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Superoxide Dismutase and No Synthase Genes in Arterial Hypertension and Its Complications: Current Scientific Perspectives and Literature Review

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Abstract This literature review is based on the results of studies focused on the investigation of pathogenetic processes associated with decreased activity of nitric oxide synthase, the enzyme responsible for nitric oxide production, as well as disturbances in the antioxidant system in arterial hypertension (AH), cardiovascular diseases, and their complications. In addition to examining the significance of biochemical markers of pathogenetic pathways, the article analyzes the prevalence of various polymorphisms of superoxide dismutase (SOD) and NO synthase (NOS) genes in patients. The features of their distribution across different races and populations are also considered, along with the relationships between genotypes and levels of pathogenetic markers in the blood. The analyzed data are both contradictory and complementary, highlighting the need for further investigation of SOD and NOS gene polymorphisms as molecular genetic markers for predicting pathogenetic processes in arterial hypertension and its complications, as well as for the development of personalized preventive strategies.

Keywords Arterial hypertension, Renal dysfunction, Superoxide dismutase, NOS gene, Polymorphism, Genotype, Allele, Homozygote, Heterozygote

1. Introduction

Despite advances in science and active efforts by healthcare systems, arterial hypertension (AH) remains one of the most significant medical and social problems. A large number of studies have been conducted to investigate risk factors and pathogenetic mechanisms that play an important role in the development and progression of AH and its complications. It has been established that the pathophysiology of AH is based on the interaction of complex regulatory systems, including the heart, blood vessels, kidneys, brain, and immune cells, with oxidative stress and endothelial dysfunction considered key factors linking these mechanisms [1,2]. In the pathophysiology of the cardiovascular system and arterial hypertension, redox homeostasis is tightly regulated by antioxidant enzymes, including SOD1 (cytoplasmic Cu/Zn superoxide dismutase), SOD2 (mitochondrial superoxide dismutase), and SOD3 (extracellular superoxide dismutase), as well as glutathione peroxidase, catalase, and the thioredoxin–peroxiredoxin system, along with non-enzymatic antioxidants (α-tocopherol, β-carotene, bilirubin, and uric acid) [3,4]. The development of complications of arterial hypertension and the formation of renal dysfunction, among other factors, are largely associated with oxidative stress [5,6]. Arterial hypertension is closely linked to increased production of the superoxide anion (O_2^-), one of the key reactive oxygen species in the vascular wall. The superoxide anion inhibits nitric oxide (NO), reducing its bioavailability and impairing the physiological mechanisms of vasodilation. The interaction between O_2^- and NO leads to the formation of peroxynitrite ($ONOO^-$), a potent oxidant capable of oxidizing proteins, lipids, and nucleic acids, thereby causing cellular damage in organs such as the brain, blood vessels, and kidneys. Superoxide dismutase (SOD) plays a key role in maintaining NO bioavailability, and its activity directly influences endothelium-dependent vasodilation and the regulation of arterial blood pressure [7–10].

Superoxide dismutase also plays a critical role in regulating mechanisms involved in the development of arterial hypertension and renal dysfunction. In particular, it modulates processes of vasodilation and vasoconstriction, thereby influencing vascular tone and microcirculation. SOD activity is also involved in structural remodeling of the vascular wall, preventing pathological hypertrophy and fibrosis, and its effects extend to cardiac adaptive processes, including myocardial hypertrophy. In addition, SOD affects both central and peripheral regulation of the sympathetic nervous system, contributing to the maintenance of arterial blood pressure and renal functional homeostasis. These multi-level effects highlight the role of SOD as a critical molecular modulator in the pathogenesis of arterial

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hypertension and its associated organ complications [9–13].

SOD1 (cytoplasmic Cu/Zn superoxide dismutase) accounts for approximately 85% of the total superoxide dismutase activity in the cells of most mammals, underscoring its key role in maintaining cellular redox homeostasis. In humans, SOD1 exhibits particularly high activity in the kidneys and vascular walls, where it is involved in the regulation of vascular tone and the protection of endothelial cells against oxidative stress [14]. In cardiac tissue, SOD1 is recognized as a crucial mediator of myocardial protection against ischemic injury; an increase in its intracellular content contributes to the reduction of oxidative damage, maintenance of cardiomyocyte viability, and a decrease in the extent of ischemic necrosis [15,16]. These findings highlight the critical importance of SOD1 as a molecular regulator counteracting pathogenetic processes associated with oxidative stress in the heart, blood vessels, and kidneys.

