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Epidemiologic basis for the comorbidity of aortic aneurysm and atherosclerosis

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ABSTRACT

Aortic aneurysm and atherosclerosis are characterized by high clinical heterogeneity. The uncertainty in their comorbidity evaluations may be related to polyetiology of these diseases and the presence of not only common but also specific risk factors, as well as the complex pathogenesis of these conditions.

The aim of this review is to summarize information on the prevalence and risk factors of aortic aneurysm and atherosclerosis, explaining the possible mechanisms underlying the comorbidity of these pathologies. We conducted a search for scientific publications in Russian (eLIBRARY.RU) and international (PubMed) electronic libraries, prioritizing works published in the last 10 years.

Aortic aneurysm and atherosclerosis exhibit an age-dependent pattern of prevalence. The high prevalence of atherosclerosis compared to aortic aneurysm, along with the approximately similar age ranges for the manifestation of these pathologies,is related to their comorbidity. Conversely, these diseases share some common risk factors, albeit with varying contributions to atherosclerosis and aortic aneurysm of different localizations. Type 2 diabetes mellitus and lipid metabolism profiles are examples of risk factors with multidirectional influences. To understand the reasons for the discordant estimates of comorbidity between aortic aneurysm and atherosclerosis from an epidemiological perspective, a comprehensive approach to patient characterization, including a detailed analysis of risk factors recorded in the analyzed groups, is essential.

Keywords: aortic aneurysm, atherosclerosis, comorbidity, risk factors

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Эпидемиологическая основа коморбидности аневризмы аорты и атеросклероза сосудов

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РЕЗЮМЕ

Аневризма аорты и атеросклероз сосудов характеризуются высокой клинической гетерогенностью. Неоднозначность в оценках коморбидности данных заболеваний может быть связана с их полиэтиологичностью и наличием не только общих, но и специфичных факторов риска, сложным патогенезом данных заболеваний.

Цель настоящего обзора заключается в обобщении информации о распространенности и факторах риска аневризмы аорты и атеросклероза сосудов с точки зрения объяснения возможных механизмов формирования коморбидности данных патологий. При проведении поиска научных публикаций в отечественной (Научная электронная библиотека – eLIBRARY.RU) и зарубежной (PubMed) электронных библиотеках в качестве приоритетных рассматривались работы, опубликованные за последние 10 лет.

Аневризма аорты и атеросклероз сосудов имеют возраст-зависимый характер распространения. Высокая распространенность атеросклероза сосудов по сравнению с аневризмой аорты и примерно равные возрастные границы манифестации данных патологий связаны с их коморбидностью. С другой стороны, данные заболевания характеризуются некоторой общностью факторов риска, но с разным их вкладом в развитие атеросклероза сосудов и аневризмы аорты разной локализации. Сахарный диабет 2-го типа и показатели липидного обмена относятся к категории факторов с разнонаправленным влиянием на риск развития данных патологий. Для понимания причин противоречивых оценок коморбидности аневризмы аорты и атеросклероза сосудов с точки зрения эпидемиологии важен комплексный подход к характеристике пациентов с детальным анализом факторов риска, регистрируемых в анализируемых выборках.

Ключевые слова: аневризма аорты, атеросклероз сосудов, коморбидность, факторы риска

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INTRODUCTION

Aortic aneurysm (AA) and atherosclerosis (AS) are two vascular pathologies that are characterized by polyetiology and clinical heterogeneity. There are thoracic aortic aneurysms (TAA), abdominal aortic aneurysms (AAA) and mixed, thoracoabdominal aortic aneurysms, when the pathological process affects both sections of the aorta [1, 2]. TAA can develop in the aortic root, ascending thoracic aorta or descending thoracic aorta, as well as in several segments of thoracic aorta simultaneously. Atherosclerosis can also affect various arteries, and in most cases, the pathological process observed in an individual patient affects multiple vascular territories [3–6]. Both AA and AS are asymptomatic for long periods of time, but they are life-threatening conditions that can lead to disabling complications and represent a major issue for society and the healthcare system [7–11].

