To

The Chairman of the Scientific Jury,

determined by Order

№ P-109-378 / 06.10.2020

of the Rector of MU-Varna

OPINION

of dissertation for awarding scientific title "Ph.D."

From Assoc. Prof. Dr. Zhivka Boneva Asyova, Ph.D.

Head of the Clinic of Endocrinology and Metabolic Diseases,

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external member of the Scientific Jury, appointed by order of the Rector of MU-Varna

№ P-109-378 / 06.10.2020

Professional field: 7.1. "Medicine"; Field of higher education: 7. "Health and Sports"

Doctoral program: "Endocrinology and metabolic diseases"

Author: Dr. Elena Stoyanova Marinova

Form of doctoral studies: independent preparation

Department: Second Department of Internal Medicine, Faculty of Medicine, Medical University - Varna

Title: "Non-invasive assessment of arterial rigidity in patients with type 2 diabetes mellitus - correlation with some biomarkers."

Scientific advisers: Assoc. Prof. Mila Boyadzhieva, MD; Prof. Branimir Kanazirev, MD

I. General presentation of the procedure

This opinion has been prepared in accordance with the requirements of the Regulations for the structure and activity of MU-Varna.

The academic set of materials presented by the doctoral student is in accordance with the Regulation for Acquisition of ONS "Doctor" and includes:

- Completed and printed by the doctoral student dissertation;

- Abstract;

- Publications and participations related to the developed topic;

- Successfully passed doctoral minimum;

- Additional materials, references and documents, in accordance with the requirements.

The dissertation was discussed and aimed at public defense by the Faculty of Medicine at the Medical University - Varna, Minutes № 29 / 28.09.2020.

II. Brief biographical reference

Dr. Elena Stoyanova Marinova was born in Shumen in 1983. She graduated from the Medical University "Prof. Dr. Paraskev Stoyanov "in Varna in 2008. In the same year she was appointed as a doctor in the Department of Cardiology at the University Hospital in Pleven, and in 2009 - in SBALK in Cardiology, Varna. The same year, after winning a competition, a specialization in Endocrinology and Metabolic Diseases began at the MHAT "St. Marina ", Varna. Since 2012 he has been a resident doctor at the Clinic of Internal Medicine and an honored assistant at the Department of Propaedeutics of the World Bank. In 2015 she acquired the specialty Endocrinology and metabolic diseases. In 2016 she was selected as a full-time assistant at the Department of Propaedeutics of the UK. In 2017 she conducted training courses in "Cervical Ultrasound" and "Clinical Neurosonology". On December 11, 2018, by Order №P-109-655, she was enrolled as a doctoral student with an independent form of study at the Second Department of Internal Medicine, Faculty of Medicine, Medical University - Varna. In the presented CV, the doctoral student indicated a very good level of English language skills.

III. Relevance and significance of the topic

The presented dissertation is dedicated to a current problem concerning the challenges in the early diagnosis of macrovascular complications in type 2 diabetes mellitus, which include the processes of vascular calcification and arterial rigidity. Attention to arterial rigidity as one of the non-traditional cardiovascular risk factors has increased in recent years due to its independent and predictive value for cardiovascular events, especially in high-risk patients such as those with T2D. Early detection of these changes, in the phase of subclinical atherosclerosis, would allow the application of measures to prevent cardiovascular complications.

Literature data show that the use of single-point echotracking technology provides information on the local arterial rigidity of the common carotid artery, which has demonstrated a correlation with aortic rigidity and therefore with the risk of developing vascular morbidity and mortality. This scientific work draws attention to another new "hot spot" in research in the last 10 years - the importance of the non-carboxylated form of osteocalcin for carbohydrate and lipid metabolism.

In recent decades, the association between vascular calcification and all-cause mortality (cardiovascular disease, especially in patients with high atherogenic status) or chronic kidney disease has been repeatedly emphasized. For more than a century, vascular calcification has been shown to be a passive, degenerative aging process without any treatment options. In recent decades, however, studies have confirmed that arterial mineralization is an active, complex process similar to bone formation. Biomarkers of vascular calcification have been identified that can be measured in serum and their role as prognostic factors (including the role of matrix Gla protein, osteoprotegerin, bone morphogenetic proteins, fibroblast growth factor-23, osteocalcin, osteoleoctin, osteolepontin, osteopontin, fibrillin-1, carbonic anhydrase II, etc.).

The hypothesis of osteocalcin participation in the processes of vascular mineralization and arterial rigidity is increasingly being developed. In a recent meta-analysis involving 46 studies, 26 of them reported a positive association between plasma osteocalcin and vascular calcification.

IV. Structure of the dissertation

The work I was introduced to proves the existence of a clearly defined profile of scientific interests, specific scientific tasks and working hypotheses.

