

OPINION

by

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on: Dissertation submitted for the award of the educational and scientific degree **“Doctor”**; Higher Education Field 7. Healthcare and Sport, Professional Field 7.1 Medicine, Scientific Specialty **“General Medicine”**, by **Nikolay Aleksandrov Bekyarov, MD**

on the topic **“Assessment and Role of Some Markers of Endothelial Dysfunction and Oxidative Stress in Outpatients with Metabolic Syndrome”**

Scientific Supervisor: Prof. Valentina Madzhova, MD, PhD

By decision of the Chair of the Scientific Jury and in accordance with Order of the Rector of the Medical University of Varna No. R-109-300 of 21.08.2026, I have been appointed to present an opinion on the dissertation of Dr. Nikolay Aleksandrov Bekyarov on the topic **“Assessment and Role of Some Markers of Endothelial Dysfunction and Oxidative Stress in Outpatients with Metabolic Syndrome”** for the award of the educational and scientific degree **“Doctor”** in the scientific specialty **“General Medicine”**.

This opinion has been prepared and is submitted in accordance with the requirements of the Act on the Development of the Academic Staff in the Republic of Bulgaria (ADASRB) and its Implementing Regulations.

Brief biographical data of the doctoral candidate.

Dr. Nikolay Aleksandrov Bekyarov was born on 07.04.1977. In 2004 he graduated with a Master's degree in Medicine from the Medical University of Varna. In 2015 he acquired the specialty of Neurology. Dr. Bekyarov also holds a Master's degree in Health Management.

The doctoral candidate began his professional career in 2005 as a resident physician at the Department of Neurology of **“MHAT Tervel”** EOOD, Tervel. From 2007 to 2013 he worked as a physician at the Emergency Department of **“MHAT – Dobrich”** AD. Since 2007 to the present he has been working as a specialist in Neurology – ward physician at **“MHAT –**

Dobrich" AD. Since 2015 to the present he has also been working as a specialist in Neurology at "Viva Feniks" Medical Center OOD, Dobrich – outpatient neurology practice.

Significance and topicality of the research topic: The dissertation of Dr. Nikolay Aleksandrov Bekyarov addresses a topical and important practical problem of interdisciplinary significance. Metabolic syndrome is a global problem affecting a growing number of people of working age. The complications of metabolic syndrome are numerous, but the most important are cardiovascular and cerebrovascular complications (heart attacks and strokes), as they frequently lead to disability or death. The development of endothelial dysfunction is regarded as the main pathogenetic factor linking metabolic syndrome with the impact of risk factors. The search for ways to reduce damage to the vascular wall is one of the most promising directions in the prevention of cardiometabolic diseases.

Volume and structure: The dissertation of Dr. Nikolay Bekyarov comprises 104 pages, illustrated with 33 figures and 4 tables. The bibliography includes 281 literature sources, all of which are in Latin script. The subject matter and content of the work are suitable for a doctoral dissertation and are of interest not only to specialists in General Medicine but also to a wider range of professionals in the fields of cardiovascular diseases and endocrinology.

The literature review consistently examines the significance of endothelial dysfunction in the development of metabolic syndrome. It presents the key role of asymmetric dimethylarginine in endothelial dysfunction, as well as the role of heme oxygenase-1 in protecting cells against oxidative stress and inflammation. The literature review concludes with findings that support the need for research on the dissertation topic.

Research methodology: The aim of the present study is to investigate and evaluate the role of some markers of endothelial activation and oxidative stress in outpatients with metabolic syndrome.

To achieve this aim, the doctoral candidate has defined 8 main objectives:

1. To investigate the plasma level of asymmetric dimethylarginine (ADMA), a marker of endothelial dysfunction.
2. To investigate malondialdehyde (MDA), a marker of oxidative stress, in individuals with metabolic syndrome.

3. To investigate the lipid profile parameters, glucose and uric acid levels, and body mass index (BMI).
4. To investigate the presence of a correlation of ADMA and MDA with the lipid profile parameters and the atherogenic indices.
5. To investigate the expression of the transcription factors Nrf2 and NF- κ B and of HO-1 in peripheral blood mononuclear cells (PBMC) in individuals with metabolic syndrome.
6. To investigate the relationship between ADMA, HO-1, Nrf2, and NF- κ B in individuals with metabolic syndrome.
7. To investigate and evaluate the change in carotid intima-media thickness (CIMT) with age in individuals with metabolic syndrome.
8. To evaluate the relationship between CIMT, ADMA, HO-1, NF- κ B, and Nrf2 in individuals with metabolic syndrome.

