The Exploration of the Pathogenesis and Treatments of Atherosclerosis

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Abstract. Atherosclerosis (AS) is a chronic disease that has complex pathogens. There have been many papers about AS until 2025 because of the serious consequences of it. The influences of cholesterol and Inflammatory factors are the core of many papers' cores. Besides, the diagnostic and treatment methods are very important points in the application aspect. However, the new methods which are used in practice are still inequitable. This article analyzes the mechanism of AS and many important factors which can impact the process of AS, such as CRP, IL-6 and TNF-α. At the same time, the advanced methods of diagnosing and treating are also discussed in this article. LDL and HDL cholesterol can increase and decrease the risk of AS respectively, many inflammatory factors can aggravate the illness by promoting the increase of immune cells. The CT can be used to diagnose the disease, Colchicine, Methotrexate and Statins can control the process of AS.

Keywords: Atherosclerosis, Lipid Metabolism, Inflammation.

1. Introduction

Cardiovascular diseases (CVDs) are global, with high mortality and high prevalence. In China, until 2020, CVD was the dominant cause of death of residents. The mortality rate of residents is 45.86% and 48.00% in urban and rural areas respectively [1]. In developing countries, with the decrease in epidemic diseases, the chronic disease caused by atherosclerosis (AS) and hypertension has been a primary health problem. Although advanced technology and medical therapy have been used, recurrence rate of acute coronary syndromes in the first year is up to 10% to 20% [2]. It means CVD is one of the most important public health problems that can affect the lifespan, health and quality of life of the residents nowadays.

AS is an important cause of CVD, it attracts lots of attention from many experts and scholars. AS is a chronic disease with complex causes. It is characterized by plaques formed by the accumulation of cholesterol, lipids, cell debris and immune cells. The inducements of AS include hypertension, hyperlipidemia, diabetes, smoking, etc [3]. With the development of modern society, many new causes of AS enter the perspective of people's research such as air and noise pollution, sedentary lifestyle, psychological pressure, intestinal flora maladjustment, etc [1]. Plaques that are in arteries rupture and flow with blood, leading to inflammatory reactions and causing the narrowing or blockage of arterial blood vessels. In addition, there are four stages of the progression of the AS. They are fatty streaks, fibrous plaque, atheromatous plaque, and secondary lesions [4]. In the end, it results in many complicated diseases such as acute CVD [4], stroke and organ ischemia. During the last few decades, advanced results have been achieved in the study of the functions of monocyte, macrophages, T-cell and smooth muscle cells, and their impacts on diseases [2]. By the studies of inflammatory factors and proteins such as IL, CRP and TNF-α, now besides statins, many medicines can be used to treat AS such as Canakinumab, Colchicine and methotrexate [1]. At the same time, emerging methods of disease treatments, like validated genetic markers, can increase the possibility of targeted therapy for this disease accurately. Due to the serious symptoms and universality of this disease, the research for it is necessary to proceed.

This article focuses on recording and summarizing the influence factors and cutting-edge treatment technologies of AS. Under the existing research conditions and the background of disease, it aims to discuss the principles, advantages and disadvantages of mainstream treatment methods and strive to make contributions to research of AS in the future.

2. Lipid Metabolism

As is caused by the imbalance in lipid metabolism and the follow-up inflammatory response in the arterial wall. And the macrophage, which is rich in cholesterolis, is the main trigger. When there is a Massive accumulation of Apolipoprotein B (ApoB), which is rich in cholesterol in the endothelium, it will lead to the formation of plaques and lead to the onset of AS [5]. Low-Density Lipoprotein (LDL) and High-Density Lipoprotein (HDL) are playing important roles during this process.

