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Pathophysiology of Abdominal Aortic Aneurysm – Genetic Factors and Homocysteine Metabolism

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1. Introduction

Homocysteine (Hcy) is a non-protein amino acid resulting from the demethylation of the essential amino acid methionine. This is an important step in the metabolism of nucleic acids, fats and high-energy bonds and for this reason, the transmethylation reaction of Hcy back to methionine requiring Vitamin B12 and folic acid, is equally important. This pathway is dependent on a form of folate produced by methylenetetrahydrofolate reductase (MTHFR). Hcy can also be metabolised to cystathionine, an intermediate of the non-essential amino acid cysteine. Vitamin B6 is necessary for this transulphuration reaction to occur (Figure 1) (Warsi et al, 2004; Guilliams, 2004; Moroz et al, 2007; Castro et al, 2006)

Excess levels of Hcy are excreted to the plasma where the liver and kidney are the organs achieving catabolism and excretion of Hcy. Despite this, mild hyperHcy is present in 5-7% of the general population, due to either inherited or acquired dietary deficiencies of vitamin B6, B12 and folic acid. Other causes include renal failure, malignancy, hypothyroidism and use of folate and vitamin B6 antagonists (Halazun et al, 2007).
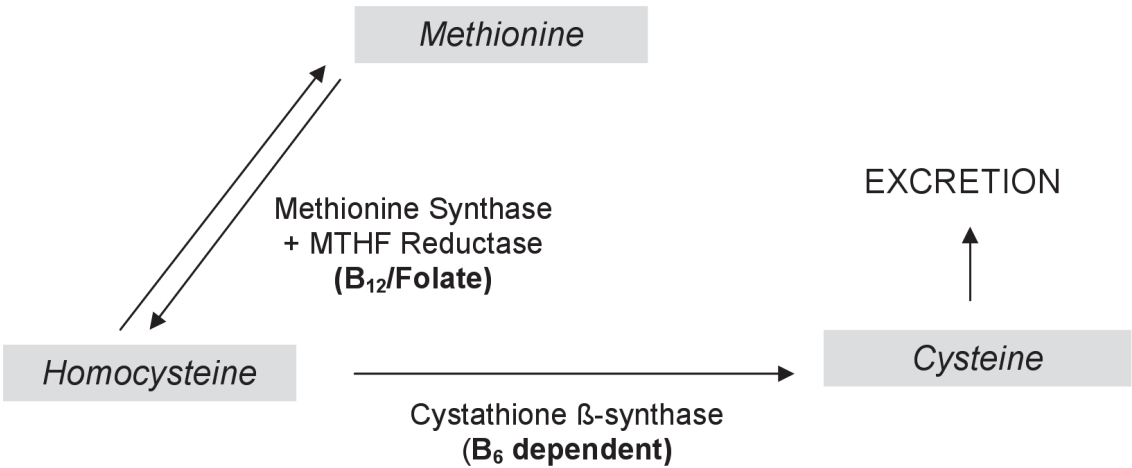

Fig. 1. Brief summary of homocysteine metabolism

2. Historical perspective

HyperHcy has been linked to vascular disease since the early 1960's when children with mental retardation, accelerated growth and propensity to arterial and venous thrombosis were found to have homocysteinuria. An emerging pattern of atherosclerosis was detected in these patients and it was concluded that genetic defects in homocysteine metabolism and associated homocysteinuria was responsible for these vascular lesions (Guilliams, 2004).

Endothelial vascular injury and atherosclerosis was subsequently demonstrated through intravenous infusion of Hcy in an animal model (Warsi et al, 2004).

Several studies followed this, reporting the association between Hcy concentrations and vascular disease and more recent large scale meta-analyses have supported these findings (Castro et al, 2006). A causal relationship between homocysteine and cardiovascular disease is felt to be highly likely and hyperHcy is now an established modifiable risk factor for cardiovascular disease. Raised Hcy levels are present in significant numbers of patients with peripheral, cerebrovascular and coronary heart disease (CHD). High values have also been proven to predict the failure of vascular intervention and more rapid progression of CHD and peripheral vascular disease (Halazun et al, 2007).

3. Evidence for homocysteine in aneurysmal disease

While the importance of homocysteine in atherosclerotic disease has been established, there is also evidence to suggest that raised Hcy levels could play a role in the pathogenesis of abdominal aortic aneurysm (AAA).

A number of recent studies have demonstrated the prevalence of raised Hcy levels in AAA to be as high as 50% and one study has demonstrated a link between Hcy levels and the rate of expansion of AAA (Halazun et al, 2007). Despite this, data is still relatively limited. Confounding has not been excluded with male sex, smoking, hypertension and raised low-density lipoprotein levels all shown to be independently associated with AAA (Naydeck et al, 1999), while the possibility of reverse causality needs consideration. Current large scale genotypic studies are attempting to deal with this and will be discussed later in the chapter.

4. How does homocysteine contribute to aneurysmal disease

Their is no doubt that the pathogenesis of AAA is multi-factorial, in brief, the degradation of key structural proteins such as elastin and collagen results in weakening of the aortic wall and subsequent dilatation and aneurysm formation. HyperHcy has been shown to enhance this process through several mechanisms.