Both AA and AS are characterized by a number of common risk factors and some similarity in the development of the pathological process, which is accompanied by disruption of the structure of blood vessels [1, 2, 12–18]. At the same time, there are different, often completely opposite, evaluations of AA and AS comorbidity, irrespective of the location of pathological changes in the aorta. In some studies, AS is considered as a significant risk factor for AA development [19, 20], in others its contribution to the risk of AA is estimated as insignificant [21]. Some authors have proposed that AS may be associated with slower AA growth [22] and may even serve as a protective factor against complications of

AA, such as dissections [23]. It is frequently postulated that AA may have a protective effect on the development of atherosclerotic vascular lesions [24–28]. There are some opinions about the mutual influence of AS and AA on each other [29]. Additionally, there are publications that do not find a correlation between these pathologies [30].

The uncertainty in the evaluations of the comorbidity of AS and AA may be related to their polyetiology and the presence of not only common but also specific risk factors, and the complex pathogenesis of these diseases [1, 2, 31, 32]. In general, despite decades of research into the comorbidity of AA and AS [24, 30, 33], many issues remain unresolved. A more thorough analysis of the relationship between AA and AS is of interest since it would clarify the pathogenesis of these diseases, the mechanisms of comorbidity formation (direct or inverse), and the clinical heterogeneity of individual pathological conditions, which is important for the formulation of criteria for identifying risk groups, determining the conditions for a severe disease course, and optimizing patient management based on the presence of a single pathology or comorbid pathologies [23, 26]. To do this, it is necessary to consider the data from epidemiological and clinical studies devoted to the analysis of AA and AS risk factors and assessment of their comorbidity, as well as ideas about the specific features of the pathogenesis of these diseases at the cellular and molecular levels.

The aim of this review is to summarize information on the prevalence and risk factors of AA and AS in terms of explaining the possible mechanisms of comorbidity formation of these pathologies. We conducted a search for information in Russian (Scientific Electronic Library – eLIBRARY.RU) and international (PubMed) online libraries. During the search for scientific publications, we gave priority to works published in 2013–2024. However, in certain cases, we also considered studies from earlier periods, which are important for understanding the development of concepts regarding the comorbidity of AA and AS.

PREVALENCE OF AORTIC ANEURYSMS AND ATHEROSCLEROSIS

There is a notable contrast in the prevalence of AA and AS. A meta-analysis of population-based studies indicates that the average incidence of TAA globally is 5.3 per 100,000 individuals/year, and the prevalence is 0.16% [10]. Aneurysms of the aortic root, ascending aorta, or of both these segments are most frequently documented in TAA, whereas aneurysms of the descending aorta, aortic arch, and mixed forms are less prevalent [1, 10, 34]. In a study of 844 patients with TAA, isolated ascending thoracic aortic aneurysms were found in 74.4% of cases, isolated descending thoracic aortic aneurysms were detected in 15.4% of cases, and combined ascending and descending aortic aneurysms – in 10.2% of cases [34]. Other studies provide slightly different estimates for the location of AA in the thoracic segment. In the study, S. Ito et al. noted that 15% of TAA cases occurred in the ascending aorta, 60% – in the aortic arch, and 25% – in the descending thoracic aorta [35]. In the study conducted by L.K. Bickerstaff et al., the corresponding indicators were 51.3, 11.1, and 37.5%, respectively [36]. These data demonstrate the clinical heterogeneity of the studied samples of patients with TAA. The meta-analysis revealed that aneurysms of the ascending aorta, aortic arch, and descending thoracic aorta are present in 45.5, 21.3, and 34.6% of patients with TAA, respectively [10]. At the same time, the authors of the cited publication [10] highlighted the lack of well-designed population-based studies to assess the prevalence of TAA and the necessity to continue epidemiologic studies in the future.

Patients with TAA display a moderately elevated prevalence of AAA and cerebral aneurysms [1, 36]. For example, 15% of patients with TAA of nonhereditary (Marfan syndrome and other monogenic connective tissue disorders were excluded) and non-inflammatory etiology were found to have aneurysms of other locations – in abdominal aorta, brachiocephalic arteries, etc. [37]. In another study, AAA was registered in 25% of patients with TAA [36]. On the other hand,

among patients with AAA, 15.2% of men and 30.7% of women (on average, every fifth patient) had synchronous or metachronous TAA [38].

