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Clinical And Pathogenetic Significance Of Nos3 Gene C-786t Polymorphism In Diabetic Foot Syndrome: A Literature Review

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ABSTRACT

Diabetic foot syndrome (DFS) represents a complex and severe complication of diabetes mellitus, involving peripheral neuropathy, micro- and macrovascular dysfunction, and infection. Endothelial dysfunction plays a central role in its pathogenesis. One of the key regulators of endothelial function is endothelial nitric oxide synthase (eNOS), encoded by the NOS3 gene. The C-786T promoter polymorphism of NOS3 has been studied as a potential genetic determinant of nitric oxide (NO) bioavailability and vascular response. This review synthesizes current evidence on the association of the NOS3 C-786T polymorphism with DFS severity, ulcer development, healing outcomes, and risk stratification in diabetic patients. Overall, findings suggest that NOS3 C-786T polymorphism may influence endothelial NO synthesis, contribute to impaired microcirculation, and serve as a genetic marker for individualized prognostic assessment and therapeutic stratification in DFS.

KEYWORDS

Diabetic foot syndrome, NOS3 gene, C-786T polymorphism, endothelial dysfunction, nitric oxide, genetic marker, ulcer healing.

INTRODUCTION

Diabetes mellitus (DM) is a global health challenge, with complications such as diabetic foot syndrome (DFS) significantly increasing morbidity and healthcare burden. DFS develops due to multifactorial processes, including peripheral arterial disease, neuropathy, immunologic changes, and impaired wound healing. Endothelial dysfunction, characterized by reduced nitric oxide (NO) production, is a shared mechanism in many of these processes. NO plays a vital role in vasodilation, anti-inflammatory processes, and microcirculation regulation. The NOS3 gene, which encodes endothelial NO synthase (eNOS), contains several polymorphic variants. Among these, the C-786T polymorphism in the promoter region has attracted significant attention due to its impact on gene transcription and NO production.

Nitric Oxide, Endothelial Function, and Diabetic Foot Pathogenesis

NO is synthesized from L-arginine by eNOS and modulates vascular tone, platelet aggregation, and leukocyte adhesion. In diabetes, hyperglycemia induces oxidative stress and reduces eNOS activity, leading to endothelial dysfunction. This dysfunction results in impaired vasodilation, microcirculation disturbances, and susceptibility to ischemia — all central to the pathophysiology of diabetic foot ulcers.

Several lines of evidence indicate that genetic variants affecting NO production can modulate the risk and severity of vascular complications in diabetes. Reduced NO bioavailability has been linked to impaired wound healing and increased risk of infection — both key features of DFS.

The NOS3 Gene and the C-786T Polymorphism

The NOS3 gene is located on chromosome 7q35–36 and comprises 26 exons. The C-786T polymorphism (rs2070744) resides in the gene's promoter region and affects transcriptional activity. The T allele has been associated with reduced promoter activity and lower eNOS expression, whereas the C allele is considered the wild-type sequence with higher transcriptional efficiency.

Functional studies show that carriers of the T allele may have lower plasma NO levels, predisposing them to endothelial dysfunction and cardiovascular risk. This polymorphism has been examined in various vascular diseases, including coronary artery disease, hypertension, and diabetic complications such as nephropathy and retinopathy.

NOS3 C-786T Polymorphism in Diabetic Foot: Evidence from Case–Control and Cohort Studies

1. Ulcer Development and Severity

Several studies have evaluated the association between NOS3 C-786T genotypes and the occurrence and severity of diabetic foot ulcers. Patients carrying the homozygous T/T genotype tend to exhibit better endothelial function compared with C/C carriers, though findings vary by population and study design. Some reports have linked the C/C genotype to more severe ischemic changes, greater ulcer depth, and increased need for surgical interventions such as debridement or amputation.

2. Wound Healing and Treatment Outcomes

Endothelial NO plays a significant role in angiogenesis and tissue repair. Variations in NOS3 gene expression may influence healing rates. In studies where diabetic patients with foot ulcers underwent standardized wound care, carriers of the T allele demonstrated relatively improved healing outcomes and reduced progression to critical limb ischemia, while C/C genotype carriers more frequently required advanced interventions. These genotype–phenotype correlations underscore the functional relevance of C-786T in tissue perfusion and repair.