Nrf2 is considered a key regulator of the fine-tuning of transcriptional activity at mRNA promoter regions and plays a significant role in regulating SOD expression, which is due to the presence of multiple binding sites for various transcription factors [17]. Polymorphic variations in nucleotide sequences within cis-regulatory elements are capable of modulating transcription levels, leading to variability in mRNA expression.

Results of *in vitro* studies indicate that a 50 base pair deletion polymorphism in the promoter region of the SOD1 gene (located 1684 base pairs upstream of the ATG start codon) is associated with reduced promoter transcriptional activity. This effect is likely due to the loss of two binding sites for the transcription factor Sp1, which in turn leads to decreased gene expression [14].

Reduced SOD1 activity appears to promote the accumulation of superoxide anion in the vascular wall, induces vascular remodeling in the form of arterial hypertrophy, and is accompanied by impaired endothelium-dependent vasodilation. The SOD1 Ins/Del and Del/Del genotypes, presumably associated with decreased enzyme expression, are significantly more frequently detected in patients with a history of arterial hypertension. In contrast, carriage of the Ins/Ins genotype in most cases is not associated with the presence of arterial hypertension [13,18].

Within the family of oxidoreductases collectively referred to as superoxide dismutases, particular importance is attributed to mitochondrial manganese-dependent superoxide dismutase (MnSOD), which represents a key component of the cellular antioxidant defense system against reactive oxygen species (ROS). This enzyme catalyzes the initial stage of their neutralization, ensuring the elimination of up to 80% of free radicals generated during oxidative phosphorylation and other metabolic reactions [19]. The SOD2 gene, which encodes MnSOD, plays a critical role in ensuring mitochondrial import of the enzyme and its localization within the matrix [19].

The SOD2 gene is localized to the 6q25.3 region of the chromosome and consists of five exons. To date, a number of single nucleotide polymorphisms of this gene have been described, among which the most extensively studied is the Ala16Val (rs4880) variant. This polymorphism, caused by the substitution of alanine with valine, is associated with conformational changes in the secondary structure of the protein, thereby affecting its intracellular transport. During post-translational processing in the mitochondrial matrix, the signal sequence undergoes cleavage, resulting in the formation of a functionally active enzyme. It has been established that the valine-containing variant of the protein is characterized by reduced transport efficiency into the mitochondrial matrix compared to the alanine variant. This, in turn, promotes the accumulation of superoxide anion in mitochondria in carriers of the Val allele and the Val/Val genotype, which is associated with increased oxidative damage to mitochondrial DNA (mtDNA) [20,21].

Literature data on the functional role of the Ala16Val (rs4880) polymorphism of the SOD2 gene in the pathogenesis of cardiovascular diseases remain limited. According to observations by **Maikopova E.V.**, a statistically significant increase in the frequency of the Val allele of the Ala16Val polymorphism ($p = 0.008$) was recorded in patients who had experienced acute myocardial infarction. Assessment of relative risk demonstrated that carriers of the Val allele have approximately a twofold increased risk of developing myocardial infarction in the context of coronary artery disease compared to carriers of the Ala allele (odds ratio = 1.89; 95% CI) [22]. The authors emphasize that the study was conducted on a mixed population sample from the Republic of Tatarstan, which limits the ability to assess the significance of this genetic marker for myocardial infarction in specific ethnic groups.

The results of another study conducted in Yekaterinburg (Russian Federation) revealed a statistically significant association between the mutant Val/Val genotype of the Ala16Val polymorphism of the SOD2 gene and elevated systolic and diastolic blood pressure. In carriers of the Val/Val genotype, reduced MnSOD enzyme activity was observed, accompanied by decreased antioxidant capacity and accumulation of reactive oxygen species in response to environmental factors [23].