The prevalence of AAA in the age cohort of 64–83 years varies between different populations, with a reported range of 1.4 to 8% [39–41]. However, regional variations exist, with a higher prevalence of AAA in developed countries compared to developing ones [42]. The lowest estimates of AAA annual incidence rate per 100,000 were documented in Central Asia (105.92 in 1990, 114.7 in 2005, and 113.43 in 2010), and the highest estimates were reported in Australia (382.65, 318.83, and 310.27 in the years indicated, respectively) [42]. Despite a decrease in the global prevalence of AAA between 1990 and 2010, certain regions observed an increase in the incidence of this condition (Oceania, tropical Latin America, the Asia-Pacific with high income, Southern, Central and Western Sub-Saharan Africa, South, West and Central Asia) [42]. Temporal dynamics in the prevalence of TAA were also observed [36].

The abdominal aorta is also characterized by differences in the incidence of aneurysms across different segments, with the infrarenal segment being most often affected [35, 43]. In the study by S. Ito et al., up to 96% of AAAs were located in the infrarenal, 2% – in the juxtarenal, and 1% – in the suprarenal segments of the abdominal aorta [35]. At this time, no data are available on the prevalence of AAA in Russia, which can be explained by the long-term asymptomatic course of AAA, as well as the absence of mandatory screening and population-based studies designed to detect this pathology [44].

In contrast to AA, AS is a more prevalent condition across various populations, but estimates of its prevalence also vary between studies, potentially due to different approaches to diagnosing AS. One of the approaches to estimating the prevalence of AS is the analysis of the prevalence of cardiovascular diseases associated with atherosclerosis, which include coronary heart disease (CHD), atherothrombotic ischemic stroke, transient ischemic attacks, peripheral atherosclerosis with atherosclerotic plaques causing > 50% stenosis [45], previous acute myocardial infarction, acute coronary syndrome, coronary revascularization and other arterial revascularization procedures, as well as aortic aneurysm [44]. In recent years, estimates of AS prevalence in populations (including subclinical forms) have been made on the basis of histologic analysis and data from instrumental examination of arteries [3, 6, 46].

A cross-sectional, population-based study was conducted in five cities of the Vladimir region of Russia between May 2018 and March 2020. The study included 1,350 men and women aged 30–69 years, and cardiovascular diseases associated with atherosclerosis were found in 17% of individuals [47]. A population-based prospective cohort study conducted in China (including more than 3,000 people aged 50 to 75 years, of whom 53.5% were women) revealed atherosclerotic plaques in at least one vascular territory in 93.6% of cases. Atherosclerotic plaques in more than one blood vessel were found in 82.8%, and in four or more vascular territories – in 46.8% of cases. Atherosclerotic plaques were mostly (79.6%) detected in the aorta [6]. A random sample of the middle-aged population (25,182 individuals without CHD, of whom 50.6% are women) was examined using coronary computed tomography angiography, and AS was found in 42.1% of individuals [46].

As indicated by various researchers, the prevalence of subclinical AS in various groups ranges from 36 to 63% (cited according to [48]). A total of 318 individuals (51% women), aged between 36 and 78 years (mean age 60 years), were examined as part of the Framingham Heart Study. In patients who were free of overt cardiovascular disease, the presence of AS was observed in 38% of women and 41% of men, as evidenced by the results of cardiac magnetic resonance (CMR) imaging [3]. Atherosclerosis of variable degree in one or more vessel segments was observed in 95.6% of Korean women who died from external causes. A total of 90 aortic samples were analyzed, each divided into 7 segments. AS was common in the distal infrarenal, proximal thoracic, and

proximal ascending segments of the aorta [4]. At the same time, for both men and women across all age cohorts, atherosclerotic plaques were more prevalent in the abdominal aorta than in the thoracic aorta, particularly in its ascending segment [3]. These data suggest that atherosclerosis-related diseases, particularly CHD, are not always detected in patients with atherosclerotic vascular lesions.

Thus, the estimates of the prevalence of AS and AA differ, but both pathologies are characterized by unequal lesions of different vascular territories, heterogeneity of prevalence estimates in different populations and age cohorts. The reasons for such heterogeneity of the prevalence of these pathologies may be attributed to inter-population (geographical) differences in the profile of AA and AS susceptibility in different sections of the aorta, differences in the significance of risk factors, peculiarities of sample formation, diagnostic methods, as well as the temporal dynamics of prevalence (since the studies were performed in different years).

