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High-risk factors related to the occurrence and development of abdominal aortic aneurysm

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ABSTRACT

Abdominal aortic aneurysm (AAA) is a common and potentially dangerous vascular disease with many risk factors related to its occurrence and development. This review collects the results from recent studies of different comorbidities including hypertension, diabetes, and hyperlipidemia and summarizes their connections with AAA development and its underlying mechanisms. We believe that hypertension, diabetes, and hyperlipidemia can affect AAA occurrence and development, but more studies are needed to further explore the mechanisms.

Abdominal aortic aneurysm (AAA) is a common vascular disease. According to the population screening conducted in the UK and Sweden, the incidence of AAA has decreased from 3.5 to 4.9% in 1980 to about 1.1–1.7% in 2016[1] with developments in imaging and treatment modalities. However, since AAA is usually asymptomatic, most patients are undiagnosed. AAA is potentially fatal because the sac could expand and even rupture, causing hemorrhagic shock or even death. Therefore, it is necessary to emphasize the importance of making the AAA diagnosis. The occurrence and development of AAA are affected by many factors, including age, sex, smoking history, blood pressure, blood glucose, blood lipids, and others. At the same time, hypertension, diabetes, and hyperlipidemia are comorbidities with a high incidence of AAA in China. Therefore, this review will comprehensively summarize the relationship between the occurrence and development of AAA, and hypertension, diabetes, and hyperlipidemia.

1. Hypertension

Due to various factors such as living habits and population aging, the number of patients with hypertension in China is increasing annually. Changes in vessel wall structure and function of the large and small arteries leads to the incidence of hypertension. Vascular issues such as impaired vascular endothelial cell function, aortic elasticity discovered simultaneously in the pathogenesis of hypertension and AAA suggest that their mechanisms are closely related. To identify the risk factors for AAA, *Li* et al. collected AAA patient data from different centers and found that hypertension is a risk factor for AAA in European populations.[2] Similarly, the statistical analysis performed by *Comzu* et al. also found that the incidence of AAA is higher in people with hypertension than in the general population.[3] Based on these studies, we suppose that hypertension is a risk factor for AAA. The main mechanism is currently believed to be large pulse pressure in patients with hypertension causing blood pressure fluctuations and shifts in elastin and collagen fiber content within the vessel walls and smooth muscle cells, resulting in an increasing risk of AAA.

Although most people believe that hypertension is a risk factor for AAA formation, controversy persists about whether hypertension can cause expansion of the aneurysm sac. *Schlosser* et al. conducted a follow-up study of 230 AAA patients for up to 10 years and divided the hypertension population into 2 groups by blood pressure (over 165/95 mmHg and 140/80 to 165/95 mmHg). The conclusion was that hypertension has nothing to do with AAA expansion.[4] On the other hand, *Shiraya* et al. found a significantly greater degree of arterial dilation in the hypertensive group than in the control group by establishing an AAA and hypertension mouse model. Further research revealed that the expression of nuclear factor-kappa beta and Ets, a member of a transcription factor family, was increased in hypertensive mouse models, which promoted the inflammatory response, increased matrix metalloproteinase (MMP) activity, and eventually accelerated the AAA expansion.[5] Due to the differences between human and animal models, it is not yet possible to compare whether these two conclusions are contradictory. Furthermore, among researchers who believe that hypertension can accelerate the incidence of AAA, consensus is lacking about how it affects AAA expansion. *Schewe* et al. reported that diastolic blood pressure was the main risk factor for AAA dilation,[6] while others also believed that pulse pressure affected blood pressure fluctuations, which can affect sac expansion. Meanwhile, there is no unified view on whether blood pressure affects AAA continuously or in stages. *Hisato* et al. recently

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conducted a meta-analysis of the relationship between hypertension and AAA, including more than 500 studies with over 6600 patients. They concluded that hypertension was related to the occurrence of AAA but not its expansion.[7] Therefore, controversy persists about the role of hypertension in facilitating AAA expansion.[8–10] In the future, further epidemiological bases and experimental studies are needed to explore this aspect. Finally, regarding AAA rupture, most researchers believe that hypertension is a risk factor, with much epidemiological evidence. However, due to the limited sample size and other factors, in-depth studies in this area are still required.