Endothelial nitric oxide (NO), along with superoxide dismutase (SOD), is considered a key endogenous vasorelaxant, playing a central role in the maintenance of normal blood pressure and the regulation of local blood flow. NO synthesis in vascular endothelial cells participates in the regulation of arterial pressure and microcirculation. The endothelial NO synthase enzyme (eNOS) and the gene controlling its expression are considered important candidates for studying the pathogenesis of arterial hypertension (AH) [24–27]. The human eNOS gene exhibits a high degree of polymorphism, with certain single nucleotide polymorphisms associated with an increased risk of developing AH [28].

According to the literature, the NO synthase system includes three isoforms: neuronal (nNOS, NOS1), inducible (iNOS, NOS2), and endothelial (eNOS, NOS3) [29]. All isoforms catalyze the conversion of L-arginine to L-citrulline with the formation of NO. The NOS1 gene is located on

chromosome 12q24.22 and consists of 33 exons. High levels of expression of this gene have been observed in the brain, kidneys, and 11 other tissues, with the greatest expression in skeletal muscle [30]. Several alternative transcripts with variations in the 5′ untranslated region have been identified for NOS1, although their full length remains unknown. In addition, transcript variants encoding different protein isoforms through alternative splicing have been identified.

Levinsson A. and colleagues demonstrated that carriage of the T allele of the NOS1 gene polymorphism rs3782218 is associated with a reduced risk of developing arterial hypertension (relative risk (RR) = 0.81; 95% confidence interval (CI) = 0.67–0.97; p = 0.02), whereas carriage of the A allele of the rs7314935 polymorphism increases this risk (RR = 2.15; 95% CI = 1.06–4.37; p = 0.03) [31].

Inducible NO synthase (iNOS), encoded by the NOS2 gene, is a key component of the adaptive endothelial response to environmental stressors and plays an essential role in the protective mechanisms of the vascular system. Activation of iNOS leads to NO synthesis, which participates in the regulation of vascular tone and modulation of inflammatory processes.

In studies by **Fu L.** and colleagues, the association of the NOS2 promoter single nucleotide polymorphism rs2779249 (−1026C/A) with susceptibility to arterial hypertension (AH) was analyzed in Han Chinese individuals [32]. The authors identified statistically significant differences in the distribution of genotypes and alleles ($p < 0.05$). After adjustment for environmental factors using multivariate logistic regression analysis, the CC genotype showed a significant association with an increased risk of AH (adjusted relative risk (RR) = 2.90; 95% CI = 2.14–3.93), indicating a functional effect of this polymorphism on vascular reactivity.

In another study, **Topchieva L.V.** and colleagues evaluated the influence of the NOS2 polymorphisms rs1800482 (−954G>C) and rs3730017 (C>T) on the development of essential arterial hypertension (AH). Carriage of the C allele of rs1800482 was associated with a 1.7-fold increased risk of the disease (RR = 1.712; 95% CI = 1.07–2.74), whereas the T allele of rs3730017 exhibited a protective effect (RR = 0.304; 95% CI = 0.192–0.482). Furthermore, in patients with essential AH, the presence of the C allele of rs1800482 correlated with increased plasma concentrations of NO metabolites, suggesting a potential functional significance of this variant for endothelial regulation [33]. Additionally, the effect of the C allele on the expression of the VCAM1 (vascular cell adhesion molecule 1) and ICAM1 (intercellular adhesion molecule 1) genes was investigated in patients with essential AH. It is suggested that the NOS2 polymorphism may contribute to the development of endothelial dysfunction and elevated blood pressure by modulating NO production in the context of an inflammatory response, thereby influencing the expression of key adhesion molecules and, consequently, vascular reactivity [33].

Data on the influence of NOS2 single nucleotide polymorphisms (rs2779249 (−1026C>A) and rs2297518 (2087G>A)) on susceptibility to arterial hypertension remain limited. Within the framework of the large TAMRISK cohort study, conducted by **Nikkari S.T.** and colleagues in the adult population of Tampere, Finland, a statistically significant association was observed between these polymorphisms and the presence of AH, indicating a potential role for NOS2 in the genetic modification of cardiovascular disease risk [28].

