Original Article

Role of Autoantibodies Against Self-Proteins, Mitochondrial Cellular Antigens, and Some Complement Proteins (C3 and C4) in Patients with Atherosclerosis

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Abstract

Background: Atherosclerosis (AS), a chronic arterial inflammatory disease, has drawn widespread attention due to its persistent progression and significant problems later in life. Some causes are contributing to atherosclerosis development, including autoantibodies and cellular immunity, both contributing to damage of the vessel wall. **Objectives:** This case-control study aimed to explore the role of autoantibodies and other components of the immunity system on the development of atherosclerotic plaque from stable to unstable angina. **Materials and Methods:** The colorimetric method was used to measure the concentration of lipid profiles, whereas the antinuclear antibodies (ANA), anti-mitochondrial antibodies (AMA), and anti-extractable nuclear antigen (ENA) were measured by chemiluminescent immunoassay. Finally, the complement components C3 and C4 were measured using nephelometry. **Results:** The results found that the male patients showed a higher frequency (66.6%) compared to females (33.4%). Furthermore, antibodies (Abs) against the self-protein antigen (ANA) were increased in the serum level of patients (82.2 ± 10.2) to healthy controls (12.2 ± 2.6) with a high significant difference ($P = 0.008$). Additionally, the concentration of Abs against mitochondrial antigens illustrated a high significant difference ($P = 0.001$) between the mean of patients (22.0 ± 2.4) and in healthy controls (3.4 ± 0.9). Notably, the odd ratio (OR) of the results of the antibody tests was high. Furthermore, C3 and C4 were also raised in the serum compared control group, with a highly significant difference. **Conclusion:** The antibodies against self-proteins, particularly mitochondrial antigens, are considered risk factors for increasing atherosclerosis plaque and developing unstable angina.

Keywords: AMA, ANA, Atherosclerosis, C3 and C4

Introduction

Atherosclerosis, a multifaceted and progressive disease, significantly contributes to cardiovascular disorders and ranks among the leading causes of morbidity and mortality worldwide.[1] The condition is characterized by the gradual accumulation of fatty plaques within arterial walls, resulting in the narrowing and hardening of blood vessels.[2] These plaques, comprised of cholesterol, lipids, calcium, and cellular debris, significantly contribute to the development of numerous cardiovascular conditions, including coronary artery disease, myocardial infarction, and stroke.[2,3] The pathogenesis of atherosclerosis encompasses a complex interplay of genetic, environmental, and lifestyle factors. Chronic inflammation is crucial to starting and maintaining this complex process.[4] Immune cells are drawn to the artery wall due to endothelial dysfunction brought on by conditions like high blood pressure, smoking, and raised cholesterol levels. Among these immune cells, macrophages are vital because they absorb lipids and

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develop into foam cells, which help atherosclerotic plaques grow.[5]

Atherosclerosis depends on chronic inflammation, which acts as a catalyst for plaque development. Multiple assaults cause endothelial dysfunction, which attracts immune cells, including monocytes and T cells, to the artery wall.[6] The emergence of autoantibodies that target self-antigens in this inflammatory milieu worsens the disease process.[7] Notably, autoantibodies, especially those that are anti-oxidized low-density lipoprotein (ax-LDL) antibodies, have contributed to the formation and instability of plaques.[8-10] Autoantibodies have the potential to function as biomarkers for both diagnosis and prognosis, in addition to contributing to the pathogenesis of atherosclerosis. Their clinical significance is emphasized because having them in circulation has been linked to a higher risk of cardiovascular events.[11,12]

Autoantibodies may also control inflammatory responses, promote the growth of foam cells, and impact plaque stability, among other functional consequences.[6,13] Atherosclerosis affects the arterial walls locally and systemically throughout the cardiovascular system. Blood vessel narrowing reduces blood flow, which reduces the amount of nutrients and oxygen that can reach vital organs and tissues; this reduced blood flow may cause claudication, angina, or even more severe issues, including heart attacks or strokes.[14] Additionally, some autoimmune conditions, including systemic lupus erythematosus and rheumatoid arthritis, are linked to a higher risk of atherosclerosis, and the chronic inflammation that characterizes these disorders is probably what causes this association.[15,16]