2. Diabetes

Diabetes is a common metabolic syndrome that can cause microcirculation disorders and microvascular basement membrane thickening, eventually causing complications including diabetic nephropathy, diabetic retinopathy, and diabetic foot. Given the fact that the incidence of other atherosclerotic events in patients with diabetes is also higher than those in the normal population, many scholars believe that diabetes is a risk factor for atherosclerosis; thus, early views suggested that diabetes was also a risk factor for AAA. Ironically, some clinical studies in recent years have reported that diabetes is not a risk factor for AAA but a protective element instead. *Lederle* et al. first proposed that diabetes could protect AAA patients in different ways after conducting a cross-sectional study of 73,945 patients in 1997.[11] *Dattani* et al. also reported that the diameter of the aneurysm sac of patients with diabetes increases more slowly than that in the general population.[12] *Sweeting* et al. performed a meta-analysis of 15475 patients and found that the rate of AAA growth in diabetic patients was reduced by 0.51 mm/year compared with non-diabetic patients.[13] Therefore, diabetes can exert a protective impact on AAA patients. Regarding its mechanism, the two main perspectives are the effects of hyperglycemia and hypoglycemic medications on AAA patients. The following is the elaboration of these two aspects.

2.1. Effect of hyperglycemia on AAA patients

The most direct manifestation of diabetes is an increase in blood glucose. However, the direct effect of an elevated blood glucose on AAA is inconclusive. The hypothesis that increased blood glucose can lead to aortic sclerosis accompanied by the possible mechanism of median membrane thickening and decreasing aortic compliance and dilatation. The current focus mainly include metabolites and cells. In terms of metabolites, *McMillan* et al. found that MMP-2 and MMP-9 were closely related to AAA, with the former related to AAA occurrence and the latter related to AAA expansion.[14] *Miyama* et al. used the AAA model to demonstrate that reduced activity of MMP-9 in hyperglycemic populations decreases degradation of the tunica elastin and reduced macrophage aggregation and microvascular formation, thereby eliminating aortic expansion.[15] At the same time, several studies have found that the cathepsin S level in the plasma and arterial wall tissues was significantly higher in AAA than normal populations, while cystatin C concentration was lower than that in normal people. Cathepsin S is also positively correlated with AAA diameter and growth rate, while cystatin C is negatively correlated with it.[16] Epidemiological studies reported that plasma cystatin C levels are higher in diabetic patients than in normal people. Related studies in diabetic mouse models have also shown reduced cathepsin S and increased cystatin C levels. Therefore, it has also been suggested that diabetes reduces the occurrence of AAA by impacting cathepsin S and cystatin C.[17] An increase in blood glucose results in increased advanced glycation end products (AGEs), stable covalent adducts produced by large molecules such as proteins, lipids, or nucleic acids spontaneously reacting with glucose or other reducing monosaccharides without enzyme participation. AGEs can increase the cytoplasmic matrix, harden the arterial wall, and ultimately reduce AAA occurrence and development.[12,18,19] In terms of cells, hyperglycemia can alleviate the inflammatory response by increasing the number of T cells, reducing the number of macrophages, and promoting the phenotypic transformation of vascular smooth muscle cells to prevent AAA progression.[20–22,28,29]

2.2. Effect of hypoglycemic medicines on AAA patients

Metformin is an important hypoglycemic medical therapy for diabetic patients. In experimental animal models, *Miyama* et al. compared metformin-treated mice with normal insulin-injected mice and found that the former treatment had a stronger protective effect on AAA.[15] In addition, many studies have suggested that metformin can impact AAA via MMP-2, macrophages, and vascular smooth muscle cells. However, the sample sizes of the current clinical studies are insufficient; thus, their credibility could been challenged. *Sweeting* et al. performed a meta-analysis and reported no significant correlation between diabetes medications and AAA development and rupture.[13] Therefore, more research is needed in this regard. Research on other medicines is also mostly limited in animal models, and reliable clinical randomized controlled trials are still lacking.