2.1. LDL

LDL and oxidized LDL (oxLDL), which is a product of its oxidative modification can derive oxidized phospholipids. The oxidized phospholipids can activate macrophages and immune responses of other nearby cells like antigens, for example, activating endothelial cells (ECs) by stimulating the expression of several cell surface adhesion molecules [6, 7]. Thus it can be seen that the increase of oxLDL and LDL will cause the further deterioration of AS because of the increase of Inflammatory substances. Consequently, the impact of the diseases and the danger of patients with CVD and cerebrovascular diseases make these two substances become the biological indicator which is applied in clinical medicine to detect AS. For example, measuring oxLDL antibody can be used as the method of monitoring risk of CVD and classifying patients because the high level of oxLDL may cause the risk of cerebrovascular recurrence [6]. Besides LOX-1 which is the receptor and can clean up the oxLDL acquires importance because it can mediate many reactions about oxLDL such as ECs' inflammatory responses and the activation of macrophages [6, 7]. The reactions it lead to are critical reactions which can impact the disease process of AS directly.

2.2. HDL

According to research, HDL has obvious characteristics of anti-atherogenic. Menno Vergeer demonstrated that each 1 mg/dl increase of HDL-C levels can decrease the risk of CVD by about 2-3%. So it has been confirmed that HDL cholesterol concentrations show a negative correlation with risks of CVD [8]. It means researching HDL can provide the new methods for curing AS. Because HDL can be the receptor of cellular cholesterol, it can accomplish reverse Cholesterol Transport (RCT) theoretically [8]. In the existing methods of treating AS, most of them focus on slowing down the disease's process and avoiding the formation of complications. So if HDL can be used to treat AS, it will provide patients with CVD the possibility of curing the disease and improve survival rates of them.

3. Inflammation

3.1. CRP

The C-reactive protein (CRP) is the important index for judging diseases and it is related to the risk of CVD. CRP is the calcium dependent ligand-binding pentraxin and it can be activated by the cytokines interleukin (IL)-6 and IL-1βand trigger the immune responses [9]. So the increase of CRP will raise the risk of AS. However, the level of CRP is only a symbol which marks the process of diseases. B.G. Nordestgaard proved that the genetic increase of CRP will not elevate the risk of CVD by Mendelian randomization studies [10]. Although CRP is a type of inflammatory factor, it is not the morbidity factor of AS.

3.2. IL-6

IL-6 is a type of immune factor that is well-known and important. IL-6 signalling can improve myeloid cells of the immune system and the vasculature and cause the development of AS. However, it has been demonstrated that IL-1β blockade can decrease the possibility of the recurrence of this disease in patients who has AS and over 60 years old [11]. So the therapy of resisting it can obtain

the effective results. Besides, IL-6 is confirmed that it related to the age-related atherosclerosis and it may be mede by the senescent adipocytes [11].

3.3. TNF-α

The tumor necrosis factor α (TNF-α) is an important factor of immunotraction. The activation of NF-κB will contributes to the synthesis of TNF-α and the TNF-α which is new will promote the activation of NF-κB more [12]. In addition, in the study of Gayle E. McKellar, TNF-α can accelerate the process of AS by leading to the endothelial cell apoptosis and avioding the cell recovery [13]. So TNF-α will raise the risk of having AS chronically. Finally, it will lead to the accumulation and the thickening of the plaque which is the cause of the disease in the arteries.

CRP, IL-6 and TNF-α are all immune factors produced by immune cells and they will aggravate the AS. So how to detect them and control them is the main direction of research. In the future, there will be more studies around these immune factors.

4. Vascular Endothelial Function

During the onset of the complicating diseases of AS such as stoke, new vessel formation inside the arterial wall is the primary factor and it contains two mechanism: ischemia and inflammation. And angiogenesis, arteriogenesis, and vasculogenesis are included in the formation of neovascularization [14]. So the treatment of targeting vascular aging and hyperplasia will be the efficient method.

5. Diagnostic and Treatment Method

AS is a chronic, tardy, impalpable and gross disease. It is hard to discover for patients or doctors and it is difficult to treat and completely cure. In the existing cases, preventing AS in advance is the best and the leading treatment. Nevertheless, as for patients who have been attacked by the AS, there are also some methods to slow down and observe the process of it. At the same time the causes of it are very complexed. So many researchers and doctors are pay attention to studying it, diagnosticing it and trying to treat it. Next may methods about AS will be shown.