Furthermore, the immune system's critical white blood cell, the monocyte, is linked to the emergence of atherosclerosis.[17] A persistent inflammatory condition of the arteries called atherosclerosis can cause heart disease, strokes, and other vascular issues. In this condition, monocytes are drawn to the artery walls, undergoing a macrophage-differentiation process. Macrophages carry out the task of ingesting and digesting foreign matter, including oxidized LDL cholesterol, a kind of cholesterol that can harm the lining of the arteries in the case of atherosclerosis.[18] As macrophages gather inside the artery walls, they develop into foam cells, which are distinguished by their high lipid content. These foam cells are crucial in forming atherosclerotic plaques, which cause arteries to constrict and obstruct blood flow. Ruptured atherosclerotic plaques can occasionally cause serious cardiovascular problems like heart attacks or strokes.[19]

It is necessary to fully comprehend how atherosclerosis, autoantibodies, and autoimmunity are related. However, the information suggests that autoantibodies may be involved in the onset and development of atherosclerosis. Autoantibodies are proteins produced by the body against its own tissues. Autoantibodies are believed to target oxidized LDL cholesterol or other elements of atherosclerotic plaques in atherosclerosis. Inflammation and additional plaque growth could result from this.[12,20] Autoantibody research is a rapidly developing field as we learn more about it. It is essential to investigate their origins, modes of action, and interactions with other immune system components to create novel therapeutic approaches and individualized treatment plans for this condition. Understanding the complex interactions between autoantibodies and atherosclerosis may open new possibilities for early identification, risk classification, and targeted therapies.

This article thoroughly explains atherosclerosis with a focus on the part that autoantibodies play in the intricate disease process. The development of autoantibodies, how they could affect plaque formation and stability, and their clinical ramifications are all covered in this article. The article shows the opportunities and challenges within this sector by providing a detailed study of cutting-edge research. This opens the door for more research and breakthroughs in identifying, preventing, and treating atherosclerosis.

Materials and Methods

Study design

This prospective study examined the relationship between immunological factors and atherosclerosis. Three hundred participants with atherosclerosis, with a mean age of 41, were enrolled in the study. A control group of 300 people, with a mean age of 42, who had no smoking habits and no chronic illnesses, was also gathered.

Study subjects

Three hundred patients with atherosclerosis were studied. A detailed history, regarding duration, precipitating factors, treatment, past and family history, diabetes mellitus, and hypertension, was recorded. These 300 atherosclerotic patients were chosen based on various factors, including blood tests, clinical symptoms, and professional medical judgments. Three hundred age- and sex-matched controls were tested.

Biochemical parameters

Cholesterol, Triglyceride, HDL, and LDL levels were examined to determine the risk factors in patients and control groups, and colorimetric methods were used to measure them.

Immunological parameters

Serum was collected for the detection of autoantibodies. Anti-mitochondrial (AMA), antinuclear antibodies (ANA), and anti-extractable nuclear antigen (ENA) were detected using chemiluminescent immunoassays. Complement C3 and C4 levels were measured by nephelometry methods.

Statistical analysis

Statistical analysis was carried out using the statistical package for the social sciences (SPSS) version 28.0 (SPSS, IBM Company, Chicago, IL 60606, USA). The GraphPad 8.0.2 software (GraphPad Software, San Diego, CA, USA) was also used to analyze the data. For demographic and clinical variables, descriptive statistics, including means, standard deviations, and frequencies, were computed. Comparative analyzes, such as *t* tests or chi-square tests, were to assess the variations between atherosclerosis and control groups.

Ethical approval

The study was conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki. It was carried out with the patient's verbal approval before a sample was taken. The study protocol, subject information, and consent form were reviewed and approved by a local ethics committee according to document number 561 on April 25, 2023.

Results

Patients in this study showed that the percentage of male participants was higher (199%/66.6%) compared to females (101%/33.4%).

Table 1 presents the lipid profiles, which include cholesterol, triglyceride, HDL, and other parameters, along with the detection of odd ratio (OR) for all items. The result showed a highly significant difference ($P = 0.007$) between the mean of Risk-1 patients (16.3 ± 2.4) compared to healthy controls (1.5 ± 0.8), and it reached an OR = 5.9, which is very high, indicating a positive association with the disease. Furthermore, Risk-2 also increased in the patients (13.6 ± 2.6) compared to the controls (1.5 ± 0.8) with high significance ($P < 0.001$) and a high OR = 4.1.