RISK FACTORS FOR THE DEVELOPMENT OF AORTIC ANEURYSM AND ATHEROSCLEROSIS

Despite differences in prevalence, a number of common risk factors for AS and AA are known (Table). These factors include: old age, smoking, male sex, as well as arterial hypertension, hyperlipidemia, vascular wall injury, and inflammation [1, 49, 50]. Genetic factors, represented by both monogenic and polygenic components, also contribute to the risk of developing both AS and AA [1, 31, 51–57]. In general, risk factors can be divided into non-modifiable (genetic factors, malformations, sex, age, ethnicity) and modifiable ones. At the same time, the relative importance of common modifiable and non-modifiable factors may differ for AS and AA, for pathological conditions of vessels of different locations and in representatives of different sexes [1, 31, 34] (Table).

Table

Common and specific risk factors for the development of atherosclerosis and aortic aneurysm of different locations*

Risk factors	Significance of risk factors for AA and AS
Age	Both AA and AS are age-dependent diseases. In the case of AA, the age of diagnosis increases based on the type: hereditary – familial – sporadic. Women tend to develop both AA and AS later in life.
Sex	The risk is increased in men.
Genetic factors	In 20–30% of cases, pathogenic variants are found in genes that cause syndromes (Marfan, Loeys–Dietz, Ehlers-Danlos, etc.), the Mendelian forms of TAA (*ACTA2*, *MYH11*, *PRKG1*, *MYLK*, etc.). These variants are more often registered in aneurysms of the aortic root and ascending aorta, less often in aneurysm of the descending aorta. Pathogenic variants in some genes leading to the development of TAA can be detected in AAA. For AS, the risk increases in monogenic forms of hypercholesterolemia (pathogenic variants in the *LDLR*, *APOB*, *PCSK9*, *LDLRAP1* genes, etc.). AS and AA are also characterized by a polygenic predisposition. Family history increases the risk of developing AA and AS.
Congenital defects	Congenital anomalies (bicuspid aortic valve, coarctation of the aorta, complex congenital heart defects) are the cause of TAA development, in some cases the defects are genetically determined.
Ethnicity	It contributes significantly to the risk of AAA development (the risk of developing pathology is higher in Caucasians), but it is less significant for AS development.
Arterial hypertension	It is characteristic of both AS and AA. It is less common in sporadic aneurysms of the aortic root and ascending aorta compared to the descending aorta.
Hyperlipidemia	It is more significant for AS and AAA and is also associated with TAA of the descending aorta.
Type 2 Diabetes Mellitus	It is not specific for AA and acts as a protective factor; it is sometimes considered to be a risk factor for AAA as well as TAA of the descending aorta. It is a significant risk factor for AS.
Obesity	It is characteristic of AAA and AS, but not of TAA.
Inflammatory diseases	Giant cell arteritis (Horton disease), Takayasu arteritis, Behcet's disease, sarcoidosis, etc. increase the risk of TAA, but these diseases are rarely reported in AAA. The inflammatory component is significant in the development of AS.

Table (continued)

Risk factors	Significance of risk factors for AA and AS
Infectious diseases	Bacterial, fungal infections, and syphilis increase the risk of TAA development. The pathogenesis of AS is affected by viral and bacterial infections.
Traumatic aortic injury	It is registered in AA and AS.
Atherosclerosis	Atherosclerosis of various locations is registered more often in AAA than in TAA. AS with an atypical clinical pattern has been described in individuals with TAA.

* compiled from sources [1, 3, 33, 43, 46, 50, 58–65].

Among the non-modifiable risk factors of AA and AS, genetic factors are of particular interest. Monogenic forms account for 20–30% of all TAA cases, and a family history without an established genetic cause is found in another 20% [1, 66, 67]. Pathogenic variants in genes of syndromic and monogenic forms of TAA are more often registered in aneurysms of the aortic root and ascending aorta, and less often – in aneurysms of the descending aorta [1, 68].

