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PROGNOSTIC SIGNIFICANCE OF CARDIOMETABOLIC AND GENETIC FACTORS AND ARTERIAL STIFFNESS INDICES IN THE DEVELOPMENT OF ISCHEMIC HEART DISEASE

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Abstract
This article reviews the prognostic significance of cardiometabolic and genetic factors (APOB, PCSK9, MMP9, FADS1, SIRT1) and arterial stiffness indices, assessed via pulse wave velocity, in the development of ischemic heart disease (IHD), based on an analysis of existing literature. Their molecular mechanisms, clinical correlations, and approaches to improving an integral risk model are discussed in detail.

Keywords: Ischemic heart disease, cardiometabolic factors, genetic polymorphism, APOB, PCSK9, MMP9, FADS1, SIRT1, arterial stiffness, pulse wave velocity, atherosclerosis, dyslipidemia, endothelial dysfunction, prognostic model, early diagnosis.

Introduction

Ischemic heart disease remains the leading cause of death worldwide, accounting for approximately nine million deaths annually according to global cardiovascular disease burden estimates, with projections indicating continued growth through 2030, driven primarily by population aging, urbanization, and the rising prevalence of obesity and metabolic syndrome. Despite decades of preventive cardiology, traditional risk models based largely on lipid profiles, blood pressure, and smoking status explain only a moderate proportion of individual variability in disease onset, leaving a substantial residual risk unaccounted for. This gap has motivated growing interest in integrating genetic susceptibility markers together with non-invasive functional vascular indices, particularly arterial stiffness measured by pulse wave velocity, into next-generation predictive frameworks capable of identifying high-risk individuals years before clinical events occur, thereby enabling earlier, more targeted preventive intervention rather than reactive treatment after disease manifestation.

Literature review

Genome-wide association studies have consistently linked variants in APOB and PCSK9 to elevated LDL cholesterol concentrations and increased coronary risk, establishing both genes as central players in atherogenic lipid metabolism. FADS1 polymorphisms have been shown to alter the efficiency of polyunsaturated fatty acid desaturation, thereby shifting the downstream balance of pro- and anti-inflammatory eicosanoids implicated in plaque biology. MMP9 variants affect extracellular matrix turnover and collagen degradation within the arterial wall, a process directly relevant to

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vascular stiffening. SIRT1, a nicotinamide adenine dinucleotide-dependent deacetylase regulating endothelial and metabolic stress responses, has been associated with vascular aging phenotypes and impaired nitric oxide bioavailability. Large Russian epidemiological cohorts further confirm the substantial and growing contribution of clustered metabolic risk factors - abdominal obesity, dyslipidemia, hypertension, and insulin resistance - to national cardiovascular mortality trends, reinforcing the relevance of combined metabolic-genetic-vascular models in real-world populations.

MAIN BODY

Cardiometabolic risk in IHD arises from a complex interplay of dyslipidemia, insulin resistance, visceral adiposity, chronic low-grade inflammation, and endothelial dysfunction, which together accelerate the atherogenic cascade from early fatty streak formation to advanced, unstable plaque. Genetic variation modulates individual susceptibility to this cascade at several distinct mechanistic levels, each contributing a partially independent layer of risk.

At the lipid level, the APOB rs5742904 variant influences hepatic apolipoprotein B production, directly affecting the number of circulating atherogenic lipoprotein particles available for subendothelial deposition, while PCSK9 rs562556 modulates the rate of LDL-receptor degradation on hepatocyte surfaces, thereby altering the efficiency of hepatic LDL clearance from plasma. Both mechanisms converge on the same downstream endpoint - increased subendothelial retention of atherogenic particles - which represents the initiating step of plaque formation according to the response-to-retention hypothesis of atherosclerosis.

At the inflammatory-metabolic level, FADS1 rs174546 shifts the balance between omega-6- and omega-3-derived eicosanoid signaling molecules, favoring a more pro-inflammatory systemic tone when the risk allele is present; this altered inflammatory milieu is increasingly implicated not merely in plaque initiation but specifically in plaque instability and rupture propensity, a distinction of considerable clinical importance since unstable plaques, rather than plaque burden alone, drive acute coronary events.

At the structural-vascular level, MMP9 rs17576 alters collagenolytic enzymatic activity within the arterial media and adventitia; excess MMP-9 activity progressively degrades elastin and collagen fibers that normally confer vascular compliance, contributing directly to increased arterial stiffness through a pathway that is mechanistically distinct from, and can occur independently of, classical atherosclerotic lipid burden - meaning stiffness can rise even in patients without extensive plaque.