The result of leukocytes, particularly monocytes, show increased average count in patients, with a mean of $1.6*10^3 \pm 22.2$, conversely noticed in the control ($2.1*10^2 \pm 1.6$) at a high significant difference ($P = 0.002$), as shown in Figure 1.

Figure 2 presents the mean levels of antibodies against multi-antigens, such as self-proteins of cell and mitochondrial antigens. We found that the antinuclear

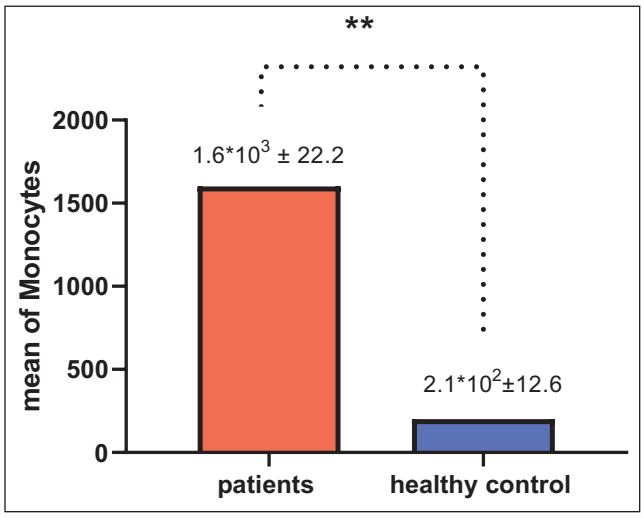

Figure 1: Mean levels of monocytes in patients compared with healthy controls

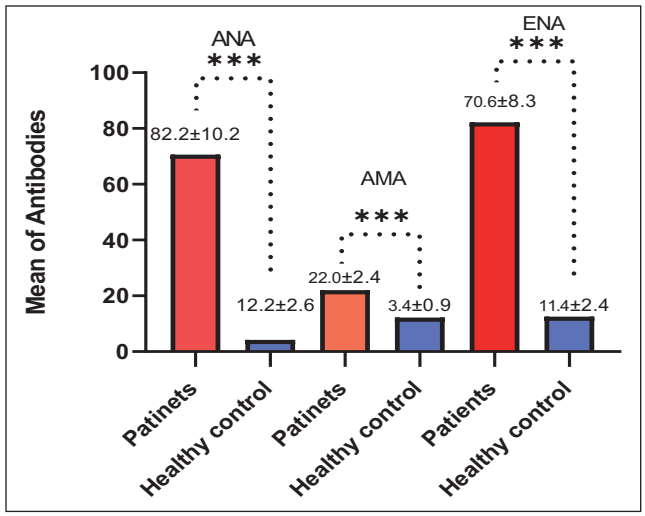

Figure 2: Mean levels of antibodies against multiantigen in patients compared with healthy control

Table 1: Means of lipid profile in patients compared with health control

Lipid types	Patients	Healthy control	OR	95% CI	*P* value
	Mean ± SD				
Cholesterol	400.2 ± 21.2	102.3 ± 10.2	5.6	5.0–7.8	0.007***
Triglyceride	308 ± 19.6	94.3 ± 5.6	6.9	5.9–7.5	0.008***
HDL	24.5 ± 3.6	65.6 ± 10.6	2.1	1.8–2.8	0.004***
VLDL	41.1 ± 4.4	18.8 ± 2.4	2.0	1.5–2.4	0.001***
LDL	160.3 ± 16.6	60.6 ± 2.6	4.2	3.5–4.9	0.008***
Risk-1 (CHOL/HDL)	16.3 ± 2.4	1.5 ± 0.8	5.9	4.9–6.8	0.007***
Risk-2 (LDL/HDL)	13.6 ± 2.6	0.27 ± 0.09	4.1	6.2–8.1	0.001***

***Significant value at 0.05, OR: odd ratio, CI: confidence interval, HDL: high-density lipid, VLDL: very low-density lipid, LDL: low-density lipid