Some studies have shown that family history is less important in relation to the risk of TAA development. For example, according to O. Leone et al. [69], in ascending TAA family history of aortic disease was rare, accounting for about 6% of cases [69]. Among the patients with a degenerative histotype of TAA, 3.9% had TAA-associated syndromes (Turner syndrome in 0.5% of cases, Marfan syndrome in 2.9%, Loeys–Dietz syndrome in 0.5%), and more than 30% of patients had bicuspid aortic valve (BAV), which is also highly heritable [1, 30, 70]. The association of genetically determined TAAs with certain histotypes has also been observed by other researchers [71].

BAV is considered as an independent risk factor for the development of TAA [1]. In some populations, this pathology is registered in 30% or more of TAA patients [69, 71–73]. BAV has also been identified in samples of non-TAA patients undergoing diagnostic tests (for example, computed tomography) for one reason or another, with a frequency comparable to that of TAA patients [73]. Such samples can potentially be used as control groups, including in the studies of AA and AS comorbidity. BAV is also characterized by genetic determination, and the monogenic component of BAV partially overlaps with that of TAA [1, 30, 70].

For AAA, genetic risk factors are not considered to be the most important, but pathogenic variants characteristic of TAA are sometimes registered in patients with this pathology [10, 74]. In addition, family history is noted in AAA [58, 75, 76]. It has been shown that the chance of developing AAA increases significantly with a family history (odds ratio OR = 1.9; 95% CI: 1.9–2.2; $p < 0.0001$) [75]. According to N. Sakalihasan et al. [58], a family history (taking into account ultrasound screening data) was recorded in 13% of AAA patients, and the highest (25%) prevalence of this pathology was found in brothers. In another study, more than 20% of patients with AAA had a family history [76].

A polygenic component is also known in the profile of the genetic predisposition to TAA and AAA [77]. According to the data of A. Gyftopoulos et al. [57], genes related to AS, lipid metabolism, and tumor development are associated specifically with sporadic AAA, while genes controlling extracellular matrix structure (remodeling), and tumor growth factor β function are associated with both AAA and TAA. Contractile element genes uniquely predispose to ascending TAA [57]. In other words, both common (but with different significance for the risk of AA development) and specific (and they are the majority) genetic factors are known for AAA and TAA [57, 77].

Dyslipidemia plays a leading role in the development of the atherosclerotic process, and the risk profile of both hypercholesterolemia and AS (as in the case of AA) also includes polygenic and monogenic components [52, 56, 77]. Familial hypercholesterolemia, which is a risk factor for AS development, is registered in various populations with a frequency of 1 per 200–500 people [51, 78]. At the same time, the prevalence of familial hypercholesterolemia in individuals with cardiovascular diseases associated with AS is 10–20 times higher than in populations [78]. In some regions, the family history of atherosclerosis-related diseases reaches 30% [47], and patients with atherosclerosis-related diseases

in most cases have four or more chronic diseases at the same time [79]. Despite the presence of a monogenic component in the determination of both AS and AA, the spectrum of causative genes for these diseases is specific [61].

AS and AA are age-dependent diseases, but they can occur at any age. A younger age of manifestation is typical of hereditary and familial TAAs, an older age is typical of sporadic AAs [1, 68, 76, 80]. At the same time, even genetically determined TAAs manifest in patients aged from 17 to 89 years [68], indicating the presence of additional factors contributing to the clinical manifestation of pathogenic variants of monogenic and syndromic TAA genes.

The prevalence of AAA also increases with age: the incidence per 100, 000 population was 55 in men aged 65 to 74 years, increased to 112 at 75 to 85, and to 298 at 85 years and older [59]. Estimates of AAA prevalence (per 100,000 people) in 1990 varied from 8.43 cases among individuals in the age group of 40–44 years to 2,422.53 in the age group of 75–79 years, and in 2010 they were 7.88 and 2,274.82, respectively [42]. For familial AAA cases, the age at diagnosis is younger than in the case of sporadic forms (67.8 and 70.2, respectively); 38.8% of patients with familial forms and 28.8% of patients with sporadic AAA were diagnosed before the age of 65 years [76].

The age at which AS is diagnosed also varies greatly. As in the case of monogenic AA, in hereditary hypercholesterolemia, signs of lipid metabolism disorders – and, consequently, AS – are seen at a young age (and even in children) [81]. In addition, the use of modern diagnostic techniques has shown that the first signs of AS can be detected in the population at a young age [65], but in general, the prevalence of AS increases with age [3].