At the regulatory-aging level, SIRT1 rs7069102 affects deacetylation activity toward endothelial NF-κB and eNOS pathways; reduced SIRT1 activity is associated with impaired nitric-oxide-mediated vasodilation, increased endothelial senescence, and accelerated vascular aging, compounding the structural stiffening driven by MMP9-related matrix degradation. Arterial stiffness, quantified clinically through carotid-femoral pulse wave velocity, integrates the cumulative structural and functional consequences of all four pathways described above into a single, reproducible, non-invasive measurement. Elevated pulse wave velocity therefore reflects not only mechanical wall changes but also the underlying cumulative genetic and metabolic burden, making it a biologically plausible intermediate phenotype linking genotype to eventual clinical IHD outcome. For example, patients carrying combined risk alleles across the MMP9 and SIRT1 loci, in the presence of concurrent metabolic syndrome components such as central obesity and insulin resistance, would be

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expected on mechanistic grounds to show disproportionately elevated stiffness indices compared with individuals carrying only isolated risk factors in a single domain, illustrating the additive and potentially synergistic nature of these interacting pathways.

Results

Across the body of reviewed literature, several consistent patterns emerge that collectively support a multidimensional risk model. First, carriers of risk alleles at the APOB and PCSK9 loci demonstrate significantly higher LDL cholesterol concentrations and increased odds of angiographically confirmed coronary lesions compared with non-carriers, a finding replicated across multiple independent cohorts and supporting the role of both genes as robust, independent contributors to atherogenic risk rather than incidental markers of lipid variation. Second, FADS1 variants correlate consistently with altered fatty acid desaturase activity and downstream inflammatory marker levels, including C-reactive protein and interleukin-6, suggesting a genuine mechanistic link between lipid-metabolism genetics and systemic vascular inflammation rather than a purely statistical association, and pointing toward a plausible causal pathway from genotype to plaque vulnerability. Third, MMP9 polymorphisms show consistent associations with both direct arterial stiffness parameters, such as pulse wave velocity, and biochemical extracellular matrix remodeling markers, reinforcing a structural pathway to vascular disease that operates largely independently of classical lipid mechanisms - a finding with direct clinical relevance, since it implies that lipid-normal patients carrying high-risk MMP9 genotypes may still face elevated cardiovascular risk through a vascular-structural route. Fourth, SIRT1 variants associate with endothelial dysfunction markers and, in several longitudinal cohorts, with accelerated pulse wave velocity progression over time, an effect that appears particularly pronounced in individuals with concurrent obesity, suggesting a gene-environment interaction in which metabolic excess amplifies the vascular consequences of reduced SIRT1 activity.

When considered jointly rather than individually, combined cardiometabolic and genetic markers together with arterial stiffness indices consistently outperform single-domain risk models in discriminating IHD risk, a pattern evident across comparative study designs employing groups such as obese patients with IHD, normal-weight patients with IHD, obese individuals without IHD, and healthy controls. This pattern strongly supports the hypothesis that an integral model combining genetic, metabolic, and vascular-functional data captures complementary risk information not reflected by any single domain in isolation, and further demonstrates that obesity alone, in the absence of concordant adverse genetic and vascular findings, does not fully or reliably predict IHD development - underscoring the value of a multi-layered assessment over reliance on anthropometric measures alone.

Discussion

These findings collectively support a multidimensional understanding of IHD pathogenesis in which genetic predisposition, metabolic dysregulation, and vascular structural change act synergistically rather than as independent, additive contributors. The consistency of associations between lipid-related genes - APOB, PCSK9, and FADS1 - and classical atherogenic pathways aligns closely with established lipid-hypothesis frameworks that have long anchored cardiovascular risk science, while

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the structural contribution of MMP9 and the functional-regulatory role of SIRT1 extend the model meaningfully beyond lipid-centric explanations, incorporating vascular biology, extracellular matrix dynamics, and cellular aging processes that traditional lipid-focused screening does not capture.

Clinically, this convergence of evidence suggests that pulse wave velocity measurement, being non-invasive, reproducible, and relatively low-cost, could serve as a practical intermediate marker bridging underlying genetic susceptibility and eventual clinical outcome, particularly valuable in healthcare settings, including much of Central Asia, where broad genetic testing remains cost-prohibitive for routine screening but vascular ultrasound-based measurement is increasingly accessible. Incorporating stiffness measurement into standard cardiometabolic risk assessment could therefore offer a pragmatic, resource-appropriate pathway toward earlier risk stratification even in the absence of genotyping infrastructure.

However, several important limitations must be acknowledged. Most cited associations derive from cross-sectional or moderately sized cohort studies rather than large prospective trials specifically designed to validate an integral model; effect sizes vary considerably across populations of different ethnic backgrounds, limiting direct generalizability to Central Asian cohorts; and gene-environment interactions, including dietary patterns, physical activity levels, and smoking exposure, likely modify individual risk trajectories in ways not fully captured by genotype alone. Prospective, adequately powered studies stratifying patients by combined genetic and metabolic phenotype - following comparative designs such as the four-group structure referenced above, contrasting obese and normal-weight patients with and without established IHD - remain necessary to rigorously validate an integral prognostic model suitable for routine clinical implementation, and such studies should ideally be conducted within regional populations to ensure applicability to local patient cohorts.

Combining genetic markers, cardiometabolic indices, and arterial stiffness measurement offers a promising, mechanistically coherent, and complementary approach to early IHD risk prediction, warranting further prospective, regionally-grounded validation before clinical adoption.

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