4.1 Oxidative damage and thrombogenicity

Homocysteine has been shown to cause endothelial dysfunction through mechanisms felt to be attributable to oxidative stress. This is an important event preceding manifestation of vascular disease and its involvement is strengthened by the fact that administration of antioxidant vitamins can prevent the impairment of endothelial vasodilator function induced by experimental hyperHcy (Stuhlinger et al, 2003).

One such mechanism is the impaired production of nitric oxide (NO) as an effect of hyperHcy. This is possibly through increasing levels of asymmetric dimethylarginine (ADMA), a strong inhibitor of endothelial nitric oxide synthase (Guilliams, 2004; Stuhlinger

et al, 2003). NO contributes to vessel homeostasis by inhibiting vascular smooth muscle contraction and growth, platelet aggregation, and leukocyte adhesion to the endothelium. The resultant over-production of oxidative free radicals has been shown to induce intimal injury, activate elastase and increase calcium deposition (Brunelli et al, 2000).

The toxic effects of hyperHcy on the endothelium extend to the prothrombotic environment that is created at several levels. These include increased platelet aggregation, activation of clotting factors V, X and XII, along with depressed activation of protein C and cell surface thrombomodulin and modulation of tissue plasminogen activator binding to its cell surface receptor, annexin II (Perna et al, 2003).

4.2 Elastolysis and proteolysis

While the above mechanisms are undoubtedly contributors to aneurysm formation, there is strong evidence to suggest that hyperHcy can enhance proteolysis and this maybe particularly relevant to the pathogenesis of AAA. In the normal aorta, arterial wall structures elastin, collagen and smooth muscle bear the vast majority of wall stress and act as a strong almost indistensible safety net to limit expansion. Histological features of aneurysmal aortic wall show failure of this safety net by way of elastin fragmentation and degeneration, collagen degradation, a medial attenuation and a reduction in tensile strength (Arapoglou et al, 2009).

4.2.1 Serine elastase

Serine elastase is a member of a large family of protein-cleaving enzymes (proteases) that play an essential role in processes like blood coagulation, apoptosis and inflammation. Regulation of proteolysis induced by these serine proteases is essential to prevent self-induced damage.

Vascular smooth muscle cells (VSMC's) are felt to contribute to the homeostasis of the vessel wall by synthesising elastin and elastinolytic enzymes. HyperHcy has been demonstrated to induce the synthesis of serine elastase in vascular smooth muscle cells. While the mechanism for this is currently unclear, through the activation of serine elastase, Hcy increases the rate of elastoylsis and subsequent degradation of the extra-cellular matrix. The associated release of elastin peptides are chemotactic for VSMC's which then proliferate and migrate into the sub-endothelium, resulting in neointimal formation and progressive vascular occlusion. This suggests a possible mechanism to explain the proposed link between aneurysmal and atherosclerotic disease. Such a mechanism is supported by studies demonstrating that inhibition of serine elastase limits the fragmentation of elastic laminae in the aortic wall while also preventing the VSMC alterations and the associated progressive vascular disease (Jourdheuil-Rahmani et al, 1997).

4.2.2 Matrix metalloproteinases

Abdominal aortic aneurysm (AAA) development and expansion are multifactorial in pathogenesis (Ailawadi et al, 2003). Inflammatory response plays a significant role in the pathogenesis of development and expansion of aneurysm. Normal aorta undergo a constant remodelling pocess involving various proteases that degrade elastin and collagen, and the production of new elastin and collagen by the smooth muscle cells of the aortic wall. Disturbance of the normal balance in this process results in AAA initiation and expansion (Davies, 1998; Grange et al, 1997). Three proteolytic systems seem to be involved in the degradation of aorta (Lindholt et al, 2003).

- The serine-dependent proteases are elastases that degrade elastin in the aorta
- The cysteine-dependent proteases are lysosomal proteases such as cathepsin K, L, S that plays a role in apoptosis of the smooth muscles cells of aorta
- The metalloproteinases (MMP) are elastases and collagenases that degrade aortic elastin and collagen. Elastin degradation is associated with aneurysm initiation and expansion and collagen destruction is responsible for eventual AAA rupture.

MMPs are the most widely studied proteolytic system in the pathogenesis of AAA. Many MMPs have been implicated in the pathogenesis of AAA including MMP-1, MMP-2, MMP-3, MMP-8, MMP-9, MMP-12, MMP-13 and MMP-14(Wilson et al, 2005a; Longo et al, 2005; Wilson et al, 2005b; Tromp et al, 2004). MMP-9 is an elastase most frequently implicated in the aneurysm initiation, expansion and rupture. MMP-9 knockout mice do not form aneurysm and their ability to form aneurysm is restored after wild type bone marrow transplantation (Pyo et al, 2000). MMP-9 has also been implicated in asymmetrical regional wall expansion in the anterior wall of aorta (Sinha et al, 2006). Its level in ruptured AAA has been found to be significantly higher than large AAA (Petersen et al, 2000). MMP-2 and MMP-12 (macrophage elastase) are elastases that are also found in increased concentration in aneurysmal aortic tissue. High concentration of MMP-2 is found in small AAA suggesting its role in early AAA formation (Crowther et al, 2000). MMP-12 is highly expressed in tissue along the leading edge of AAA suggesting a role in AAA initiation (Warsi et al, 2004). MMP-1, MMP-3, MMP-8, MMP-13 are collagenases involved in degradation of extracellular matrix during aortic wall remodelling (Tromp et al, 2004; Pyo et al, 2000; Sinha et al, 2006; Petersen et al, 2000; Crowther et al, 2000; Abdul-Hussien et al, 2007). MMP-14 is a membrane type MMP expressed at cell surface and is responsible for activation of MMP-2 (Apte et al, 1997). The exact mechanism of MMPs interactions with other inflammatory cytokines, inflammatory cells, microbes and aortic wall tissue is unknown. MMPs can be activated by a range of stimuli including other MMPs, cytokines released by the inflammatory cells, elastin degradation products, microbes such as chlamydiae pneumoniae, reactive oxygen species, and mechanical alteration in the aortic wall stress (Warsi et al, 2004).