The incidence of AA (TAA and AAA) and AS differs between the sexes [30, 42, 46, 69, 71, 76]. According to M.H.C.Pham et al., while the overall prevalence of AA among participants in the Copenhagen General Population Study was 2.1%, the incidence of this pathology was 4.0% in men and 0.7% in women [82]. The incidence of AAA is 4.1–14.2% in men and 0.35–6.2% in women [49]. Among patients with TAA, men account for 70% or more in some studies [34, 69, 71, 83]. AS manifests in women later than in men (10 years later on average in some populations) [46]. At the same time, earlier reports have shown no differences in the incidence of TAA between the sexes, but differences were recorded in the mean age of men and women (the age of patients ranged from 47 to 93 years, with a mean age of 65 years for men and 77 years for women) [36].

It should be noted that the combination of various risk factors in patients with AA may vary between different age cohorts, geographic regions, between sexes, between groups with familial and isolated forms of AA, with the presence or absence of syndromic or monogenic forms of AA, and even between AA of different locations. For example, compared with isolated ascending TAA, descending and mixed types of TAA are more often registered in men, in older individuals who smoke more often, have hypertension, type 2 diabetes mellitus (T2DM), and AAA [34].

The analysis of the published data showed a strong positive correlation between ascending TAA and genetic causes and a negative correlation with dyslipidemia, atherosclerosis, and diabetes, whereas the last three pathologies as well as hypertension are risk factors for descending AA [60]. According to the authors of the cited study, the data presented in the review support the hypothesis that ascending TAA is genetically mediated, and descending TAA is predominantly an acquired pathology [60]. The samples of patients with and without syndromic forms of TAA differ in the frequency of registration of risk factors, such as arterial hypertension, hypercholesterolemia, and diabetes mellitus [69]. Among patients with thoracic aortic dissection, the carriers of pathogenic variants in the genes of Mendelian forms of TAA had significantly lower rates of hypertension and smoking [68]. Despite the high heritability of BAV (from 47 to 89%), its incidence is higher in men than in women (9.2 vs. 3.5%, respectively) (cited in [84]). In the study by S. Ito et al., risk factors such as AS (intima-media thickness of carotid

arteries), smoking, hypertension, and type 2 diabetes mellitus were less significant for familial forms of AAA compared to sporadic forms [35]. Aortitis was more common in Asia, whereas in Western countries, inflammatory AAAs were commonly associated with AS [85]. At the same time, ethnicity is more significant as a risk factor in the AAA development (the risk of pathology is higher among Caucasians) than in the AS development [31].

TAA and AAA are also characterized by varying degrees of significance of different risk factors. CHD, chronic obstructive pulmonary disease, and diabetes mellitus are associated with the risk of AAA, while body mass index, arterial hypertension, and cerebral infarction are associated with TAA [35]. A recent population-based study [82] showed that common risk factors for TAA and AAA were sex, age, and body surface area; the specific risk factor for TAA was hypertension, and specific risk factors for AAA were hypercholesterolemia and smoking.

Additionally, there are also known risk factors not only with different significance for AA and AS, but also with multidirectional effects on the risk of their development, which some researchers find debatable. For example, diabetes mellitus, hypercholesterolemia, and obesity are highly significant for the development of AS, but their effects are not as expressed in AAA, whereas smoking, sex, and ethnicity are highly significant risk factors for AAA, but have a lesser effect on the risk of AS (cited in [31]).

In a number of studies, type 2 diabetes mellitus, which is a risk factor for the development of AS [31, 32], has been considered as a protective factor for AA [32, 64, 73, 86]. In patients with ascending aortic aneurysm (both with BAV and TAV), diabetes mellitus was documented at a frequency that was more than twofold lower than in individuals with a normal aorta [37]. Additionally, T2DM was less often identified in individuals with isolated ascending TAA (5%) compared to those with descending TAA (12%) and mixed type (13%) [34]. It is interesting to note that the presence of diabetes mellitus in patients with AAA was associated with a 43% reduction in the risk of developing both synchronous and metachronous TAA [38]. According to I.Y.Cho et al., this endocrine pathology led to a decreased risk of AAA development [64]. During dynamic follow-up (mean follow-up period was 23.1 years) of 5,381 individuals from Malmö Diet and Cancer Study cardiovascular cohort, no participant with diabetes mellitus at baseline developed isolated AAA [32]. At the same time, in some publications, type 2 diabetes is classified as a risk factor for both TAA and AAA [35].

