the local tissue level and systemic circulation, indicating a dysregulation of the extracellular matrix degradation process.[51] Furthermore, several authors have shown an association between MMP-1 and MMP-13 activity and recurrent inguinal and incisional hernia, suggesting a disturbed process of wound healing as their underlying etiology (Table).[42,44-46] Inflammation is an integral part of wound repair and hernia formation, as shown by inflammatory cells marginating into injured tissue and cytokines and growth factors propagating inflammatory reactions in injured connective and wound-healing tissues.[6] Rosch et al found increased connective tissue-like growth factor in recurrent inguinal hernia patients, which promotes angiogenesis, inflammation, proliferation, and collagen synthesis.[46]

Common pathogenic mechanisms of collagen metabolism for aneurysm and hernia. Both AAAs and abdominal wall hernias are characterized by an increased proteolytic activity and disruption of protease/antiprotease balance. This, in turn, results in an abnormal connective tissue remodeling process, with disorganized collagen synthesis and enhanced degradation. Inflammation is an important feature in the pathologic process of both conditions.

There is evidence to presume that a defect in connective tissue metabolism is a systemic process. This presumption is supported by initial findings of increased serum proteolytic activity in smokers with direct inguinal hernia and a similar imbalance in smokers with AAAs.[21] Furthermore, several investigators have demonstrated elevated circulating levels of MMPs, which reflect the dynamic and heterogeneous nature of extracellular matrix metabolism. Plasma MMP-9 levels have been found to be higher in patients with AAAs than those in patients with aortoiliac occlusive disease.[52,53] Patients with inguinal hernias have recently been demonstrated to have increased plasma MMP-2 activity.[54] Theoretically, highly expressed metalloproteinase at the local tissue level could be continuously released into the systemic circulation and be measurable in the plasma of patients with aneurysms and hernias.

Genetic aspects of aneurysm and hernia

Genetic influences appear to be independently associated with both disease states. A genetic predisposition to AAA development has been documented by both familial and segregation observational studies.[55-57] Baird et al found an aneurysm prevalence of 19% in siblings of patients with AAAs as compared with 8% in controls using ultrasound examination.[56] Thompson et al have undertaken a meta-analysis of all aneurysm candidate gene analysis studies and identified three polymorphisms associated with a significant risk of aneurysm (ACE relative risk [RR], 1.33 [95% CI, 1.20-1.48], MTHFR RR, 1.14 [1.08-1.21], and MMP-9 RR, 1.09 [1.01-1.18]).[58] Polymorphic sites and gene mutations of proteins of the structural components of the connective tissue (elastin, collagen), extracellular matrix degrading enzymes and their inhibitors (MMPs, TIMPs) and inflammation promotion agents have separately been investigated in gene association observational studies. Nevertheless, no single gene has yet been isolated as the key factor interpreting the genetic basis of aortic aneurysms. A small number of families have genetically determined Type III collagen defect (COL3A1), in which cases the AAA is considered to be a manifestation of Ehlers-Danlos syndrome.[59] Furthermore, mutations in the fibrilin-1 gene (15q21.1) are responsible for Marfan syndrome, which is a hereditary connective tissue disorder associated with thoracoabdominal aortic aneurysms and dissections.[60]

The ultimate etiology of abdominal wall hernia seems to be underlined by the contribution of genetic, intrinsic patient-related and extrinsic environmental factors. A recent case-control study evaluating the risk factors for inguinal hernias suggested the familial component of inguinal hernias as the most important risk factor.[61] Genetic abnormalities of extracellular matrix constituents are characterized by a high risk of inguinal hernia. Of these, Marfan syndrome and Ehlers-Danlos syndrome are genetically and clinically heterogenous conditions, which involve both arterial aneurysms and abdominal wall hernias in their clinical manifestations.[62,63] However, no gene association studies exist investigating the role of polymorphic sites and mutations of other components integral to the connective tissue degradation and inflammatory process in patients with aneurysms and hernia disease.

CONCLUSIONS AND FUTURE PERSPECTIVE

Sufficient clinical evidence exists to connect AAAs and abdominal wall hernias to a common pathology. However, the underlying pathogenic mechanisms of this relationship have not been explained in full. Even though there appears to be a systemic disorder affecting collagen and elastin synthesis and degradation, no studies exist to compare and investigate the biological processes in abdominal wall fascial tissues and/or aortic wall tissue in patients with hernias and aneurysms. Furthermore, no gene association studies investigating their common genetic background have ever been performed. Whole genome studies may define subgroups of patients at risk for developing both aneurysms and hernias.

Further knowledge on common underlying pathogenic mechanisms and genetic influences might have significant implications in clinical practice. Demonstrating of abdominal wall hernia as an independent risk factor for AAAs might warrant selective screening in these high-risk populations. Additionally, targeted approaches with the design of specific inhibitors of key players in the connective tissue degeneration process might provide novel pharmacologic methods of deceleration of aneurysm progression and hernia development and recurrence. Further knowledge about mechanisms of regulation of MMP gene expression may direct therapeutic strategies toward tissue-targeted gene therapies with agents that selectively inhibit specific MMPs.

AUTHOR CONTRIBUTIONS

Conception and design: GA, ML
Analysis and interpretation: GA, GG, SA, FG, AG, ML
Data collection: GA, GG, SA
Writing the article: GA
Critical revision of the article: GA, GG, SA, FG, AG, ML
Final approval of the article: GA, GG, SA, FG, AG, ML
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