Several genetic polymorphisms are associated with MMP and some have been linked with increased frequency in AAA (Thompson et al, 2008; Sandford et al, 2007). Genetic polymorphism is a difference in DNA sequence among the population that gives rise to different forms such as in the case of human blood groups. Its occurrence cannot be accounted for by just recurrent mutation and is present in greater than 1% of the population. MMP-9 polymorphism has been implicated in AAA. A cytosine to thymidine substitution in position 1562 of the promoter region (MMP-9 -1562C>T) produces a 1.5 fold increase in promoter activity (Zhang et al, 1999). Jones et al. reported increased frequency of TT and CT genotypes in people with AAA compared to normal population (Jones et al, 2003). However, other studies on MMP-9 had not demonstrated similar genetic predisposition (Yoon et al, 1999; Higashikata et al, 2004). Platelet activating factor (PAF) can induce MMP-1, MMP-2, and MMP-9 transcription. The activity of PAF is regulated by PAF acetylhydrolase (PAF-AH). A guanine to thymidine substitution in position 994 of the exon 9 (PAF-AH +994 G>T) results in lower enzymatic activity of PAF-AH with increased PAF level. GT and TT genotype are associated with AAA with an odd ratio of 2.48 (CI 1.36-4.65) (Thompson et al, 2008). In general there is a lack of clear evidence that upregulation of MMPs in AAA has a genetic basis (Sandford et al, 2007).

Dampening the overactivity of MMPs in AAA can potentially slow the progression of AAA. Recent review in the area suggest that statins, non steriodal antiinflammatory drugs (NSAIDS) and antibiotics hold the most promise (Bergqvist et al, 2011). Statin has been shown in metaanalysis to be beneficial in slowing the expansion of AAA (Takagi et al, 2010). The median expansion rate decreased by about 1.2mm per year. Aortic tissue obtained at the time of surgery has shown a reduction in the level of MMP-3 and MMP-9 for patients who are taking statin (Wilson et al, 2005a). The evidence for antibiotics and NSAIDS is less convincing. Roxythromycin and doxycycline have been shown to modulate MMP concentrations and were associated clinically with decreased aneurysm expansion rate in some studies but not others (Hogh et al, 2009; Karlsson et al, 2009; Morosin et al, 2001; Vammen et al, 2001). NSAID's reduce the release of cytokines (IL-1β and IL-6) and in turn reduce the production of elastases in rat aortic tissue (Parodi et al, 2006). A case control study shows that it potentially can reduce AAA expansion rate (Lindholt et al, 2008).

4.2.3 Tissue Inhibitors of MMP's and plasminogen activator Inhibitors

Regulation of the MMP system is provided by Tissue Inhibitors of Metalloproteinases (TIMP's) and Plasminogen Activator Inhibitors (PAI's), which inhibit the action of plasmin (an MMP activator). Platelet Activating Factor (PAF) has been shown to induce MMP formation.

An imbalance of MMP's and their inhibitors/activators leads to an excess of MMP's resulting in the degradation of the structural proteins elastin and collagen and subsequent aneurysm formation (Thompson et al, 2008; Sandford et al, 2007).

Polymorphisms have been identified in the genes encoding each of these protein systems. A relative decrease in TIMP expression has been found in aneurysmal aortas. Although this study concluded that this deficiency was not a result of a primary gene mutation (Tilson et al, 1993), more recent studies have identified both a TIMP-1 and TIMP-2 polymorphism to be expressed in higher frequencies in patients with AAA (Ogata et al, 2005; Wang et al 1999). Despite this, the observed single base pair change does not change translation and is therefore unlikely to be involved in the pathogenesis of AAA. It does however, raise the possibility that other polymorphisms identified within the TIMP gene (G418C and C177T), maybe linked to AAA formation (Sandford et al, 2007), although this has not been investigated to date.

Polymorphisms of both PAF and PAI genes have also been linked to AAA. A 5G allele in position 675 of the PAI-1 gene is associated with reduced transcription and is expressed more frequently in patients with a family history of AAA (Rossaak et al, 2000). Those patients with homozygosity for the 5G allele were found to have more rapid rates of aneurysmal expansion (Jones et al, 2002).

