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ROLE OF APOE GENE POLYMORPHISM IN THE DEVELOPMENT OF METABOLIC SYNDROME DURING MENOPAUSE

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Abstract

Menopause represents a critical biological transition accompanied by profound endocrine restructuring and progressive metabolic vulnerability. Although estrogen deprivation is a fundamental trigger of metabolic disturbances, interindividual variability in cardiometabolic outcomes suggests a decisive role of inherited molecular determinants. Among genetic factors, the apolipoprotein E (APOE) gene occupies a central position due to its regulatory influence on lipid transport, remnant clearance, inflammatory modulation, and metabolic homeostasis.

This paper explores the mechanistic contribution of APOE polymorphic variants (ε2, ε3, ε4) to the development of metabolic syndrome in menopausal women. Special emphasis is placed on genotype-specific lipid handling, insulin signaling interference, adipose tissue remodeling, mitochondrial efficiency, and gene–environment interaction. The menopausal decline in estrogen is analyzed as a biological amplifier of genetically predetermined metabolic risk.

Understanding APOE-dependent metabolic heterogeneity may provide a foundation for precision-based preventive and therapeutic strategies in menopausal medicine.

Keywords: menopause, APOE polymorphism, metabolic syndrome, dyslipidemia, insulin resistance, visceral adiposity, cardiometabolic risk

Introduction

Menopause is not merely the cessation of ovarian activity but a systemic metabolic reprogramming phase. The reduction in circulating estrogens alters hepatic lipid metabolism, endothelial function, glucose utilization, and adipose tissue distribution. As a result, the prevalence of metabolic syndrome markedly increases during the menopausal transition.

However, clinical expression of metabolic syndrome varies considerably among women exposed to similar hormonal changes. This divergence indicates that endocrine decline alone is insufficient to explain metabolic outcomes. Genetic architecture likely determines the threshold of metabolic adaptability and resilience.

The APOE gene, located on chromosome 19, encodes apolipoprotein E — a multifunctional glycoprotein involved in cholesterol transport, lipoprotein receptor binding, and lipid redistribution. Three major isoforms (ε2, ε3, ε4) differ structurally by amino acid substitutions, which modify receptor affinity and metabolic consequences. These structural differences translate into measurable alterations in plasma lipid profiles and cardiovascular susceptibility.

Within the menopausal context, APOE polymorphism may become a critical modifier of cardiometabolic stability.

Molecular and Pathophysiological Mechanisms

Estrogen Deficiency as a Metabolic Amplifier

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Estrogens regulate hepatic LDL receptor expression, promote favorable HDL metabolism, and suppress visceral fat deposition. Their decline leads to:

- Increased LDL cholesterol concentration
- Enhanced triglyceride accumulation
- Reduced insulin sensitivity
- Redistribution of fat toward abdominal depots

When this hormonal shift coincides with APOE variants associated with impaired lipid clearance, metabolic imbalance intensifies.

APOE and Lipoprotein Dynamics

Apolipoprotein E serves as a ligand for hepatic LDL receptors and related receptors responsible for removing triglyceride-rich remnants from circulation.

- **ε4 allele carriers** typically demonstrate reduced receptor binding efficiency and elevated LDL cholesterol levels.
- **ε2 carriers** may exhibit altered remnant clearance and, in some contexts, elevated triglycerides.
- **ε3**, considered the reference isoform, maintains comparatively balanced lipid transport.

In menopausal women, the absence of estrogen-mediated lipid protection accentuates genotype-dependent dyslipidemia, thereby accelerating atherogenic processes.

Interaction with Insulin Signaling

Lipid excess interferes with intracellular insulin signaling via accumulation of diacylglycerols and activation of inflammatory kinases. APOE-related disturbances in lipoprotein metabolism contribute to ectopic lipid deposition in liver and skeletal muscle.

Such lipid-mediated metabolic stress reduces insulin receptor substrate phosphorylation efficiency and diminishes glucose uptake.

Menopause further potentiates this process by promoting visceral adiposity and inflammatory cytokine secretion, thereby creating a synergistic interaction between genetic susceptibility and endocrine alteration.

Adipose Tissue Remodeling

Visceral adipose tissue becomes metabolically dominant after menopause. It secretes pro-inflammatory mediators and exhibits enhanced lipolytic activity.

APOE influences adipocyte lipid storage and turnover. Experimental observations suggest that ApoE expression affects adipocyte differentiation and intracellular lipid droplet formation.

Genotype-specific differences may therefore determine:

- Degree of visceral fat expansion
- Systemic inflammatory burden
- Adipokine secretion balance

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- Propensity toward insulin resistance

These mechanisms collectively contribute to metabolic syndrome development.

Inflammatory and Oxidative Pathways

Metabolic syndrome is characterized by persistent low-grade inflammation and oxidative stress. ApoE participates in immunomodulation by regulating macrophage lipid uptake and cytokine production.

The ε4 isoform has been associated with heightened inflammatory reactivity. In the menopausal milieu, where systemic inflammation increases due to hormonal withdrawal, this pro-inflammatory tendency may aggravate endothelial dysfunction and vascular remodeling.

Mitochondrial Efficiency and Energy Metabolism

Emerging evidence indicates that ApoE may influence mitochondrial dynamics and oxidative phosphorylation efficiency. Reduced mitochondrial adaptability enhances lipid accumulation and decreases metabolic flexibility.

Age-related mitochondrial decline combined with genotype-dependent inefficiency contributes to reduced metabolic resilience during menopause.

Gene–Environment Synergy

The phenotypic expression of APOE polymorphism is not deterministic but modulated by lifestyle factors. Nutritional composition, caloric balance, physical activity, sleep quality, and psychosocial stress influence lipid metabolism and inflammatory tone.

Dietary patterns rich in unsaturated fats and fiber may attenuate LDL elevation in genetically predisposed individuals. Structured exercise improves insulin sensitivity and reduces visceral adiposity, partially counteracting genotype-associated risk.

Thus, APOE polymorphism should be interpreted within a dynamic environmental context rather than as an isolated predictor.

Clinical Implications

Incorporation of APOE genotyping into menopausal risk assessment may refine cardiometabolic stratification. Potential benefits include:

- Identification of women requiring intensified lipid monitoring
- Personalized dietary and physical activity prescriptions
- Early pharmacological intervention in high-risk genotypes
- Precision hormone therapy evaluation

However, ethical considerations and cost-effectiveness analyses are necessary before widespread implementation.

Preventive Strategy Framework

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A precision-based preventive model for menopausal women may include:

1. Baseline metabolic screening (lipid profile, glucose tolerance, anthropometry).
2. Genetic risk assessment in selected populations.
3. Lifestyle optimization tailored to genotype-associated vulnerabilities.
4. Longitudinal monitoring of metabolic parameters.

Such integrative strategies aim to reduce cardiometabolic morbidity and improve long-term health outcomes.

Conclusion

The APOE gene significantly influences metabolic adaptation during the menopausal transition. Structural differences among ε2, ε3, and ε4 isoforms modify lipid transport efficiency, inflammatory regulation, and insulin responsiveness.

Estrogen withdrawal acts as a biological stressor that unmasks genotype-dependent metabolic vulnerabilities. Women carrying high-risk APOE variants may exhibit accelerated development of dyslipidemia and metabolic syndrome in the postmenopausal period.

Recognition of these mechanisms opens перспективы for personalized preventive medicine, targeted therapeutic intervention, and improved cardiometabolic prognosis in menopausal healthcare.

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