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Interaction Of Genetic Predisposition And Environmental Factors In The Development Of Atherosclerosis

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Abstract: Atherosclerosis is one of the most common cardiovascular diseases and a major pathology contributing to increased mortality. This article analyzes the interaction between genetic and environmental factors in the development of atherosclerosis based on current scientific literature. The aim of the study is to identify the combined role of inherent, hereditary characteristics and external environmental factors in predisposing individuals to certain diseases and to assess their interrelationship. The methodological basis involved a comparative analysis of international medical journals, clinical studies, and molecular-genetic research findings.

The analysis demonstrates that mutations in the LDL receptor gene, which regulates low-density lipoprotein levels in the blood, and APOE polymorphisms, i.e., small variations at specific locations in the APOE gene that exist among individuals, influence lipid metabolism and thereby modulate the risk of atherosclerosis. Overactivity of the PCSK9 gene disrupts the mechanism controlling LDL cholesterol levels, increasing the likelihood of atherosclerosis. Environmental factors enhance the manifestation of these genetic changes through epigenetic mechanisms, which modify gene expression without altering the DNA sequence. The results highlight the complex etiology of atherosclerosis and emphasize the necessity of considering gene-environment interactions in developing preventive strategies.

Keywords: Atherosclerosis, genetic factors, environmental factors, gene-environment interaction, epigenetics, dyslipidemia.

Introduction: Atherosclerosis is currently recognized as the cardiovascular pathology with the highest mortality rate worldwide. According to the World Health Organization, cardiovascular diseases remain the leading cause of global mortality [1]. This trend is also observed in Uzbekistan, where over 60% of deaths are attributable to diseases of the circulatory system, highlighting the regional relevance of the problem [2][3].

Recent epidemiological studies have demonstrated that congenital predisposition, hereditary lipid metabolism disorders, and APOE gene polymorphisms play a significant role in the development of atherosclerosis [4]. Additionally, environmental factors—such as poor nutrition, hypercholesterolemia (elevated blood cholesterol levels), tobacco use, stress, and air pollution—further exacerbate the pathogenesis of the disease [5]. Modern scientific literature interprets atherosclerosis not merely as a lipid metabolism disorder but as a complex multifactorial disease that develops under the combined influence of genetic and environmental factors.

The aim of this article is to analyze the interrelationship between genetic and environmental factors in the development of atherosclerosis based on current scientific sources and to assess their role in the pathogenesis of the disease.

METHODOLOGY

This scientific article was prepared using the method of scientific-theoretical literature analysis. During data collection, international scientific databases such as PubMed, Scopus, Google Scholar, and Web of Science were utilized. The analysis included fundamental and clinical studies published in recent years, focusing on atherosclerosis, congenital predisposition,

environmental risk factors, and gene-environment interactions.

During the analysis, the molecular mechanisms involved in atherosclerosis development, including disruptions in lipid metabolism, APOE gene mutations, and PCSK9 gene activity, as well as the influence of environmental factors, were comparatively examined.

RESULTS AND DISCUSSION

1. Role of Genetic Factors in Atherosclerosis Development

Genetic predisposition is recognized as an independent risk factor in the pathogenesis of atherosclerosis. Literature analysis indicates that variations in genes regulating lipid metabolism contribute to the early onset of the disease [6].

LDLR gene: Mutations in the gene encoding low-density lipoprotein (LDL) receptors lead to familial hypercholesterolemia. In this condition, LDL levels rise sharply, accelerating the formation of atherosclerotic plaques even in early life [7][8].

APOE and PCSK9: The ε4 allele of the apolipoprotein E (APOE) gene, which regulates the distribution of fats and cholesterol in the blood, is frequently observed in groups at high risk of atherosclerosis. Additionally, the PCSK9 gene, which regulates LDL receptor activity, may harbor gain-of-function mutations that enhance LDL receptor degradation, thereby increasing lipid accumulation in the vascular wall [9][10].

Inflammation-related genes: Genetic factors also influence the vascular wall's susceptibility to inflammation. IL-6 and TNF-α are signaling proteins that regulate inflammatory and immune responses, playing a crucial role in atherosclerosis [11]. Polymorphisms in the genes encoding these cytokines contribute to endothelial dysfunction, i.e., impaired functioning of the inner lining of blood vessels [12][13].

2. Environmental Factors: The Impact of External Stressors

Environmental factors act as catalysts that trigger the expression of genetic predisposition.

Diet: Diets rich in trans fats and saturated fatty acids, as well as foods high in low-density lipoproteins, lead to dyslipidemia—elevated blood lipid and cholesterol levels—and consequently increase the risk of atherosclerosis two- to threefold [5].

Air pollution: Recent studies indicate that fine particulate matter in ambient air, such as PM2.5, adversely affects not only the lungs but also the cardiovascular system. These particles induce systemic inflammation and vascular damage through oxidative stress, i.e., an increase in harmful free radicals in cells [14].

Smoking: Free radicals present in tobacco smoke accelerate the oxidation of LDL, initiating the early stages of atherogenesis.

3. Epigenetics: The Bridge Between Genes and Environment

Epigenetic mechanisms play a decisive role in understanding the interaction between genetic and environmental factors. Epigenetics refers to the regulation of gene activity without altering the DNA sequence [15].

Research has shown that environmental factors significantly affect gene expression through epigenetic mechanisms, such as DNA methylation and covalent histone modifications. DNA methylation is an epigenetic mechanism that regulates gene activity by "activating" or "silencing" genes without changing the nucleotide sequence of DNA. For example, exposure to smoking alters the methylation levels of the AHRR and F2RL3 genes; these changes are considered molecular biomarkers that increase the risk of atherosclerosis. Thus, adverse environmental factors can activate previously silent pathogenic genes through epigenetic pathways.

4. Integrative Model of Gene-Environment Interaction

Analyses indicate that the relationship between genetic mutations and environmental factors is not simply additive but synergistic, meaning that they amplify each other's effects. This implies that the combined impact of genetic risk and environmental exposure increases the risk of atherosclerosis more strongly than either factor alone [13].

Clinically, for example, an individual carrying the APOE ε4 allele who smokes and consumes a high-fat diet develops atherosclerosis several times faster than a person without this genetic variant. In other words, a healthy lifestyle can partially mitigate genetic risk, whereas harmful environmental factors can exacerbate hidden genetic susceptibility and promote disease progression.

CONCLUSION

The complexity of atherosclerosis etiology lies in the fact that it should be viewed not only as an isolated genetic disorder or solely as the effect of environmental factors, but rather as the outcome of the continuous dynamic interaction between these two influences. The analyses conducted allow the following key conclusions:

1. Genetic background and triggers: Genetic predisposition represents an “inherited risk” that creates susceptibility to disease. For example, mutations in the LDL receptor gene or various forms

(polymorphisms) of the APOE gene provide a biological basis for the development of atherosclerosis. However, environmental factors such as smoking, poor diet, and air pollution act as accelerators through epigenetic modifications, effectively activating latent genetic risk.

2. Epigenetic potential: Although the genetic code itself cannot be altered, lifestyle modifications can positively influence gene expression, offering significant potential for preventive interventions.

Considering the study results and the epidemiological situation observed in Uzbekistan, the following practical recommendations are proposed:

Implement early genetic screening in families suspected of hereditary hypercholesterolemia.

Monitor PM2.5 particulate levels in urban areas and strengthen systems for warning the population on high-risk days.

Introduce personalized dietary and treatment plans based on the patient's genetic profile as part of atherosclerosis prevention programs.

This approach can serve as an important strategic step toward reducing mortality from cardiovascular diseases in Uzbekistan.

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