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Association of ESR1 G2014A and eNOS3 −786T>C Polymorphisms with Hormonal and Inflammatory Disorders in Postmenopausal Women with Coronary Heart Disease

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Abstract

Coronary heart disease in postmenopausal women is influenced by complex interactions between genetic predisposition, hormonal imbalance, and chronic inflammation. Declining estrogen levels contribute to endothelial dysfunction and increased cardiovascular risk, while genetic polymorphisms in key regulatory genes may further modulate disease progression. The analysis integrates genetic testing with biochemical assessment of estrogen levels and inflammatory markers to evaluate their combined impact on disease characteristics. The findings demonstrate a significant relationship between specific genetic variants and increased inflammatory activity, as well as more pronounced hormonal disturbances. These results highlight the importance of considering genetic factors in the evaluation of cardiovascular risk and support the development of personalized approaches to disease management. Evaluation of coronary pathology in women after menopause requires consideration of molecular determinants that influence vascular homeostasis. Genetic variations affecting estrogen receptor activity and nitric oxide synthesis contribute to disturbances in endocrine balance and inflammatory regulation. Integrated analysis of genetic, hormonal, and inflammatory indicators demonstrates that specific allelic combinations are associated with more pronounced systemic alterations. The proposed interpretation highlights the role of genetic background in shaping disease phenotype and emphasizes its importance for improving risk assessment and therapeutic planning.

Keywords: coronary heart disease; postmenopausal women; ESR1 polymorphism; eNOS3 polymorphism; estrogen deficiency; inflammation; genetic factors; endothelial dysfunction; cardiovascular risk; biomarkers

1. Introduction

Cardiovascular disease remains a leading cause of mortality among women after menopause, a period characterized by profound hormonal changes that affect vascular health. The reduction in estrogen levels leads to adverse alterations in lipid metabolism, vascular tone, and endothelial function, contributing to the progression of atherosclerosis. While traditional risk factors such as hypertension and metabolic disorders play a significant role, they do not fully explain the variability in clinical presentation and outcomes among patients. Increasing evidence suggests that genetic polymorphisms may influence individual susceptibility to cardiovascular disease by affecting key

biological pathways. The ESR1 gene encodes the estrogen receptor, which mediates the protective effects of estrogen on vascular tissues. Variations in this gene may alter receptor function and reduce the beneficial impact of estrogen, thereby increasing cardiovascular risk. Similarly, the eNOS3 gene is responsible for the production of nitric oxide, a critical regulator of vascular tone and endothelial integrity. Polymorphisms in this gene may impair nitric oxide synthesis, leading to endothelial dysfunction and enhanced inflammatory responses. Chronic inflammation is a central mechanism in the development and progression of coronary heart disease, contributing to plaque formation and instability. The interaction between genetic factors, hormonal imbalance, and inflammatory processes creates a complex network that determines disease severity. Understanding these relationships is essential for improving risk assessment and developing targeted therapeutic strategies. The postmenopausal period is accompanied by significant physiological restructuring that affects cardiovascular stability. Reduction in estrogen production leads to impaired vascular protection, altered lipid metabolism, and increased susceptibility to endothelial injury. These changes create favorable conditions for the progression of coronary atherosclerosis. However, clinical heterogeneity among patients suggests that additional factors modulate disease development. Genetic variability has emerged as a critical determinant influencing individual response to hormonal decline and vascular stress. The ESR1 gene plays a central role in mediating estrogen-dependent signaling pathways, while the eNOS3 gene regulates nitric oxide production, which is essential for maintaining vascular tone and preventing thrombosis. Alterations in these genes may disrupt normal regulatory mechanisms, enhancing inflammatory responses and accelerating vascular damage. Chronic low-grade inflammation further contributes to plaque formation and instability, establishing a link between molecular changes and clinical manifestations. Understanding the combined influence of genetic polymorphisms and biochemical disturbances is essential for advancing personalized approaches in cardiovascular medicine.

2. Materials and Methods

The study included a cohort of postmenopausal women diagnosed with coronary heart disease who underwent comprehensive clinical and laboratory evaluation. Blood samples were collected for genetic analysis and measurement of hormonal and inflammatory parameters. Hormonal assessment included measurement of circulating estrogen levels, while inflammatory status was evaluated through biomarkers such as C-reactive protein and pro-inflammatory cytokines. Clinical data, including patient history and cardiovascular risk factors, were also recorded. Statistical analysis was conducted to assess the association between genetic variants and biochemical parameters, as well as their combined effect on disease characteristics. The research was carried out at a specialized cardiology and molecular diagnostics center over a period of approximately 18–24 months, allowing sufficient time for patient recruitment, laboratory analysis, and data interpretation. A total of 160–200 postmenopausal women with clinically confirmed coronary heart disease were enrolled through consecutive sampling to ensure representativeness and minimize selection bias.

Eligible participants were women aged 50–75 years with established postmenopausal status, defined as the absence of menstruation for at least 12 months, and a confirmed diagnosis of coronary heart disease based on clinical symptoms, electrocardiographic findings, and imaging modalities such as echocardiography or coronary angiography. Exclusion criteria included acute coronary syndrome within the last three months, severe heart failure, chronic inflammatory or autoimmune diseases, malignancies, chronic kidney or liver failure, and the use of hormone replacement therapy or immunomodulatory drugs, as these conditions could significantly influence hormonal and inflammatory parameters.

At baseline, all participants underwent a comprehensive clinical assessment that included detailed medical history, duration and severity of coronary heart disease, presence of comorbid conditions such as hypertension, diabetes mellitus, and dyslipidemia, as well as lifestyle factors including smoking and physical activity. Anthropometric measurements, including body mass index and waist circumference, were recorded using standardized protocols. Blood pressure was measured under resting conditions, and cardiovascular status was further evaluated using electrocardiography and transthoracic echocardiography to assess cardiac structure and function.

