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Reply to the Letter to the Editor: NOS3 T-786C: Methodological Considerations

Editöre Mektup Yanıtı: NOS3 T-786C: Metodolojik Hususlar

LETTER TO THE EDITOR REPLY
EDİTÖRE MEKTUP YANITI

To the Editor,

We sincerely appreciate the authors' interest in our article, "T-786C Polymorphism of the NOS3 Gene and Its Role in the Development of Renal Dysfunction in Patients of the Uzbek Population with Chronic Heart Failure,"[1] as well as their thoughtful comments.[2] We value the opportunity to clarify several aspects of our study. Our detailed responses are provided below.

We appreciate the authors' insightful observation. We agree that symmetric dimethylarginine (SDMA) and asymmetric dimethylarginine (ADMA) are important modulators of endothelial dysfunction and nitric oxide metabolism, particularly in patients with chronic kidney disease. Unfortunately, because of financial and technical limitations at the time of the study, these biomarkers were not evaluated.[3]

Our intention was not to imply that the lower NO concentration was solely attributable to the NOS3 T-786C polymorphism. Rather, we proposed that, in patients with chronic heart failure and renal impairment, this polymorphism may represent one of several factors contributing to endothelial dysfunction. We agree that NO production may be influenced by multiple biological mechanisms, including oxidative stress, inflammation, the accumulation of endogenous NOS inhibitors such as ADMA, renal dysfunction itself, and other genetic and environmental factors.

We also agree that future studies incorporating oxidative stress markers, ADMA, SDMA, and functional assessments of endothelial function would provide a more comprehensive understanding of these mechanisms.

We appreciate the authors for raising this important methodological issue. Our study was designed as an exploratory genetic association analysis involving patients from the Uzbek population, for whom published data on NOS3 T-786C allele frequencies and expected effect sizes were unavailable at the time of the study design. Consequently, it was not possible to perform a reliable a priori sample size calculation.

The final study cohort consisted of 200 patients with chronic heart failure and 120 healthy controls. These participants represented all eligible individuals recruited during the study period according to the predefined inclusion and exclusion criteria. Although we acknowledge that formal power calculations strengthen genetic association studies, our sample size is comparable to those of several previous candidate-gene studies investigating cardiovascular diseases.[4]

We agree that larger cohorts and formal statistical power calculations in future multicenter studies are necessary to validate our findings.

We appreciate this important statistical observation. We fully agree that statistically non-significant results should not be interpreted as evidence of a true association and should instead be interpreted with caution.

Our objective was to explore a plausible biological hypothesis regarding the role of endothelial nitric oxide synthase in cardiovascular disease, supported by previous experimental and clinical evidence, rather than to claim a definitive association between the C allele and renal dysfunction. Accordingly, the terms "possible role" and "trend" were used to emphasize the exploratory nature of our findings rather than to imply statistical evidence.[5]

Gulnoza Zakirova[1*]
Dilyafruz Masharipova[1]
Qodirjon Boboev[2]
Dilnoza Tagaeva[1]

[1]*Republican Specialized Scientific and Practical Medical Center of Therapy and Medical Rehabilitation, Tashkent, Uzbekistan*
[2]*Republican Specialized Scientific and Practical Medical Center of Hematology, Tashkent, Uzbekistan*

**The current affiliation of the author: Tashkent State Medical University, Tashkent, Uzbekistan*

Corresponding author:
Dilnoza Tagaeva
✉ dilnoza_tagaeva@mail.ru

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We acknowledge that this wording may have been interpreted too literally, and we appreciate the opportunity to clarify our intent. We agree that larger prospective studies are needed before definitive conclusions can be drawn regarding the clinical significance of the NOS3 T-786C polymorphism.

We are sincerely grateful to the authors for their valuable comments. We believe their observations will contribute to improving future research in this important field. Although we recognize the limitations of our study, we believe our findings provide preliminary evidence supporting a potential role of the NOS3 T-786C polymorphism in cardiorenal dysfunction among Uzbek patients with chronic heart failure and may serve as a foundation for larger multicenter investigations.

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