PAF acetylhydrolase controls the activity of PAF. A common polymorphism (G994T) in this gene reduces enzyme activity and results in increased levels of PAF. A significant association with the T-allele and AAA has been demonstrated (Thompson et al, 2008).

4.2.4 Fibrillin

In addition to the mechanisms described above, in a process known as homocysteinylation, Hcy can damage elastin and other matrix proteins through non-enzymatic chemical reactions resulting in protein inactivation (Moroz et al, 2007).

Firbrillin is a glycoprotein essential for the formation of elastic fibres found in connective tissue. It is secreted into the extracellular matrix by fibroblasts and becomes incorporated

into the insoluble microfibrils which appear to provide a scaffold for the deposition of elastin (Kielty et al, 2002).

Fibrillin appears to be particularly susceptible to the process of homocysteinylation. This involves a post-biosynthetic acylation of free amino groups in proteins and is mediated by Hcy thiolactone, an intermediate of Hcy metabolism. It is felt that the epidermal growth factor (EGF)-like domains found in fibrillin are preferential sites of homocysteinylation (Krumdieck & Prince, 2000).

The effect of homocysteinylation is protein damge with an altered electrophoretic mobility and loss of enzymatic activity through protein denaturation. This essentially renders the protein useless and may result in elastolysis and damage to other matrix proteins.

When we consider that Marfans syndrome is due to a mutation in the fibrillin 1 (FBN1) gene and the clinical manifestations include aortic aneurysmal disease, it strengthens the evidence that the toxic effects of hyperHcy and associated homocysteinylation of fibrillin, are directly implicated with AAA formation.

5. Genetic polymorphisms and homocysteine

There is increasing evidence supporting an inheritable component to AAA. Although several factors, including age, vitamins and hormones can influence plasma Hcy levels, candidate gene analysis has recently demonstrated that mutations in genes coding for enzymes involved in Hcy metabolism may also play a role in HyperHcy and subsequently the pathogenesis of AAA.

5.1 MTHFR gene

As mentioned previously, the metabolism of Hcy requires several enzymes, nutrient co-factors and a methyl donor. Genetic control of all of these pathways is essential, however, as with any gene their are inherited or acquired errors that effect the efficiency by which Hcy can be metabolised.

The most common of these errors are felt to occur in the gene encoding for the enzyme MTHFR. This enzyme catalyses the conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, a cosubstrate for Hcy remethylation to methionine.

Currently, 33 MTHFR gene mutations have been reported as causing severe hyperHcy. Perhaps more clinically relevant to aneurysmal disease is a polymorphism in the MTHFR gene at the 677 locus which involves substitution of a cytosine nucleotide for a thymine (Strauss et al, 2003; Jones et al, 2005; Khandanpour et al, 2009; Sunder-Plassman & Fodinger, 2003; Klerk et al, 2002). It is subsequently referred to as the T-allele. This polymorphism leads to an alanine to valine change in the enzyme, resulting in 55-65% loss of enzyme activity. Individuals who are homozygous for the T-allele (TT homozygous) are most likely to manifest this level of enzyme inactivity, while those who are CT heterozygous will experience only 25% loss of activity compared to a CC homozygous individual (Guilliams, 2004).

The frequency of the T allele exhibits marked geographic variability. In those of African descent the frequency is <1%, ranging to >20% in the Hispanic population. The frequency of TT homozygotes shows similar variability (Castro et al, 2006).

The homozygous and heterozygous genotypes (CT) and (TT) have been shown to be associated with raised Hcy levels and lower MTHFR enzyme concentrations. In one study

there was a 36% difference in mean Hcy levels between wildtype and TT genotypes (Khandanpour et al, 2009), while a 47% difference was demonstrated in another study (Rassoul et al, 2000). Further to this, a strong association has been demonstrated between the TT genotype, hyperHcy and coronary, cerebro and peripheral atherosclerotic disease (Khandanpour et al, 2009; Klerk et al, 2002; Moat et al, 2004). Significantly, the association of the MTHFR genotype with Hcy levels is only observed when concomitant inadequate folate concentrations are present (Guilliams, 2004; Castro et al, 2006), although low folate levels independent of MTHFR have not been shown to cause hyperHcy (Spark et al, 2003).

Several studies have investigated the link between MTHFR gene polymorphisms and AAA (Brunelli et al, 2000; Jones et al, 2002; Strauss et al, 2003; Ferrara et al, 2006). All but one of these demonstrated a link between the T allele polymorphism and AAA, a meta-analysis of these studies confirmed a significant effect in favour of the T-allele variant increasing the risk of AAA (Thompson et al, 2008). Interestingly, the study that did not provide evidence to suggest a link between the T-allele and AAA, did suggest that it may be a contributory factor in AAA severity as indicated by aneurysm size (Strauss et al, 2003). This is consistent with results suggesting that hyperHcy patients have faster expansion rates of AAA when compared to patients with normal Hcy (Halazun et al, 2007).

Two further known polymorphisms exist in the MTHFR gene. The T1317C polymorphism has been found to show no association with vascular disease. A1298C alone influences neither folate status or Hcy levels. However, compound heterozygosity for the C677T and A1298C alleles can be associated with decreased folate concentrations and raised levels of Hcy (Sunder-Plassman & Fodinger, 2003). To date there has been no link demonstrated between the A1298C allele and AAA.