The NOS3 gene, which encodes endothelial NO synthase (eNOS), is located in the p35–p36 region of chromosome 7 and spans approximately 21 kilobases of DNA, including 26 exons and 25 introns. The encoded mRNA is translated into a protein consisting of 1,203 amino acids. Under normal physiological conditions, continuous endogenous NO production, which maintains vascular tone and regulates blood flow, is primarily mediated by eNOS activity. Polymorphisms of the eNOS gene can alter the functional activity of the enzyme, modifying NO concentrations in endothelial cells and, consequently, influencing the development of arterial hypertension (AH). The most extensively studied eNOS polymorphic variants associated with AH include the G894T mutation in exon 7, variable number tandem repeats (VNTRs) in intron 4, and the T786C mutation in the promoter region [34–36]. In intron 4 of the eNOS gene, VNTRs approximately 27 base pairs in length have been identified, dividing alleles into two types: the “a” allele contains four repeats, while the “b” allele contains five repeats. These structural variations may influence the regulation of eNOS expression and, consequently, NO production, highlighting their potential significance in the pathogenesis of AH.

Reduced nitric oxide (NO) production is considered a key factor in the imbalance of vascular homeostasis, leading to prothrombotic and proinflammatory changes and decreased elasticity of the vascular wall [37,38]. In this context, functional polymorphisms of the eNOS (NOS3) gene represent biologically plausible potential biomarkers of susceptibility to arterial hypertension (AH).

One of the most extensively studied polymorphisms is the single nucleotide variant in exon 7, rs1799983 (G894T), which results in an amino acid substitution of glutamate to aspartate (Glu298Asp). This polymorphic variant alters the structural conformation of the enzyme, reducing its catalytic activity and, consequently, NO production. Clinical observations demonstrate that basal NO production in patients with arterial hypertension is significantly lower compared to healthy control populations [39].

Another functionally significant polymorphism, rs2070744 (T-786C), is located in the 5′ promoter region of the eNOS gene and involves a thymine-to-cytosine substitution. Mechanistic studies indicate that this polymorphic variant modulates the transcriptional activity of the gene, affecting translation efficiency, mRNA stability, and the level of the synthesized enzyme, ultimately contributing to the development of hypertension [40].

Epidemiological studies confirm the clinical significance of these polymorphisms. In a northern population cohort, the C allele of T-786C was associated with a significant increase in diastolic blood pressure, serving as a predictor of hemodynamic disturbances [40]. In a cohort of the Han

Chinese ethnic group (n = 2,459), a statistically significant association was identified between the rs1799983 (G894T) and rs2070744 (T-786C) variants and the risk of developing arterial hypertension (AH) [41]. A meta-analysis of 63,258 participants demonstrated that both polymorphisms substantially increase the likelihood of hypertension development, and analysis of a small Asian subgroup confirmed the role of the rs1799983 T allele and the rs2070744 C allele as factors of increased susceptibility to AH [42].

The molecular mechanisms underlying endothelial dysfunction in hyperhomocysteinemia include suppression of NO production, direct inhibition of eNOS activity, upregulation of caveolin-1 with subsequent enzyme inactivation, and restricted transport of L-arginine via cationic amino acid transporters, thereby impairing NO synthesis through eNOS [43,44]. These findings highlight the complex role of eNOS polymorphisms in the regulation of vascular tone and the pathogenesis of arterial hypertension.

Oxidative stress induced by elevated homocysteine concentrations is considered a key pathogenetic factor in arterial hypertension (AH), as it promotes the accumulation of the endogenous inhibitor of endothelial NO synthase (eNOS)—asymmetric dimethylarginine (ADMA)—leading to an imbalance in vascular homeostasis [45]. The literature indicates that the eNOS gene polymorphisms G894T and intron 4a/b significantly affect blood pressure levels in individuals with elevated total homocysteine [46].

A study by **Uwabo** and colleagues in a northern Japanese population demonstrated a statistically significant increase in the frequency of the "a" allele of the 27-bp VNTR eNOS polymorphism in patients with AH compared to a control group. Logistic regression analysis adjusted for environmental factors indicated that the "a" allele may serve as a potential genetic marker of susceptibility to AH in this ethnic group [36].