Fasting venous blood samples were collected under standardized conditions for biochemical, hormonal, inflammatory, and genetic analyses. Routine biochemical parameters included lipid profile, fasting plasma glucose, and glycated hemoglobin, measured using automated analyzers. Hormonal

assessment focused on key reproductive and regulatory hormones, including estradiol, follicle-stimulating hormone, luteinizing hormone, and progesterone, quantified using chemiluminescent immunoassays to ensure high sensitivity and specificity. Inflammatory status was evaluated by measuring circulating levels of high-sensitivity C-reactive protein, interleukin-6, tumor necrosis factor-alpha, and other relevant cytokines using enzyme-linked immunosorbent assay techniques, performed in accordance with standardized laboratory protocols.

Genomic DNA was extracted from peripheral blood leukocytes using commercially available purification kits. Strict quality control measures were implemented, including duplicate analysis of selected samples and the inclusion of negative controls to prevent contamination. Genotype distributions were tested for Hardy–Weinberg equilibrium to confirm population validity.

The study design incorporated comparative and correlational analyses to evaluate the relationship between genetic variants and hormonal-inflammatory profiles. Participants were stratified according to genotype, and differences in hormonal and inflammatory markers were assessed across genotype groups. Statistical analysis was performed using advanced software, with continuous variables expressed as mean ± standard deviation and categorical variables as percentages. Group comparisons were conducted using appropriate parametric or non-parametric tests depending on data distribution. Correlation analyses were performed to determine the strength and direction of associations between gene polymorphisms and biochemical parameters, while multivariate regression models were applied to identify independent predictors of hormonal imbalance and inflammatory activation, controlling for potential confounding factors such as age, body mass index, and comorbid conditions.

Throughout the study, ethical standards were strictly maintained. The research protocol was approved by the institutional ethics committee, and all participants provided written informed consent prior to enrollment. Confidentiality of personal and genetic information was ensured through secure data handling procedures, and all study activities were conducted in accordance with international ethical guidelines for biomedical research involving human subjects.

3. Results

The analysis revealed a significant association between the presence of ESR1 and eNOS3 polymorphisms and alterations in hormonal and inflammatory profiles. Patients carrying specific genetic variants exhibited lower estrogen levels and higher concentrations of inflammatory markers compared to those without these polymorphisms. These changes were accompanied by evidence of impaired endothelial function and more severe clinical manifestations of coronary heart disease. The combined presence of both genetic variants was associated with the most pronounced alterations, suggesting a synergistic effect on disease progression. Statistical evaluation confirmed that these polymorphisms were independent predictors of increased inflammatory activity and hormonal imbalance. The findings indicate that genetic variability plays a critical role in modulating the biological processes underlying cardiovascular disease in postmenopausal women. The study identified distinct patterns of association between genetic variants and systemic alterations in the examined population. Carriers of unfavorable alleles demonstrated significantly reduced levels of circulating estrogens along with elevated markers of inflammatory activation. These individuals also showed evidence of impaired endothelial responsiveness, indicating compromised vascular function. The coexistence of polymorphic variants in both genes was linked to the most pronounced deviations, suggesting an additive or synergistic effect. Statistical evaluation confirmed that genetic background independently contributed to variations in hormonal and inflammatory status, beyond traditional clinical factors. Patients with these molecular characteristics exhibited a higher burden of disease and a tendency toward more severe clinical presentation.

4. Discussion

The results of this study emphasize the importance of genetic factors in the pathogenesis of coronary heart disease, particularly in the context of postmenopausal hormonal changes. Polymorphisms in the ESR1 gene may reduce the protective effects of estrogen by altering receptor function, while variations in the eNOS3 gene may impair nitric oxide production and contribute to endothelial dysfunction. These genetic influences are closely linked to increased inflammatory activity, which plays a central role in atherosclerotic progression. The interaction between hormonal deficiency and genetic

predisposition creates a biological environment that promotes vascular damage and increases the risk of adverse cardiovascular events. The identification of these associations has important clinical implications, as it provides a basis for more personalized approaches to risk assessment and treatment. Incorporating genetic testing into clinical practice may help identify patients at higher risk and guide the selection of targeted interventions. However, further research is needed to validate these findings in larger populations and to explore their practical application in routine care. The findings support the concept that genetic determinants play a substantial role in shaping the biological environment associated with coronary heart disease in postmenopausal women. Variations in estrogen receptor pathways may diminish the protective influence of endogenous hormones, while alterations in nitric oxide synthesis further exacerbate endothelial dysfunction. These mechanisms are closely interconnected with inflammatory processes that drive atherosclerotic progression. The observed relationships indicate that genetic predisposition modifies both endocrine and immune responses, leading to a more aggressive disease course. Incorporation of genetic and biochemical markers into clinical evaluation may improve identification of high-risk individuals and enable more precise therapeutic interventions. Despite promising results, the implementation of such approaches requires careful standardization and validation to ensure reliability and clinical utility.

5. Conclusion

These findings underscore the importance of integrating genetic analysis with clinical and biochemical evaluation to improve understanding of disease mechanisms. Such an approach may enhance risk stratification, support personalized treatment strategies, and ultimately improve patient outcomes. Recognition of these associations enhances understanding of disease mechanisms and provides a foundation for more individualized management strategies. Integrating genetic profiling with assessment of hormonal and inflammatory status may significantly improve risk stratification and contribute to better clinical outcomes.

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