5.2 Other genes effecting homocysteine metabolism

In addition to genetic errors effecting folate metabolism and causing subsequent hyperHcy, it is worth mentioning that hyperHcy can also result from genetic mutations in the genes encoding cystathione beta-synthase (the enzyme responsible for the trans-sulphuration of Hcy to cysteine) and enzymes responsible for B12 metabolism or absorption (the co-factor required for remethylation of Hcy to methionine) (Guilliams, 2004).

These mutations occur at a significantly lower frequency than those in the MTHFR gene and are classically associated with severe hyperHcy, leading to clinical features including marfanoid features, mental retardation and early onset of vascular disease (Lievers et al, 2003).

6. Genetics and AAA

The burden of evidence for genetic influence on the aetio-pathogenesis of aneurysmal disease is small. Genetic links have been shown in the initiation and formation of abdominal aortic aneurysms (AAA). There have also been studies showing genetic evidence of familial clustering of AAA (Johansen & Koepsell, 1986).

It is estimated that about 15% of patients with AAA without any recognizable connective tissue disorders, such as Ehlers-Danlos syndrome or Marfan syndrome, have a positive family history for AAA (Frydman et al, 2003; Rizzo et al, 1989). A few studies favoured a genetic model in explaining the familial aggregation of AAA and suggested the presence of a major gene effect. However, these studies do not agree on whether the gene inheritance is recessive or dominant.

Finding a familial susceptibility gene could lead to easy identification of individuals prone to AAA's due to the fact that AAA's are largely asymptomatic prior to their rupture. The study of gene pathways may also provide potential new targets for pharmacological intervention.

It is difficult to independently assess familial tendency by gene analysis due to the presence of confounding overlap by other risk factors that have been described to have a genetic predisposition such as hypertension and atherosclerosis.

6.1 Candidate genes and AAA

If sibling risk results from genetic susceptibility, it may be inferred that this would be attributable to a few gene polymorphisms. Candidate genes for AAA that have been investigated in population studies include those encoding type III collagen, matrix metallo-proteinases and protease inhibitors, angiotensin converting enzyme, nitric oxide synthase and HLA loci. Mutations in any of these candidate genes may explain the hereditary background of AAA (Thompson et al, 2008; Sandford et al, 2007).

There are several plausible candidate genes implicated in the pathogenesis of AAA. *IL15* (interleukin 15; a plausible candidate gene with respect to inflammation in AAA), *GAB1* (GRB2-associated binding protein 1; an important mediator of branching tubulogenesis and a central protein in cellular growth response, transformation, and apoptosis), and *EDNRA* (endothelin receptor type A; an endothelin-1 receptor expressed in many human tissues with the highest level in the aorta) around 140 cM on chromosome 4, as well as *LRP3* (LDL receptor–related protein 3), *HPN* (transmembrane protease, serine 1; a serine-type peptidase involved in cell growth and maintenance), *PDCD5* (programmed cell death 5; a protein expressed in tumor cells during apoptosis independent of the apoptosis-inducing stimuli), and *PEPD* (peptidase D; an Xaa-Pro dipeptidase important in collagen catabolism) on chromosome 19.

Candidate gene studies have certainly shown causal pathways predisposing to developing AAA. Isolated mutations of one of several candidate genes are seen in some patients with AAA. But those did not always translate to similar mutations in first-degree relatives who were found to have AAA.

6.1.1 ACE gene

The renin-angiotensin-aldosterone (RAS) system plays a major role in cardiovascular homeostasis at many levels. The angiotensin converting enzyme (ACE) converts angiotensin I into the active angiotensin II. In an animal model, infusion of angiotensin II produces large AAA (Daugherty et al, 2000), while ACE has been shown to be highly expressed in human aneurysmal aorta (Nishimoto et al, 2002). This suggests a role for increased local levels of angiotensin II in the pathogenesis of AAA and may explain the protective effect to the medial layers of the infra-renal aorta provided by treatment with captopril-hydrochlorothiazide. This was shown to reduce MMP activity, both directly and by inhibiting the release of the MMP activator Angiotensin II from smooth muscle cells (Moroz et al, 2007). This suggests a role for ACE-inhibitors in the treatment and prevention of AAA.

There is a polymorphic site in the ACE gene which consists of the presence or absence of 287 base pairs. It has been termed 'I' for insertion of the fragment or 'D' for its deletion. The polymorphism accounts for three genotypes (DD and II homozygotes and ID heterozygotes. Because the alleles are co-dominant with an additive effect on plasma levels, DD

homozygotes have the highest plasma levels of ACE, while II homozygotes have the lowest (Thompson et al, 2008; Sandford et al, 2007; Fatini et al, 2005). Patients in whom the polymorphism is present have been found to have a 50% reduction in ACE levels with subsequent reduction of angiotensin II levels (Fatini et al, 2005). Given the physiological processes undertaken by these enzymes, it fits therefore that the D allele has been associated with hypertension and IHD.