An analysis conducted by **Xiru Xu** and colleagues revealed that the intron 4a/b locus (allele "a") of the eNOS gene is associated with an increased predisposition to arterial hypertension (AH) across different populations. In the overall and European populations, the risk of AH was elevated under both dominant and heterozygous models; among African Americans, the association was observed under the heterozygous model; and in mixed populations, it was evident under the allelic model. Notably, although intron 4a/b is a non-coding sequence, it retains significant regulatory influence on eNOS expression and vascular function. In the overall population, the "a" allele of intron 4a/b showed a significant association with increased AH risk under both dominant and heterozygous models; in mixed populations, under heterozygous and allelic models; and among Asian populations, under the heterozygous model [34].

Fan and colleagues demonstrated that the rs2241766 polymorphism significantly increases the risk of AH, whereas the rs1501299 polymorphism appears to have a protective effect in the Caucasian population [47]. According to **Jiao** and coauthors, polymorphisms of the serotonin transporter gene (5-HTT L/S) and endothelin-1 (END1) rs5370 are associated with increased susceptibility to pulmonary arterial hypertension (PAH); specifically, the 5-HTT L allele increases the risk of PAH in idiopathic cases and in patients with chronic obstructive pulmonary disease [48]. **Wang** and colleagues found no significant correlation between polymorphisms of the atrial natriuretic peptide (ANP) genes T2238C and G1837A and AH risk; however, the ANP T1766C polymorphism may be potentially associated with altered risk, with the 1766C allele demonstrating a protective effect [49].

The results of studies investigating the association between arterial hypertension (AH), gestational hypertension, and eNOS gene polymorphisms are contradictory and reflect ethnic and regional differences. Most studies have focused on individual genetic loci, whereas the combined effects of multiple loci have been examined only to a limited extent. Advances in molecular biology techniques allow for a more detailed investigation of genetic factors underlying AH using diverse animal models.

For a deeper understanding of the pathogenesis of AH and the development of effective therapeutic strategies, it is recommended to conduct large-scale, multigenic studies in populations from various ethnic and geographic groups, which would provide more reliable and reproducible results. Although **Xiru Xu** and colleagues evaluated study heterogeneity in their meta-analyses using χ^2 and I^2 tests, the available data were limited [34]. Therefore, expanding sample sizes and conducting studies across different populations is a necessary step to confirm the observed associations.

The **eNOS gene** is a key regulator of molecular mechanisms involved in nitric oxide (NO) signaling. The most functionally significant and frequently studied variants of this gene are single nucleotide polymorphisms (SNPs) in the promoter region (-786T/C, rs2070744) and in exon 7 (G894T, rs1799983, Glu298Asp) [50]. Current research indicates that eNOS polymorphisms can modify transcriptional activity and/or post-transcriptional processing, leading to reduced enzymatic activity, which underscores their clinical relevance in arterial hypertension (AH) and other cardiovascular disorders [51].

Charinya Chaichanabut and colleagues identified statistically significant associations between the SNPs rs1799983 and rs2070744 and an increased risk of AH [52]. In the studied Thai population, the allele frequencies of these polymorphisms (0.18 for rs1799983 and 0.10 for rs2070744) were comparable to Chinese and Korean cohorts (0.13 and 0.10, respectively), but substantially lower than in Caucasian populations (0.25 and 0.37) [53,54].

Studies among Chinese men demonstrated that carriers of the rs1799983 genotype exhibited significantly higher systolic and diastolic blood pressure compared with carriers of the wild-type allele (161.8 ± 20.2 mmHg vs. 154.3 ± 8.1 mmHg, $p = 0.013$; and 102.8 ± 9.6 mmHg vs. 99.5 ± 7.8 mmHg, $p = 0.02$) [55]. Furthermore, a covariate analysis in hypertensive men revealed that this polymorphism, in combination with alcohol consumption and smoking, exerted a joint effect on systolic and diastolic blood pressure ($p = 0.034$

and p = 0.043, respectively) [56]. These findings highlight the importance of genetic factors and their interactions with lifestyle in the pathogenesis of AH and may serve as a basis for developing personalized prevention and treatment strategies.