Table 2: Mean concentrations of immunological

Antibodies against Ags	Patients	Healthy control	OR	95% CI	*P* value
	Mean ± SD				
ANA	82.2 ± 10.2	12.2 ± 2.6	7.6	4.5–6.2	0.008***
ENA	70.6 ± 8.6	11.5 ± 1.7	4.2	6.2–8.1	0.006***
AMA	22.0 ± 2.4	3.4 ± 0.9	6.5	5.2–7.2	0.001***

***Significant value at 0.05, OR: odd ratio, CI: confidence interval, ANA: antinuclear antibodies, AMA: anti-mitochondrial antibodies, ENA: extractable nuclear antigen, Ags: antigens

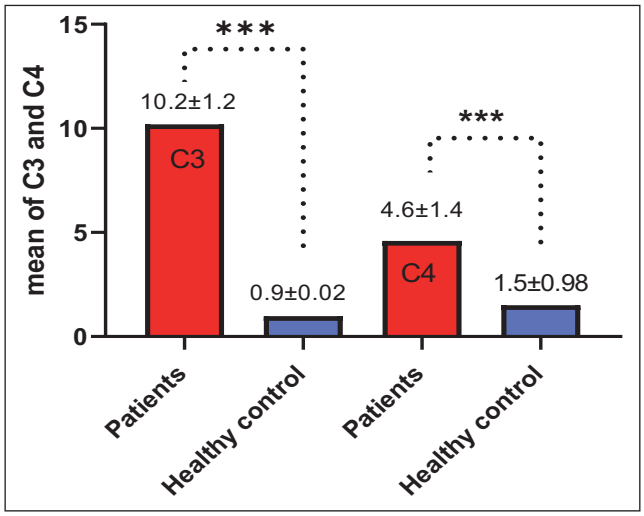

Figure 3: Mean concentration for complement proteins C3 and C4

antibodies (ANA) were a highly significant difference ($P = 0.008$), with the mean serum concentration of Abs in patients being higher (82.2 ± 10.2) compared to the control group (12.2 ± 2.6), typically for ENA. Furthermore, the mean concentration of antibodies against mitochondrial antigens in the serum of patients was increased (22.0 ± 2.4 AU/mL) compared to the control and observed a reduction in the mean (3.4 ± 0.9 AU/mL) with a significant difference ($P = 0.001$).

The results of OR for each antibody against antigens are shown in Table 2. The results of ANA and AMA demonstrated that the OR was high, where ANA scored the highest (OR = 5.6) in patients, and AMA scored OR = 6.5. Notably, the result found an increase in OR of ENA (OR = 4.2).

Figure 3 presents the concentration of complement proteins C3 and C4, revealing that both C3 and C4 increased in the serum of patients compared to the control. C3 was scored 10 ± 1.2 in the patients and 0.9 ± 0.02 in the control with a high significant difference between them ($P = 0.005$). Furthermore, the concentration of C4 was also higher in patients (4.6 ± 1.4) compared to control group (1.5 ± 0.98) with a highly significant difference ($P = 0.002$).

Discussion

In the current study, results showed increased average numbers of patients with atherosclerosis plaque in males compared to females of matching age. This difference belongs to several reasons, we suggested, including males' greater exposure to environmental factors and higher stress levels in males. Our suggestion agreed with Vakhtangadze *et al.*,[21] who demonstrated that male suffering from atherosclerosis incidence than females due to their negative exposure to a difficult lifestyle.[21]

Table 1 displays the lipid profile in patients and healthy controls. A comparison between the patient and healthy control groups reveals notable differences in cholesterol, triglycerides, and LDL levels between the two groups. The findings highlight that the patient group generally exhibits higher mean cholesterol, triglycerides, and LDL levels than the healthy control group. This discrepancy suggests a potential association between dyslipidemia and the presence of the condition under investigation, and these increases in all lipid risk factors of lipid have a strong probability for the formation of atherosclerotic plaque, where the blood of patients has free radicals that oxidation of lipid to conversed for foreign antigen will allow the immune response and initiate the inflammatory plaque, Sharifi-Rad *et al.*[22] that agreed with the suggested by their study demonstrated that the increase of lipids in the blood leads to an inflammatory focus in the coronary vessels.[22] Elevated levels of cholesterol, triglycerides, and LDL are well-known risk factors for the development of atherosclerotic plaque and other cardiovascular diseases.[23] These findings highlight the significance of lipid profile assessment in the diagnosis, treatment, and follow-up of individuals with the illness under investigation. The observed variations in lipid parameters imply that dyslipidemia-specific therapies may help control and avoid the condition.