More recently, an association with AAA has been demonstrated by several studies who have found a significantly increased D allele frequency in AAA patients compared to controls (Fatini et al, 2005a). Furthermore, it has been shown that this polymorphism affects AAA development independently of any association with blood pressure (Pola et al, 2001). Interestingly, aldosterone does not mediate angiotensin induced increases in AAA diameter. This suggests that increased ACE levels found in aneurysmal wall may be independent of the physiological RAS system (Cassis et al, 2005).

6.1.2 Nitric oxide synthase gene

Nitric oxide (NO) contributes to vessel homeostasis by inhibiting vascular smooth muscle contraction and growth, platelet aggregation, and leukocyte adhesion to the endothelium. Humans with atherosclerosis, diabetes, or hypertension often show impaired NO pathways (Dessy & Ferron, 2004).

Endothelial Nitric Oxide Synthase (eNOS) is responsible for the production of NO. Several polymorphisms have been identified in the gene coding for eNOS and these may affect the function of the enzyme.

One polymorphism consists of a 27 base pair repeat, present in intron 4 of the eNOS gene. Commonly, 5 repeats are identified at this polymorphic site, however, when analysing patients with AAA, it was found that 4 repeats at this site may be associated with rapid progression of AAA (Kotani et al, 2000).

A further polymorphism is the G894T, in which the rarer T allele has been found to be more frequent in AAA patients compared with age/sex-matched controls (Fatini et al, 2005b). The reduction in NO tissue levels resulting from the T-allele has been suggested to contribute to AAA formation (Thompson et al, 2008).

6.1.3 Chemokine receptor genes

Chemokines are a family of small secreted proteins that selectively recruit monocytes, neutrophils, and lymphocytes to sites of vascular injury, inflammation, and developing atherosclerosis.

Recently, a polymorphism of the chemokine receptor gene 5 (CCR5) has been identified. This is a 32 base pair deletion in the promoter region of the gene, resulting in reduced receptor expression, inhibition of leukocyte recruitment and reduction of inflammatory infiltrate (Smith et al, 1997). This deletion polymorphism has been investigated in vasculopaths with a higher incidence detected among AAA patients compared with patients exhibiting peripheral arterial or carotid disease and healthy controls (Ghilardi et al, 2004).

6.1.4 Interleukin genes

Adventitial and medial inflammatory responses have been implicated as playing a key role in AAA pathogenesis (Arapoglou et al, 2009). Interleukins are associated with this inflammatory process and studies have investigated a link between interleukin gene

polymorphisms and AAA. Only the gene encoding the anti-inflammatory cytokine IL-10 was found to have a polymorphism expressed more frequently in AAA patients than controls. It is felt the reduced production of IL-10 as a result of this polymorphism impairs the ability to regulate inflammatory processes, leading to AAA formation (Bown et al, 2003).

6.1.5 Human leukocyte antigen genes

The Human Leukocyte Antigen (HLA) system is a genetically determined series of antigens that are expressed on leukocytes and tissues. They control a variety of cell-cell interactions and certain subtypes have been associated with chronic inflammatory conditions such as rheumatoid arthritis (Sandford et al, 2007).

An autoimmune component to the pathogenesis of AAA has been proposed, implicating HLA subtypes. In a Japanese population, an increased frequency of the HLA-DR2(15) allele has been demonstrated in aneurysm patients. Other studies have shown HLA-DR B1*02 and B1*04 subtypes as well as HLA-A2 and HLA-B61 antigens to be more common in AAA patients (Rasmussen et al, 2002; Monux et al, 2003; Hirose et al, 1998). Despite this, a more recent study of 241 AAA patients failed to demonstrate a risk association between AAA and these alleles suggesting that the role of these particular genes and the autoimmune component in AAA etiology does not appear to be as crucial as previously proposed (Badger et al, 2007).

Several additional candidate gene association studies have been performed in AAA patients in genes encoding proteins ranging from collagen to heme-oxygenase. No statistically significant difference has been observed in such studies, however, the evolution of genetic analysis is likely to uncover several new potential genetic links to AAA in years to come.

Inevitably, whole human genome studies in the future will identify a combination of polymorphisms contributing to the pathogenesis of AAA and it is unlikely that a single gene will underpin this process.

6.2 Collagen and AAA

Collagen (type I and III) is the principle component of the aortic adventitia. The tensile characteristics are attributed to type III collagen and the load-bearing characteristics to type I collagen. The tensile strength of the aortic wall can be influenced by synthesis of structurally abnormal type III collagen that constitutes the basis for the aneurysm formation (Rizzo et al, 1989). A mutation of the Type III collagen gene could result in inherited propensity to develop AAA (Kontusaari et al, 1990).

Abdominal aortic aneurysms, dissections and ruptures are common disorders in different syndromes that are caused by collagen defects. Phenotypic overlap of heritable disorders of connective tissue might be a possible explanation of familial aneurysms. Ehlers Danlos Syndrome (EDS) IV is caused by genetically determined type III collagen (COL3A1) defect or a deficiency. There were some initial studies that correlated levels of Type III collagen and AAA, suggesting even that some of the familial AAA patients could be a manifestation of a subclinical EDS IV. Subsequent studies measuring Type III collagen levels in family members of patients with AAA were inconclusive to suggest a causal relationship between familial clustering and type III collagen.