5.1. Diagnostic Method

Though the physical symptoms of AS does not show as many as other illness such as rheumatism, the diagnostic methods in clinic are the very important way to help people control and realize the process of disease. Seeing the organ ischaemia and visualization of atherosclerosis directly is viewed as the main way to definitive diagnosis, for example, CT angiography is regarded as a invasive way and invasive angiography is regarded as invasive way to indicate the treatment [15].

5.1.1 CT

There are many ways to diagnose the AS. Aortic valve calcification (AVC) can lead to the vascular occlusion and stenosis. And the calcium score on CT can show the situation of the AVC. Toshiro Kitagawa thinks 18F-NaF, which can increase the risk of AVC and lead to AS by increasing and its molecular conditions, can be detected by 18F-NaF PET/CT [16]. This advanced and practical molecular imaging can help people to control this disease.

5.1.2 Angiography

Coronary computed-tomography angiography (CCTA) is a newer technology than Invasive coronary angiography (ICA) which is the only way to check the arteria coronaria before. Joachim Eckert put forward that it can test coronary artery disease with precision. But the results it did may have problems that the severity may be overrated [17].

The two methods listed in this article have undergone development over few decades of development have made a lot of improvement and created more opportunities to detect the disease in safer, cheaper and more sensitive ways.

5.2. Medicine Treatment

How to treat the AS is a longstanding topic in the medical care personnel and researchers for a long time. Nowadays, many potential and useful drugs such as Colchicine, Methotrexate and Statins are studied widely by the professional people. In this article, these medicines will be discussed in detail. The mechanism of action, curative effects, merits and demerits of these drugs will be shown. Besides, the different views from different researchers around the situation of usage will be listed.

5.2.1 Colchicine

Colchicine is a type of botanical alkaloid which can be extracted from Colchicum autumnale. It can avoid the neutrophile granulocyte adhering endothelium and restrict its ability to deform and move. At the same time, it can also affect platelets' function [18]. It means Colchicine can be a possible type of effective medicine for AS due to its pertinence of the immune factors which trigger the disease. According to the research by Leticia González, the usage of Colchicine can decrease the myocardial damage of patients who have finished coronary bypass [18]. If this drug can become a service for treating the AS, it will be the new therapeutic direction.

5.2.2 Methotrexate

Methotrexate is a type of drug that has a long history of use in treating cancer. However, in recent decades, it was found that the potential of stabilizing vascular function and blood pressure [19]. It means if more studies are used to research the effect of this substance, there will be more medicines to avoid AS. Arduino A. Mangoni. et discuss the effect of this drug by injecting it (which is the safer way than take it directly). They found that Methotrexate can inhibit the synthesis of purines and pyrimidines through restraining the effect of enzymes [19]. And it can decrease the mortality of patients who are under CVD.

5.2.3 Statins

Statins are a drug that is widely used for AS. It can decrease the LDL cholesterol synthesis in the liver and increase the number of LDL receptors, and decrease the incidence rate of CVD by about 30% [20]. It is no doubt that statins are efficient and useful. However, Okuyama H. et al. presented an opposite point that statins may cause the calcification of coronary artery [21]. So the usage about it is controversial and worth to exploring. More research and discussion in the future will be worth expecting. These medicines show the effect of the immune factors and the regulation effect of the immunoreaction. In the future, there will be more treatments based on these drugs and the research about them.

6. Conclusion

By analysing the mechanism, causes and control methods of the AS which is a complex, common and chronic disease, the details and the treatments are shown in this article. The results provide the possibility for the researchers in the future to become easier to find the directions and the potential for AS and CVD which are the main topic of this article. It is worth noting that this article sums up the research status nowadays based on the different papers from different authors. Because of the high prevalence, AS troubled the patients and professionals for many years. And in the future, its prevalence and mortality can be decreased due to the advanced study of the methods listed in this article. But as the heated discussion and the contrary views mentioned above, the specific, correct and entire solutions still take people's time to explore. In author's opinion, although the disease is refractory, the new solutions are ambiguous and the causes are complexed, the improvement of the technology is rapidly increasing.

However, in this article many problems are still existing, for example, the study samples are not sufficient. And the viewpoints cited in the article are mostly hypotheses, which may lead to the mistakes in this study. In years to come, due to the adherence to the study by professionals, more and safer ways to treat the disease will be achieved.

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