The presented scientific work is written on 136 pages and includes: introduction - 2 pages; literature review - 39 pages; working hypothesis, goal and tasks - 2 pages, material and methods - 6 pages, results - 38 pages, discussion - 11 pages, conclusions - 3 pages, conclusion and contributions - 3 pages. The bibliographic reference is on 16 pages. and contains 207 titles, of which 1 in Cyrillic, the remaining 206 in Latin. The literature review is detailed and extensive and is entirely topic-oriented. Data on the association between arterial rigidity and diabetes mellitus, the relationship with macrovascular complications and the importance of osteocalcin for vascular calcification and arterial rigidity are presented in depth and analytically. The significance of the ultrasonic measurement of local arterial rigidity by means of a high-frequency single-point echotracking technique is described in detail. The review covers all aspects of the given topic and logically presents the arguments for conducting the research. It reflects the good scientific training and developed knowledge on the problem of Dr. Marinova. It is supported by appropriate literature sources, as 127 of the sources, or 61.3% of the bibliography are from the last 10 years, and 56 (27%) are from the last 5 years, which shows good awareness of the doctoral student for theoretical discussion on the topic in modern science. literature.

The aim is formulated specifically, clearly and precisely in the direction of obtaining data on the local arterial rigidity of the carotid arteries in patients with T2HD without macrovascular complications by echotracking technique; to look for connection of the indicators of arterial rigidity with glucometabolic, lipid, hemodynamic parameters and the levels of serum osteocalcin, as well as to evaluate the effect of vitamin K2 supplementation in some persons with diabetes.

To achieve this goal, 6 tasks have been set, which derive from it and allow the comprehensive development of the study.

Research methodology: the study was originally designed, prospective, covering a Bulgarian population of 100 patients with type 2 diabetes mellitus with a mean age of 57.7 ± 7.48 years and 30 persons without a history of diabetes mellitus with a mean age of 56.7 ± 6.98 years. Participants were selected according to specific inclusion and exclusion criteria, ethical requirements were met and clinical, imaging and statistical methods were used. The results are summarized in 31 tables, 20 charts and 11 graphs on 38 pages. They are clearly structured and illustrated and demonstrate compliance with the set tasks and support of the set working hypothesis. A number of modern statistical methods have been used to process the data from the studied cohorts, which shows that the doctoral student uses them well. The discussion of the results of the conducted research is 11 pages and is presented in 4 sections: Analysis of the characteristics of the studied group; Analysis of the results of echotracking measured indicators

of arterial rigidity of the carotid arteries; Discussion of the results of the studied serum levels of osteocalcin; Discussion of the results of the performed supplementation with vitamin K2. In each of them the doctoral student objectively compares the obtained own results with data from the scientific literature, which shows the ability of Dr. Marinova to analyze, synthesize and interpret the scientific information. The formulated 10 conclusions correspond to the results and cover the overall scientific development.

The contributions are 8 and are in full accordance with the obtained results, as they are divided into contributions of scientific-theoretical, scientific-practical and confirmatory nature. The study is the first in Bulgaria to measure arterial rigidity in patients with T2DD using echotracking methodology; which examined osteocalcin as a marker of arterial rigidity in patients with T2DD and which examined the change in carotid rigidity after vitamin K2 supplementation. It is stated that the determination of increased carotid rigidity by ultrasound echotracking in patients with T2HD is non-invasive, fast and reliable and suitable for clinical practice, as it would allow early diagnosis of vascular involvement and allow for early prophylactic measures.

The listed contributions are undoubtedly important both scientifically and practically.

V. Assessment of the doctoral student's publications and personal contribution

Dr. Marinova presents 3 publications. The doctoral student is the first author in all publications, which is proof of her leading role in research.

VI. Abstract

The content and quality of the presented abstract are in accordance with the requirements for acquiring ONS "Doctor" at MU-Sofia and reflects the main results achieved in the dissertation.

VII. Critical notes

I have no critical remarks on the research and the materials presented. It is recommended in future works to use a wider range of Bulgarian authors in the literature, who have written on the problem and a better structuring of the sources in the bibliography.

VIII. Conclusion

The dissertation I have reviewed shows that the doctoral student Dr. Elena Marinova has in-depth theoretical knowledge and professional skills. She demonstrates qualities and abilities for independent research. The dissertation contains scientific and applied results, which represent an original contribution to science and meet the requirements of the Law for development of the academic staff in the Republic of Bulgaria, the Regulations for application of ZRASRB and the Regulations of MU- Varna.

What has been stated so far gives me a reason to strongly support Dr. Elena Marinova, as I believe that there is every reason to award her the educational and scientific degree 'Ph.D.', as well as to recommend the esteemed members of the scientific jury to vote positively for this decision.

18.11.2020

assoc. prof. Zhivka Bŏneva, MD, PhD