The results obtained are presented in text form and through 4 tables and 33 figures. The statistical processing applied is adequate. The discussion is thorough and well systematized, comparing the author's own results with international studies. It is precisely in this chapter that Dr. Bekyarov's sound awareness of the field, rich clinical experience, and capacity for critical analysis of the results obtained become evident. The results presented are fully sufficient for the fulfillment of the stated objectives.

The conclusions number 8 in total and follow logically from the results obtained. They are well formulated, clear, and precise.

The contributions presented number 14 in total and are divided into three groups:

Contributions of an original character

1. For the first time in Bulgaria, the relationship between ADMA and HO-1, an antioxidant and marker of oxidative stress, has been investigated in individuals with MetS. The investigation of HO-1 makes it possible to evaluate the body's adaptive mechanisms under conditions of oxidative stress, as well as the opportunities for therapeutic intervention.

2. For the first time in Bulgaria, the relationship between ADMA, HO-1, and the transcription factors Nrf2 and NF- κ B has been investigated, which would contribute to clarifying the complex mechanisms of endothelial damage; this is of practical importance for the prevention, early diagnosis, and treatment strategy in individuals with MetS.
3. Associations have been outlined between parameters such as ADMA and markers of oxidative stress (MDA, HO-1, and Nrf2), the lipid profile (total cholesterol, triglycerides, HDL), BMI, and glucose, which is of practical importance for the follow-up and prevention of cardiovascular complications in these individuals.
4. The importance of a comprehensive assessment has been highlighted, including ADMA as a marker of endothelial dysfunction, together with markers of oxidative stress (MDA, HO-1, and Nrf2) and CIMT as a marker of subclinical atherosclerosis and cardiovascular risk.
5. The comprehensive investigation of ADMA, a marker of endothelial activation, and of markers of oxidative stress (MDA, HO-1, and Nrf2) may be a promising step toward the development of an effective model for monitoring CIMT and for the early detection of vascular damage in individuals with MetS.
6. For the first time, the relationship between biochemical markers of endothelial activation and CIMT, a parameter reflecting structural vascular changes, has been investigated, taking into account the role of the balance between factors of endothelial damage and factors of endothelial protection.

Contributions of a confirmatory character

1. Individuals with MetS show changes in the lipid profile and atherogenic indices, glucose levels, and BMI compared with healthy controls.
2. In individuals with MetS, there is a positive correlation between ADMA, a marker of endothelial activation, and the lipid indices.
3. In individuals with MetS, an increase in CIMT with advancing age has been established.
4. In individuals with metabolic syndrome, changes in the levels of ADMA, a marker of endothelial activation, occur early, before measurable structural changes in the vascular wall, such as CIMT.

5. The biochemical assessment of lipid profiles/indices and changes in CIMT prove to be effective approaches for cardiovascular risk stratification.

Contributions of a scientific-applied character

1. The investigation of the transcription factors Nrf2 and NF- κ B provides a more reliable and comprehensive picture of the mechanisms of endothelial damage than the investigation of individual markers of oxidative stress and inflammation alone.
2. The present study points the way for future therapeutic approaches aimed primarily at targeting the transcription factors Nrf2 and NF- κ B, which regulate the expression of the genes of damaging and protective vascular factors in individuals with MetS.
3. The set of methods presented in the study can be effectively applied as an innovative approach in clinical practice for the diagnosis of endothelial damage in individuals with MetS.

Conclusion: The dissertation of Dr. Nikolay Aleksandrov Bekyarov contains significant and original results, which have been adequately formulated into conclusions and contributions. The dissertation meets the requirements of the Act on the Development of the Academic Staff in the Republic of Bulgaria (ADASRB) and the Regulations for the Development of the Academic Staff at the Medical University of Varna.

All of the above gives me grounds to award a "Positive" evaluation for the conferral of the educational and scientific degree "Doctor" in the scientific specialty "General Medicine" upon Dr. Nikolay Aleksandrov Bekyarov.

15.10.2026

Prepared by:.....

Заличено на основание чл. 5,
§1, б. „В“ от Регламент (ЕС)
2016/679

(Assoc. Prof. Zhenya Ruseva, MD, PhD)