Dyslipidemias may be regarded as one of debatable risk factors for AA and AS. A number of dyslipidemia-specific lipid parameters (higher levels of low-density lipoprotein (LDL) cholesterol and lipoprotein (a), lower levels of high-density lipoprotein cholesterol), have been demonstrated to correlate with the presence of such a risk factor for TAA as BAV [87]. In turn, hyperlipidemia is usually considered as a risk factor for AS and AAA [88]. However, according to different researchers, the lipid profile of patients with AAA is highly variable, particularly the levels of lipoprotein A [88]. Moreover, a higher probability of developing ascending TAA was identified in patients with relatively low LDL levels (at 75 mg/dl, OR = 1.21; 95%CI: 1.05–1.38), and a lower risk of aneurysm development was observed at high LDL levels (at 150 mg/dl, OR = 0.62; 95%CI: 0.46–0.84; at 200 mg/dl, OR = 0.29, 95%CI: 0.14–0.65) [89]. In an earlier study [21], the atherogenic lipid profile was found to be negatively associated with the diameter of the ascending aorta. Specifically, higher levels of high-density lipoprotein cholesterol and apolipoprotein A-I were associated with larger diameters, while higher levels of triglycerides and apolipoprotein B-100 were associated with smaller diameters of the ascending aorta.

The list of risk factors for AA and AS, which is presented in Table, is continually expanding. Atrial fibrillation, degenerative scoliosis, type 1 diabetes mellitus, chronic kidney disease, physical inactivity, and other factors have been considered as risk factors [2, 63, 90]. For example, adult degenerative scoliosis may act as a risk factor for aortic dilation and aortic

atherosclerosis [90]. The altered composition of the gut microbiota, as well as air pollutants, increases the risk of AAA, especially in individuals with a genetic predisposition [91, 92]. Sleep disorders, microbiome alteration, air pollution, environmental stress, etc. are considered as risk factors for the development of AS [93, 94]. At the same time, in some patients with AS, vascular risk factors are not detected at all [6]. Thus, a population-based study in China revealed no traditional risk factors for AS in 16% of patients, 1 risk factor – in 41.4%, 2 risk factors – in 21.3%, 3 and more risk factors – in 21.3% [6].

The study of risk factors for both AS and AA of different locations has recently undergone a significant shift towards the search for biochemical and molecular markers [89, 95–100]. However, even on the basis of the analysis of classical risk factors we can conclude the presence of both common and specific factors for AS and AA, as well as for AA of different locations, and, in addition, some relationships between different risk factors.

Thus, AA and AS differ in prevalence, but in both cases the age-dependent nature of the manifestation is found. Given the higher prevalence of AS compared to AA and the approximately equal age limits of manifestation of these pathologies, a high level of comorbidity of these diseases could be expected. On the other hand, despite the differences in AA and AS prevalence, they are both characterized by some common risk factors for their development, but with their different contribution to the risk structure of AS and AA development, as well as AA of different locations. Type 2 diabetes mellitus and, potentially, lipid parameters can be attributed to the category of factors with a multidirectional influence.

CONCLUSION

Different combinations of risk factors in patients may determine the features of the clinical patterns of AS, AA and their comorbidity [69, 101]. O. Leone et al. [69] demonstrated that BAV was more often registered in patients with TAA, in the case of a degenerative histological type of aorta; the group with atherosclerosis was older and exhibited higher incidence of hypertension, hypercholesterolemia, diabetes mellitus, current smoking, and CHD; the group with aortitis was the oldest, predominantly comprised of women, and exhibited high prevalence of classic cardiovascular risk factors, such as hypertension, hypercholesterolemia, and diabetes mellitus. Therefore, the inconsistency of comorbidity estimates across different studies may be related to the specific characteristics of the patient groups used in each study. In view of the above, in order to understand the causes for conflicting estimates of AA and AS comorbidity, it is important to apply an integrated approach to the characterization of patients with these aortopathies (both isolated and combined) with a detailed analysis of risk factors registered in the analyzed groups.

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