6.3 Aneurysmal disease in twins

The sibling risk for developing AAA has led to research into associations of AAA in twins. The most significant study is from the Swedish Twin Registry. The investigators provide robust epidemiologic evidence that heritability contributes to aneurysm formation. Concordances and correlations were significantly higher in MZ (monozygotic, identical) compared with DZ (dizygotic, non-identical) compared with DZ twins, indicating genetic effects. There was a 24% probability that the MZ twin of a person with an AAA will have the disease. The twin of an MZ twin with an AAA had a risk of an AAA that was 71 times that of the MZ twin of a person without an AAA. When looking at twins over the age of 55 with an AAA, then possibly excluding genetic connective tissue disorders such as Ehlers-Danlos and Marfan syndrome, the odds ratio was still significantly higher for MZ twins compared to DZ twins. They noted that in other regions the proportions of type of effects could differ because of environmental factors. Also in the cases of aneurysmal disease with several genetic and environmental factors, the liability model assumes that the disease will occur when there are enough contributory factors to push the individual's liability above the threshold (Wahlgren et al, 2010).

The familial clustering of AAA is unlikely to be due to chance alone; the odds ratios for sibling risk in case–control studies are too high. But almost 20 years of work has yielded little persuasive evidence for specific genes underlying this phenomenon. Large, collaborative research proposals are needed to address the reasons for familial clustering of AAA.

7. Therapeutic interventions on homocysteine

The detection of elevated levels of Hcy in patients with large, symptomatic AAA is unlikely to change the treatment because such patients need repair of their AAA. It is in the management of small (30-50mm) AAA's that Hcy levels may have a role. Although surgery is not indicated for these AAA's, a proportion will expand until they are large enough to warrant elective intervention before rupture occurs. Current practice is to monitor the diameter of AAA's with periodic ultrasound or CT scanning, but our understanding of the natural history of these aneurysms remains incomplete.

The identification of risk factors such as Hcy that are associated with greater rates of expansion, may help in the planning of AAA surveillance, the identification of high risk patients who may benefit from early intervention and the development of strategies to prevent expansion (Halazun et al, 2007).

To briefly review the metabolism of Hcy, we know that B12 and folic acid are required for transmethlyation to methionine and that B6 is required for trans-sulphuration to cystathionine. Deficiencies of these vitamins have been implicated with hyperHcy, while normal levels of folate, even in the presence of the MTHFR polymorphism seem to be sufficient to regulate Hcy levels. In fact, it has been proposed that the single most important determinant of Hcy levels in the general population is folate status (Castro et al, 2006).

It seems logical therefore that supplementation with folic acid and vitamins B6 and B12 could act as Hcy lowering therapies, potentially preventing the progression/onset of aneurysmal disease (a risk factor reduction technique).

7.1 Folate, B6 and B12 supplementation

Dietary supplementation with folate has been shown to reduce Hcy levels on average by 25% in individuals with cardiovascular disease. Further reduction in levels has been

demonstrated with the addition of B6 and B12, suggesting a synergistic effect. Such a reduction in Hcy has previously been linked to an 11% lower risk of coronary heart disease and 19% lower risk of stroke. Despite this, collective evidence recently published in a large-scale meta-analysis suggests that treating hyperHcy with folate and other B-vitamins had no significant effects within 5 years on cardiovascular morbidity and mortality (Clarke et al, 2010).

Interestingly, these results are associated with patients who already have established cardiovascular disease and may be explained by the potential detrimental effects of B vitamin supplementation. In patients with established atherosclerotic disease it is suggested that B vitamins have the potential to enhance inflammation and proliferation in atherosclerotic lesions (Smulders & Blom, 2011). In contrast to this, several animal studies have suggested that B vitamins delay initial development of atherosclerosis. This is supported by a study in which healthy siblings of patients with premature atherosclerotic disease received dietary folate and B6 supplementation for 2 years, a reduced frequency of abnormal exercise stress tests was detected, which is associated with a reduced risk of ischaemic coronary events. This suggests that Hcy lowering therapy as prophylaxis for at risk patient groups may be beneficial. One such group are patients with small AAA's, in who hyperHcy has been linked with more rapid rate of expansion (Halazun et al, 2007), or indeed patients with familial AAA disease who are at high risk of AAA.

7.2 Trimethylglycine (Betaine)

Trimethylglycine (TMG) is a small trimethylated amino acid that can react with the enzyme betaine methyl-transferase, donating a methyl group to remethylate Hcy to methionine (Steenge et al, 2003).

Moderate Hcy lowering effects have been demonstrated, however, this requires high dose (>6gm/day) TMG and it is not as effective as folate supplementation. To date, TMG administration has not been shown to lower the risk of cardiovascular disease, however, studies are continuing (Steenge et al, 2003).

7.3 N-Acetyl Cysteine (NAC)

NAC is a pharmaceutical drug and nutritional supplement used primarily as a mucolytic agent for the treatment of paracetamol overdose. Recently it has been shown to increase plasma free Hcy, the form removed by the kidney, by breaking the disulfide links of the bound form.