Yasudzima M. and colleagues investigated the potential role of the **NOS3 gene** in genetic predisposition to arterial hypertension (AH) [57]. The study analyzed genotypes of two single nucleotide polymorphisms (SNPs) of the NOS3 gene in hypertensive and normotensive populations in northern Japan. For **rs1799983** (Glu298Asp, +894G>T, missense polymorphism) and the **variable number tandem repeat (VNTR) in intron 4, 4b/4a**, genotypes were determined using allele-specific amplification and restriction fragment length analysis.

The results demonstrated that carriers of the 298Asp allele had a statistically significant increased risk of AH (OR = 1.8; 95% CI = 1.1–3.2). Among patients with AH, the frequency of the 298Asp allele was higher than in normotensive participants (0.136 vs. 0.083, $p < 0.05$), whereas no significant differences were observed between groups for the NOS3 4b/4a VNTR polymorphism. These findings support **rs1799983** as a potential genetic marker for susceptibility to AH [57].

Russian studies have reported that the presence of the 786C allele **and the** homozygous CC genotype **of the NOS3 gene in hyper**tensive patients may contribute to early kidney damage, with increased peripheral resistance in the renal arteries considered a marker of hypertensive nephropathy development [58]. Additional studies conducted in Ryazan demonstrated that the **C** allele of the NOS3 −786C/T polymorphism in comorbid patients with bronchial asthma and hypertension was associated with decreased levels of nitric oxide (NO) metabolites. In both comorbid and isolated hypertensive patients, the blood concentration of NO metabolites increased in the order CC < CT < TT (p = 0.033 and p = 0.024, respectively) [59], indicating a functional effect of the polymorphism on NO production and its role in the pathogenesis of AH and comorbid conditions.

Moe K.T. and colleagues investigated the relationship between NOS3 gene polymorphisms and arterial hypertension (AH) in a Singaporean population. Genotypes of rs1799983 in exon 7, the variable number tandem repeat in intron **4** (NOS3 4A/B/C), and the promoter polymorphism rs2070744 (−786T>C) were analyzed using allele-specific amplification and restriction fragment length analysis. This approach allowed assessment of genotype and allele frequency associations with AH in both study groups [60].

Italian researchers Rossi G.T. and colleagues reported that the rs2070744 polymorphism and its interaction with rs1799983 influenced endothelium-dependent vasodilation in both patients with mild-to-moderate AH and healthy normotensive Caucasians [61].

Comparable results from other studies demonstrate that polymorphisms of the eNOS gene in exon 7 and the promoter region, as well as elevated levels of specific plasma biomarkers, are associated with the development of arterial hypertension (AH), confirming endothelial dysfunction as a key mechanism of vascular pathology. These findings on genetic predisposition have practical significance for the identification of individuals at high risk of AH and the **development of** molecularly targeted preventive and therapeutic strategies [27,52,62].

The GT (heterozygous) and TT (homozygous) genotypes, as well as the T allele of the NOS3 G894T polymorphism, were significantly more frequent in the hepatorenal syndrome group and associated with renal dysfunction, whereas no significant differences were observed for the T-786C polymorphism between groups [63].

In the Uzbek population, the impact of the NOS3 G894T polymorphism on resistant arterial hypertension, as well as the role of the NOS3 T-786C polymorphism in renal dysfunction among patients with chronic heart failure, was investigated. It was found that these polymorphisms negatively affect NOS3 gene activity, reducing nitric oxide synthesis and impairing vascular regulation, thereby contributing to the progression of hypertensive nephropathy and resistant AH [62,64].

Overall, the literature review underscores the central role of oxidative stress, superoxide dismutase dysfunction, and endothelial dysfunction in the pathogenesis of arterial hypertension. The complex interactions of these systems with elevated blood pressure and hypertensive organ damage involve a significant influence of polymorphisms in superoxide dismutase and NO synthase genes, which serve as potential genetic markers of susceptibility, despite partially conflicting evidence. International studies demonstrate variability in the frequency and functional significance of these gene polymorphisms across different populations. In particular, investigating superoxide dismutase and NO synthase polymorphisms within populations provides a basis for developing personalized preventive and therapeutic strategies.

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