Regarding diabetes, some supplemental studies have been published. A population screening in Denmark suggested that glycated hemoglobin may be associated with AAA, but no further studies have been conducted.[23] In addition, the protective effect of diabetes on AAA has been recognized by most scholars, but its impact on AAA surgery, particularly whether it can affect open surgery or EVAR, and its postoperative recovery, remains controversial.[24,25] *Diem* et al. suggested that the postoperative complications and postoperative mortality of EVAR in AAA patients with diabetes did not differ from those in the general population.[26] On the other hand, after performing a meta-analysis, *De Rango* et al. proposed that the early mortality of patients with diabetes increases after EVAR and that long-term survival decreases after 2–5 years. The possible reason for this is that diabetes increases the vascular burden on patients and increases mortality.[27] Some researchers have suggested that the protective effect of diabetes on AAA differs between the sexes, indicating a promising research interest in this regard.

3. Hyperlipidemia

Hyperlipidemia, also known as dyslipidemia, refers to the abnormal lipid types and contents in the plasma. Clinically, cholesterol, triglycerides, and high-density lipoproteins are usually considered. Dyslipidemia can lead to atherosclerosis, which can result in cardiovascular diseases such as coronary heart disease. Therefore, hyperlipidemia is often considered as a risk factor for AAA. The *Wanhainen* et al. study suggested that triglyceride level was significantly related to AAA and that triglyceride levels in AAA populations were higher than those in normal populations.[30] Similarly, after collecting information for many patients, *Forsdahl* et al. found that cholesterol was also positively correlated with the incidence of AAA.[31] The specific mechanism has two possible explanations. One explanation is that a large amount of cholesterol crystals is deposited in the intimal layer of blood vessels, damaging the vascular endothelium, promoting inflammatory reactions, causing intimal degeneration, and ultimately causing AAA occurrence and development. Some statements have described that cholesterol metabolism directly leads to the occurrence of AAA, but no clear experimental evidence has been shown. Another viewpoint is that most lipids can promote the secretion of inflammatory factors by endothelial cells and promote the inflammatory response, leading to vascular endothelial damage and arteriosclerosis. At the same time, the inflammatory response can aggravate the lipid metabolism disorder. The vicious circle between the two events eventually causes AAA occurrence and development.[32–36] Lipoproteins are also thought to be significantly correlated with AAA occurrence and development. The relevant physiological effects of lipoproteins have not yet been clarified, but existing research suggests that lipoprotein(a) plays an important role in atherosclerosis and arterial thrombosis.[32,37,38] *Takagi* et al. conducted a meta-analysis and reported

that lipoprotein(a) content in the AAA population was higher than that in the general population, suggesting that lipoprotein(a) is a potential factor and whose blood level could be a diagnostic basis of AAA.[39] Some researchers reported that lipoprotein(a) may promote the occurrence of AAA by inhibiting fibrinolysis and promoting inflammatory response and thrombosis. However, due to the complex composition of lipoproteins, specific pathways and functions of other lipoproteins remain to be elucidated. In summary, the current research suggests that dyslipidemia mainly affects the vascular inflammation response and that reducing the inflammatory response in patients with hyperlipidemia could play a role in decreasing the incidence of AAA. Furthermore, some researchers have studied people who took statins and suggested that long-term statin use can reduce the development of AAA and have a positive effect on EVAR patient outcomes.[40]

Taken together, the occurrence and development of AAA are affected by many factors, and blood pressure, blood glucose, and blood lipid can play different roles. Although there have been many studies in this area, drawbacks such as the limited sample size in early studies remain distinct, and specific mechanisms and underlying pathways require clarification. Accordingly, much work is required in the future.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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