

OPINION

from

Prof. Dr. Dobrin N. Konstantinov, PhD,

**external member of the Scientific Jury, appointed by Order No. P-109-
139/04.05.2024 of the Rector of MU-Varna,**

for the doctoral dissertation of Dr. Kristina Ivaylova Petrova

on the subject:

**"Assessment of oxidative stress and early vascular damage in children and
young adults with beta-thalassemia major",**

**in the field of higher education 7. "Health and sport", code 7.1. "Medicine",
scientific specialty "Pediatrics"**

Biographical data. Dr. Kristina Ivaylova Petrova graduated from MU-Varna with a master's degree in medicine in 2013. Since 2014, he has been a phisician at the Children's Clinical Hematology and Oncology Department in the University Multiprofile Hospital "St. Marina", Varna, and since 2019 she is a professor-assistant at the Department of Pediatrics, MU-Varna. Since 2020, she has been included in a Doctoral program of MU-Varna. After successfully passing the state exam in 2019 she acquired a specialty in Pediatric Clinical Hematology and Oncology.

Importance of the topic. The topic choice "Evaluation of oxidative stress and early vascular damage in children and young adults with beta-thalassemia major" is appropriate and significant for a dissertation work. The transfusion program applied from early childhood and the accompanying chelation therapy allow in recent decades patients with the congenital homozygous form of beta-thalassemia to reach an overall survival similar to healthy children. However, a specific disease profile and health risks have been observed among this cohort of patients and these facts impose a justified scientific interest.

Structure. The doctoral thesis is presented on 137 standard pages. The text includes 21 figures and 36 tables. The distribution of main parts is appropriate and proportional and is carried out as follows: "Literature overview" covers 34 pages; "Aim and tasks" - 2 pages; "Materials and methods" - 8 pages; "Results and Discussion" - 51 pages. Main conclusions, contributions, list of publications and communications and

appendices are contained in 18 pages. The list of literature sources is presented on 31 pages.

In general, the layout of the dissertation - structurally, linguistically and graphically, deserves a very high rating.

In connection with the dissertation, the author has 3 publications in the Bulgarian specialized press (in one of them, she is the first and only author, in the second she is the first author in co-authorship) and 2 participations in national scientific events as a sole author of the presentations.

Dissertation analysis. The overview of literature sources is extensive, including 358 published articles, of which 21 are in Cyrillic and 337 are in English, with a significant part of the sources being from the last 5 years. The overview itself is appropriately divided into main topics, starting with general explanations about beta-thalassemia syndrome, including more in-depth information about its severe, homozygous form – beta-thalassemia major. In the following parts of the review, Dr. Kristina Petrova dwells in detail on the description of the essence of oxidative stress and the various processes of cellular and tissue damages related to it, as well as the compensatory, protective mechanisms of counteraction in the body. The oxidation product - malondialdehyde and its role as a marker of the body's oxidative status are examined in detail. Current understanding of oxidative stress in beta-thalassemia and, in particular, the role of iron overload in the formation of toxic free radicals, as well as the role of malondialdehyde in the specific disease are presented. In another section, oxidative stress and its relationship in causing vascular disorders, influencing lipid homeostasis and atherosclerotic changes; the role of the endothelium and its influence by induced oxidative stress; methods for measuring arterial stiffness, etc are discussed in detail. A separate section discusses the cardiovascular risk in beta-thalassemia and the possibilities for its assessment. At the end of the overview section, Dr Petrova has appropriately drawn conclusions from the extensive literature review, which allow her to clearly approach defining the purpose and tasks of the dissertation work.

The **purpose of the study** is well formulated - to identify the presence of early vascular involvement by means of the study of arterial stiffness of peripheral vessels

and the study of its correlations with oxidative stress markers, lipid profile indicators and lipid indices in children and young adults with beta-thalassemia major.

The tasks to achieve the goal are maximally specified and grouped. Most significant among them are: comparative evaluation of initial hemodynamic indicators (heart rate, arterial pressure and pulse pressure); comparative assessment of hematological parameters and indicators of iron overload; analysis of lipid metabolism indicators and some atherogenic indices as markers of cardiovascular risk; determination of serum concentrations of malondialdehyde; measurement and comparison of the local arterial stiffness of the two carotid arteries, by means of echo-tracking; study of correlations between serum ferritin levels and indicators of lipid metabolism and some atherogenic lipid indices; search for correlations between hemoglobin values and lipid profile indicators and lipid indices; study of correlations of ultrasound parameters of carotid arteries with gender, age, indicators of lipid exchange and atherogenic lipid indices, as well as serum ferritin and malondialdehyde levels; study of the correlations between available splenectomy on the one hand and ultrasound parameters of both carotid arteries, indicators of lipid exchange and atherogenic lipid indices, etc. in patients with beta-thalassemia major.

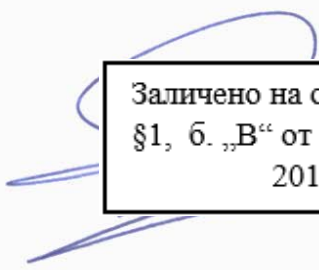
Material and methods. Selected for participation, according to precise inclusion and exclusion criteria, were 78 children and young adults, of which 38 patients with beta-thalassemia major (18 males and 20 females) and 40 healthy controls (20 males and 20 females gender). All of them were treated and monitored at the expert center for coagulopathies and rare anemias at the "St. Marina" University Hospital in Varna for a period of 1 year and 4 months. Appropriate documentation, informational materials, informed consents are provided. Research methods include - survey, medical history, description of status and anthropology and directed, in relation to the tasks, laboratory research. The main instrumental examination carried out personally by Dr. Petrova herself, who has passed relevant qualification training and certification, is an ultrasound examination of the two common carotid arteries. The results are subjected to appropriate statistical analysis suitable for their objectification and evaluation.

Results and discussion. The results of the study are summarized and presented comprehensively and in an appropriate form. They are grouped by categories specified in the survey tasks. The selected tabular and graphic presentation is precise

and gives a complete picture of the obtained data and the results of the statistical analysis. In the comparative studies between patients and controls, the theses of Dr. Petrova are clearly proven and with the corresponding statistical significance. As a very positive feature of the dissertation work, I appreciate the in-depth discussion of results immediately after each presentation by categories, which helps the specific interpretation of the data, the comprehensive comparison of scholar's own results with those of the literature data, and the objectification and early conclusions. I fully agree with the conclusions presented. Dr. Petrova is critical in her conclusions based on objective statistical criteria and this allows proper assessment of her own contributions. I also agree with the presented contributions of the dissertation work. The doctoral work is first of its kind in Bulgaria and the achieved goal and tasks, fully in sync with international experience, allow, in practical terms, to add new indicators for follow-up, prevention and early therapeutic behavior of the serious complications in the contingent of children and young adults with beta - thalassemia major.

Abstract. The proposed abstract, in terms of form and content, meets the requirements and presents the essence of the dissertation development in an appropriate and comprehensive manner.

In conclusion, on the basis of the above positive opinion, I consider that the dissertation fully meets all academic requirements and I would confidently recommend to the respected Scientific Jury to award Dr. Kristina Ivaylova Petrova the scientific and educational degree "Doctor"(PhD).



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