One recent study randomised patients with confirmed hyperHcy and coronary artery disease to 5mg folic acid, 600mg NAC or placebo daily for 8 weeks. Both folic acid and NAC had a similar Hcy lowering effect and improved endothelial function compared to placebo (Yilmaz et al, 2007). A further study found that plasma Hcy levels were reduced during treatment with NAC by 45% (Wiklund et al, 1996).

NAC might therefore be a highly efficient nutritional supplement for reducing plasma Hcy and further research large scale randomised trials are required to identify a potential benefit in lowering risk of aneurysmal and cardiovascular disease.

7.4 Omega-3 Polyunsaturated Fatty Acids (PUFA's)

A growing body of research on marine lipids has revealed that omega-3 rich fish oil supplementation can reduce elevated Hcy levels.

An animal model study examined the effect of fish oil rich in omega-3 PUFA's on Hcy metabolism, treating rats with olive oil, tuna oil or salmon oil for 8 weeks. The plasma Hcy level was significantly reduced in the group fed tuna oil, rich in omega-3 PUFA's (Huang et al, 2011). Similarly, a human trial randomised patients with type 2 diabetes mellitus to either 3g of omega-3 PUFA's or placebo daily for two months. Hcy levels were found to decrease significantly in the treatment group compared with those receiving placebo (Pooya et al, 2010).

7.5 Taurine

Taurine is an organic acid and a major constituent of bile. It is a derivative of the sulphur containing amino acid cysteine and is one of the few known naturally occurring sulfonic acids. Recent studies have shown that taurine can block methionine absorption from the diet, thereby reducing available substrate for Hcy synthesis. One animal study found that taurine normalised hyperHcy and reduced atherosclerosis by 64% over control animals (Zulli, 2011). While in a study of healthy, middle-aged women, plasma Hcy levels exhibited a significant decline after taurine supplementation (Ahn, 2009). The investigators concluded that sufficient taurine supplementation might effectively prevent cardiovascular disease.

8. Conclusion

The pathogenesis of abdominal aortic aneurysm is complex and multi-factorial. The true mechanism underlying the disease process is likely to be underpinned by an interaction between a genetic predisposition and environmental risk factors including smoking and hypertension.

HyperHcy and polymorphisms in the MTHFR gene have been implicated as risk factors for cardiovascular disease and there is some evidence that raised levels of Hcy are associated with an increased risk of having an AAA. Despite this, on the current evidence available, we can not confidently state that hyperHcy is a causative factor in the pathogenesis of AAA, although it may help to explain the variation in expansion rates.

In addition to studies of the MTHFR gene, recent candidate gene analysis has provided us with an improved understanding of the genetic predisposition to AAA development. It is unlikely however, that a single gene polymorphism will hold the key to aneurysm formation and such analysis is susceptible to confounding influences of genetic stratification, in particular genetic overlap with risk factors such as hypertension.

Unanswered questions will remain until large scale genome wide association studies are undertaken to enable a complete understanding of the genetic influence on the pathogenesis of AAA.

With regard to the medical management of AAA, the current available evidence would suggest that pharmacotherapy with statin and ACE-Inhibitor should be implemented to attenuate aneurysmal expansion. Macrolides and NSAID's may play a similar role and are currently being investigated.

There is insufficient evidence to support the routine use of B6, B12 and folate supplementation, though multicentre, prospective randomised trials are urgently recommended. This also applies to the use of PUFA's, NAC and taurine.

Ultimately, as these studies progress and our understanding of the pathophysiology of AAA evolves, it is likely that additional pharmacological and dietary supplements will be identified to form an armamentarium aimed at the prevention of AAA rupture.

9. References

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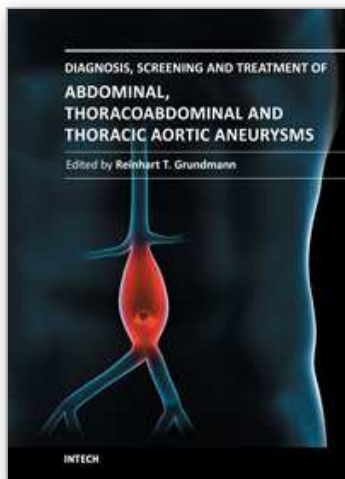
Diagnosis, Screening and Treatment of Abdominal,

Thoracoabdominal and Thoracic Aortic Aneurysms

Edited by Prof. Reinhart Grundmann

This book considers mainly diagnosis, screening, surveillance and treatment of abdominal, thoracoabdominal and thoracic aortic aneurysms. It addresses vascular and cardiothoracic surgeons and interventional radiologists, but also anyone engaged in vascular medicine. The high mortality of ruptured aneurysms certainly favors the recommendation of prophylactic repair of asymptomatic aortic aneurysms (AA) and therewith a generous screening. However, the comorbidities of these patients and their age have to be kept in mind if the efficacy and cost effectiveness of screening and prophylactic surgery should not be overestimated. The treatment recommendations which will be outlined here, have to regard on the one hand the natural course of the disease, the risk of rupture, and the life expectancy of the patient, and on the other hand the morbidity and mortality of the prophylactic surgical intervention. The book describes perioperative mortality after endovascular and open repair of AA, long-term outcome after repair, and the cost-effectiveness of treatment.

How to reference

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