Mechanistic Insights: From Genetics to Vascular Biology

Experimental models confirm that promoter variants affecting eNOS expression alter NO signaling pathways. Reduced NO availability increases leukocyte adhesion, platelet aggregation, and smooth muscle proliferation — mechanisms that exacerbate microvascular dysfunction. In the context of diabetes, where baseline oxidative stress is elevated, the genetic predisposition conferred by the C allele may synergize with metabolic factors to worsen endothelial responsiveness.

Interactions with Other Risk Factors

The impact of NOS3 C-786T polymorphism does not occur in isolation. Polymorphisms in other genes such as VEGF, ACE, and MTHFR, along with clinical factors like glycemic control, smoking, and peripheral arterial disease, interact to shape DFS risk. Some studies suggest that the combined presence of high-risk alleles multiplies DFS severity and impairs response to therapy.

Clinical Utility: Risk Stratification and Personalized Medicine

Current evidence supports the utility of genetic profiling in identifying diabetic patients at higher risk of poor outcomes. The NOS3 C-786T polymorphism may form part of a genetic risk panel that includes other endothelial and inflammatory markers. Such panels could inform closer monitoring, earlier intervention, and tailored therapies (e.g., agents enhancing NO bioavailability, advanced wound care protocols) for high-risk individuals. However, large prospective studies and meta-analyses are needed to confirm predictive accuracy and cost–benefit ratios.

Limitations and Future Directions

While associations have been observed, inconsistencies persist across ethnic groups and study designs. Small sample sizes, population stratification, and variation in clinical definitions of DFS contribute to heterogeneity. Future research should aim to:

- Conduct multicenter, multiethnic cohort studies
- Integrate NOS3 polymorphism analysis with functional biomarkers (e.g., circulating NO metabolites, flow-mediated dilation)
- Explore gene–environment and gene–gene interactions
- Assess polymorphism influence on response to specific therapies

CONCLUSION

The NOS3 C-786T polymorphism represents a promising

genetic marker linked to endothelial dysfunction and diabetic foot complications. Evidence suggests that the C/C genotype may predispose to more severe purulent-necrotic lesions and surgical necessity, while the T/T genotype may be associated with relatively milder disease expression and better therapeutic response. Although not yet established for routine clinical use, NOS3 genotyping could contribute to risk stratification and personalized management strategies in diabetic foot syndrome.

REFERENCES

1. International Diabetes Federation. IDF Diabetes Atlas. 10th ed. Brussels: IDF; 2021.

2. Boulton A.J.M., Armstrong D.G., Albert S.F., Frykberg R.G., Hellman R., Kirkman M.S., et al. Comprehensive foot examination and risk assessment. Diabetes Care. 2008;31(8):1679–1685.

3. Edmonds M., Foster A. Managing the Diabetic Foot. 3rd ed. Oxford: Wiley-Blackwell; 2014.

4. Casas J.P., Bautista L.E., Humphries S.E., Hingorani A.D. Endothelial nitric oxide synthase gene polymorphisms and cardiovascular disease: a HuGE review. Circulation. 2004;109(11):1359–1365.

5. Förstermann U., Sessa W.C. Nitric oxide synthases: regulation and function. European Heart Journal. 2012;33(7):829–837.

6. Tesauro M., Cardillo C. Obesity, blood vessels and metabolic syndrome. Acta Physiologica. 2011;203(1):279–286.

7. Moncada S., Higgs A. The L-arginine–nitric oxide pathway. The New England Journal of Medicine. 1993;329(27):2002–2012.

8. Cheng J., Jiang J., Liu Y., Chen H. Association between endothelial nitric oxide synthase gene polymorphisms and diabetic microvascular complications: a meta-analysis. Molecular Biology Reports. 2014;41(4):2295–2304.

9. Wang X.L., Mahaney M.C., Sim A.S., Wang J., Wang J., Blangero J., et al. Genetic contribution of the endothelial nitric oxide synthase gene to plasma nitric oxide levels. Arteriosclerosis, Thrombosis, and Vascular Biology. 1997;17(11):3147–3153.

10. Stehouwer C.D.A., Lambert J., Donker A.J.M., van Hinsbergh V.W.M. Endothelial dysfunction and pathogenesis of diabetic angiopathy. Cardiovascular Research. 1997;34(1):55–68.

11. Hinchliffe R.J., Brownrigg J.R.W., Apelqvist J., Boyko E.J., Fitridge R., Mills J.L., et al. IWGDF guidance on the diagnosis, prognosis and management of peripheral artery disease in patients with foot ulcers in diabetes. Diabetes/Metabolism Research and Reviews. 2016;32(S1):37–44.