

To the Chairman of the Scientific Jury,
determined by order No. R-109-5/06.01.2023
of the Rector of Medical University – Varna
and Protocol No. 1/18.01.2023

OPINION

By Assoc. Prof. Irena Ivanova Gencheva – Angelova, MD, PhD
scientific specialty Clinical Laboratory,
Associate Professor at the Department of "Clinical Laboratory, Clinical Immunology and
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On the dissertation

Of Dr. Gergana Mladenova Chausheva with dissertation title:

"Laboratory assessment of cardiovascular risk in persons with long-standing type I diabetes
mellitus - adipokines, osteoprotegerin, asymmetric dimethyl-arginine",
PhD student on a full-time basis, professional direction 7.1 Medicine
In "Clinical Laboratory" doctoral program

1. General presentation of the procedure

The submitted set of materials complies with the requirements of the procedure for obtaining
PhD degree according to the regulations of MU – Varna and includes all necessary documents.

2. Brief biographical data about the PhD student

Dr. Gergana Chausheva was born in 1987. She graduated from the IV Language High School
"Frederic Joliot-Curie" in 2006 and Medicine in MU - Varna in 2012. Since 2013 works as a
medical doctor in the Clinical Laboratory Department at "St. Marina" - Varna, and since 2017
is an assistant professor at MU "Prof. Dr. Paraskev Stoyanov" in the "Clinical Laboratory"
Department. In 2018 acquires a specialty in Clinical Laboratory. From 2020 is enrolled as a
PhD student on a full-time basis in "Clinical Laboratory" doctoral program, professional
direction 7.1 Medicine.

3. Relevance of the topic

Diabetes mellitus (DM) is a chronic, socially significant disease with a progressively increasing frequency worldwide and in Bulgaria. As life expectancy increases, cardiovascular disease (CVD) is becoming a major cause of mortality in patients with type 1 DM (T1D). Currently, risk stratification and screening programs to assess cardiovascular risk (CVR) in T1D are mostly extrapolated from studies in patients with type 2 DM (T2D) or the general population. This approach is unsatisfactory due to substantial differences in the pathophysiological mechanisms of CVD development between T1D and T2D.

The laboratory evaluation of cardiovascular risk through the introduction of new biomarkers, such as asymmetric dimethylarginine (ADMA), osteoprotegerin (OPG), adiponectin (ADNC) and leptin (Lep), which is the subject of the scientific research of Dr. Gergana Chausheva's dissertation work, would allow optimization of diagnostic and therapeutic approaches in patients with T1D. By means of these biomarkers, the degree of CVR in patients with T1D can be determined. The scientific study makes it possible to determine whether the quantification of serum asymmetric dimethylarginine, osteoprotegerin, adiponectin and leptin is of high informative value for clinical practice in terms of CVD risk stratification with aim to achieve a better quality of life and survival for patients with T1D.

All this determines the topic of the dissertation work as relevant and useful for clinical practice. The results are relevant for the development of science and practical behavior for the prevention of CVD in persons with long-standing T1D.

4. Evaluation of the dissertation work

The presented dissertation covers a total of 175 pages, illustrated with 56 tables and 52 figures, and is organized into the following sections: Title Page, Contents (3 pages), Abbreviations used (1 page), Introduction (2 pages), Literature review (42 pages), Aim and objectives (1 page), Material and Methods (6 pages), Results (67 pages), Discussion (28 pages), Conclusions and contributions (3 pages). The bibliography contains 307 literary sources, 14 of them in Cyrillic and 293 in Latin.

5. Structure of the dissertation work

The structure and content are presented correctly and in detail. The most frequently used abbreviations are listed. The individual chapters and sub-chapters are properly designed, which gives clarity and clarity to the dissertation work.

The literature review is very well structured and includes up-to-date information on the topic. Epidemiological data on type 1 DM, on a global and national scale, are presented in detail. They summarize some particular aspects of the atherosclerotic process in T1D, associated with age of diagnosis, disease progression and asymptomatic course of IHD. Cardiovascular risk in these

patients was assessed, as well as candidate biomarkers for assessing CVR in T1D - asymmetric dimethylarginine, osteoprotegerin, leptin and adiponectin. The PhD student knows the state of the problem very well and presents a thorough analysis.

The aim of the dissertation is clearly stated, namely to analyze the prognostic value of: asymmetric dimethylarginine (ADMA), osteoprotegerin (OPG), leptin (Lep) and adiponectin (ADNC) against specific tools for the evaluation of CVR – STENO Type 1 Risk Engine (STIRE) and ESC 2019, and compared to hematological indicators in persons with long-standing T1D.

Material and methods - for the purposes of this dissertation, Dr. Chausheva selected 59 healthy volunteers and 124 patients with long-term T1D. The laboratory tests were carried out in the MDL Clinical Laboratory at UMHAT "St. Marina" - Varna. The inclusion and exclusion criteria of the study are well defined. Calculators were used to estimate CVR - STENO Type 1 Risk Engine (STIRE); RiskFactor3. The capabilities of the SPSS 19 statistical package were used for statistical processing of the data.

Results - the results of the study are presented in 6 sections, well illustrated in tabular and graphical form, accompanied by commentary. Hematomorphological parameters were compared between patients with T1D and healthy subjects. Links are made with OPG, ADMA, ADNC and Lep; with STIRE, ESC from 2019 and Riskfactor3.

Associations have been made between leukocytosis and anemia, and CVR in individuals with long-standing T1D. ADNC and Lep values are also associated with anemia, leukocytosis, and thrombocytosis

In the discussion, the clinical and laboratory characteristics of the examined persons are commented in detail. In five sections, the prognostic value of each of the studied biomarkers is presented and discussed. The influence of gender, age and duration of diabetes on their values is commented on. Their average levels depending on the CVR category according to STIRE and ESC from 2019 in patients with T1D are presented. The relationships made with AlbU, CRP, HbA1C and with RiskFactor3 were evaluated, as well as ROC analyzes for deriving threshold values of the studied indicators in T1D. Section 6 discusses the relationships between hematomorphological changes and CVR in patients with T1D. The trends for the development of anemia and leukocytosis in these individuals are presented. The dependences between the four investigated indicators and the hematomorphological indicators are derived.

In the dissertation, 12 **conclusions** are drawn, which are in accordance with the obtained results and are logically deduced from the set tasks.

The contributions in the dissertation work are divided into two categories: of an original nature and of a theoretical and scientific-applied nature.

Abstract and publications related to the dissertation work:

The abstract, in terms of content and quality, fully presents the results of the scientific research in the dissertation. The dissertation student has 2 scientific publications and 4 participations in scientific forums related to the dissertation work.

Conclusion:

The dissertation of Dr. Gergana Mladenova Chausheva "Laboratory assessment of cardiovascular risk in persons with long-term type I diabetes mellitus - adipokines, osteoprotegerin, asymmetric dimethyl-arginine" is up-to-date and properly structured.

The dissertation meets all the requirements of the Law on the Development of the Academic Staff in the Republic of Bulgaria, the Regulations for its implementation and the Regulations for the Development of the Academic Staff at MU - Varna for the acquisition of the scientific and educational degree "Doctor".

I confidently give a **positive** opinion on awarding the educational and scientific degree "Doctor" in the scientific specialty "Clinical Laboratory" to Dr. Gergana Mladenova Chausheva.

06.02.2023

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Signature:



/Assoc. Prof. Irena Gencheva, MD, PhD/