In addition, Figure 2 shows the average monocyte levels in individuals with atherosclerosis compared to a healthy control group. According to the results, patients with atherosclerosis have higher mean counts of monocytes than the healthy control group. Consequently, we believe that monocyte differentiation to foam cells after engulfing oxidant lipids accumulated on the wall of vessels which helps atherosclerotic plaques grow and develop into unstable angina. Finally, it is also plausible that the monocytes of people with atherosclerosis are different in some way, which increases the likelihood that they will develop into foam cells. It is an essential observation that

atherosclerosis patients have high amounts of monocytes. It implies that the immune system has a role in the development of the disease, and it may be used to identify people at risk of complications.[17,18,24,25]

The mean levels of antinuclear antibodies (ANA) and anti-ENA in patients with atherosclerosis are also shown in Figure 3, and Table 2. These values are contrasted with those in a healthy control group. According to the results, patients with atherosclerosis have higher mean levels of ANA and anti-ENA compared to healthy control group.

This study has argued that autoantibodies contributed to the development of atherosclerosis to unstable angina by increased growth of atherosclerosis plaques and trigger complements protein to damage plaque and cause clot formation and cause complicated diseases such as myocardial infarction. There are a few theories, though. According to one view, the damage brought on by atherosclerosis may result in the production of ANA and anti-ENA. The arteries release proteins when injured, which might cause an immunological reaction. Anti-ANA and anti-ENA can be produced because of this immunological reaction. There is also the possibility that cells involved in the growth of atherosclerosis have ANA and anti-ENA. For instance, immune cells called macrophages, which assist in removing the body's injured cells and waste, can produce ANA and anti-ENA. ANA and anti-ENA may also be indicators of inflammation, to sum up. Inflammation is a common feature of atherosclerosis, and ANA levels may be elevated in response to the inflammation.[6,26,27]

Furthermore, the mean levels of anti-mitochondrial antibodies (AMA) in patients with atherosclerosis are also shown in Figure 3 and Table 2 compared to a healthy control group. According to the research, patients with atherosclerosis have significantly higher mean AMA levels compared to the healthy control group. An anti-mitochondrial antibody, or AMA for short, is created in reaction to injury to mitochondria, the cell's energy-producing organelles. There are a few reasons why AMA levels might be high in atherosclerosis patients. One possibility is that the damage to the arteries that is caused by atherosclerosis can also damage mitochondria in the cells of the artery walls. This could lead to the production of AMA. This idea has not been argued by other researchers, but they are satisfied with the role of other antibodies in atherosclerosis.

Besides, Figure 3 displayed the mean concentrations of complement proteins C3 and C4 in the patient group compared to the control group. The data indicates that the mean concentrations of C3 and C4 are significantly higher in the patient group compared to the control group. C3 and C4 are two of the most important components of the complement system, a group of proteins that help the body fight infection.[28] In atherosclerosis, the complement system is activated, which leads to the production of C3 and C4. C3 and C4 levels are elevated in atherosclerosis patients for several causes.[29,30] One explanation is that atherosclerosis causes an inflammatory response, which includes activation of the complement system. Atherosclerosis frequently exhibits inflammation, which is thought to contribute to the disease's onset. The fact that the complement system is engaged in the removal of apoptotic cells is another factor contributing to the high levels of C3 and C4 in atherosclerosis patients. Cell death, known as apoptosis, can cause an accumulation of apoptotic cells in the arterial walls.[31,32] The synthesis of C3 and C4 may result from the complement system's assistance in removing these cells from the artery walls.[33-35]

Conclusion

Atherosclerosis is a major cause of illness and death globally, raising concerns about the value of research in this area. In accordance with the present results, the antibodies of self-proteins, mitochondrial antigens, other antigens such as oxidized fat, and complement proteins C3 and C4 were considered risk factors and contributed to the atherosclerosis plaque and developing to unstable angina. We will hope to conduct genetic studies to analyze this problem and find solutions.

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Conflicts of interest

There are no conflicts of interest.

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