Statement

by Prof. Kiril Hristov Hristozov MD, PhD
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Regarding: The dissertation of Dr. Elena Stoyanova Marinova, PhD student on a self-study basis, Second Department of Internal Medicine, educational sector Endocrinology, Medical University Varna to acquire the educational-scientific degree "PhD" in the field of higher education 7. Health and Sports, in the professional field 7.1. Medicine and scientific specialty "Endocrinology"

By order No. R-109-378/06.10.2020 of the Rector of Medical University - Varna and by decision of the Scientific Jury (Protocol № 29/28.09.2020) I was appointed to prepare an opinion on a dissertation on a topic „*Non-invasive assessment of arterial stiffness in patients with type 2 diabetes mellitus – correlation with some biomarkers*"for obtaining the scientific-educational degree "PhD" in the professional field 7.1. Medicine and scientific specialty "Endocrinology"

Brief CV data of the applicant

Dr. Elena Stoyanova Marinova was born in 1983 in Shumen. She completed her higher medical education with honors from the semester and state exams in 2008 at MU-Varna. As a trainee doctor she works in Emergency medical care in Varna. In the period November 2008- September 2009 she works in the Department of Cardiology at the University Hospital in Pleven and specialized hospital for active treatment in Cardiology Varna. After winning a competition she started specialization in endocrinology and metabolic diseases at the University Hospital 'St. Marina" Varna. Since 2012 she is a resident doctor at the Clinic of Internal Medicine and a part-time assistant at the Department of Propaedeutics of Internal Medicine of the Medical University of Varna. In 2015 she has acquired specialty in Endocrinology and metabolic diseases, and in 2016

she was elected a full-time assistant at the Department of Propaedeutics of Internal Medicine. In 2017, she conducted training for a highly specialized activity "ultrasound of the cervical region". In the same year she conducted a training course in Clinical Neurosonology.

1. Assessment of the significance of the topic

The topic of the dissertation is relevant. It refers to the early assessment of macrovascular complications occurring in patients with type 2 diabetes mellitus, performed with ultrasound machine equipped with modern and innovative software. It examines a possible link between molecules known in the scientific literature, which have recently discovered new effects and which are relevant to subclinical atherosclerosis. The present work is the first in our country, as far as I know, to study the relationship of bone protein with atherosclerotic vascular changes in patients with diabetes.

2. Structure and evaluation of the dissertation sections

The dissertation is well structured in 136 standard pages and includes the following sections:

Literature review (41 pages) – modern, in-depth and reflecting the important aspects of the researched scientific theses. It provides clarity regarding the measurement of arterial stiffness in patients with type 2 diabetes mellitus and their association with osteocalcin. The literature review ends with conclusions, which become the basis for formulating the tasks of scientific research.

Aim and tasks (1 page)– The aim is clearly formulated. For its implementation 6 tasks were designed, which cover all aspects of the studied purposes.

Materials and methods (6 pages) - The dissertation included 100 patients with type 2 diabetes mellitus (of which 52 females and 48 males) without macrovascular complications and 30 healthy controls. In part of the group of patients with T2DM (18 patients, of which 11 females and 7 males), supplementation with vitamin K2 (Kinone) 75 mmg / day was performed for a period of 4 weeks. Serum carboxylated and non-carboxylated osteocalcin levels were studied in 47 patients with T2DM and 18 subjects in the control group. The inclusion and exclusion criteria for participation in the study are clearly formulated. Ethical requirements were preserved. The instrumental methods for examination of patients are well described, in particular the echo-tracking

methodology. The methods used correspond to the achievement of the aim and tasks.

Results (45 pages) - The results of the conducted research are presented sequentially on the set tasks. They are presented in 31 tables, 20 diagrams and 11 graphs with the corresponding text to them. The statistical methodologies used to prove the scientific hypotheses are clarified in detail. Data on increased pulse wave velocity in patients with type 2 diabetes are particularly valuable, which is another additional cardiovascular risk factor in these patients. The early onset of elevated PWV and its non-invasive examination make the echotracking technique valuable for clinical practice. Analysis of the results for serum osteoclacin levels showed reduced values in patients with T2DM, and revealed correlations with some of the parameters of arterial stiffness. The need to search for new molecules to tip the scales in favor of medicine in the fight against atherosclerotic vascular complications in patients with T2HD is reflected in the studied subgroup in which vitamin K2 supplementation was performed.

Discussion (14 pages) - consistently and in accordance with the purpose of the dissertation, Dr. Elena Marinova compares her scientific results with modern scientific knowledge on the studied issues. She shows criticism in the analysis of the obtained results.

Conclusions and contributions (5 pages) - 11 conclusions are clearly presented, which correspond to the set tasks. Pulse pressure stands out as the most important hemodynamic parameter associated with increased arterial stiffness in T2DM. Carboxylated osteocalcin is associated with an increased β-stiffness index. A total of 8 contributions were presented, divided into three groups of scientific-theoretical, scientific-practical and confirmatory nature, which I accept as valid. The final conclusion is concise and clear and reflects a summary of the important results in the dissertation.

Publications related to the topic. Three publications (2 articles in Bulgarian and 1 in English) and two participations in an international congress were presented. Dr. Marinova is the first author of all these.

Bibliography - (16 pages) The described bibliographic sources are 207 (206 of them in Latin and 1 in Cyrillic), and sources from the last 5 years are predominant.

Conclusion: In conclusion, I consider that the presented dissertation is original, with a significant theoretical and applied contribution to cardiovascular diabetology. By structure, content and volume this dissertation meets the requirements for awarding the educational and scientific degree "PhD"

according to Academic Staff Development Act in the Republic of Bulgaria and the Rules for the Academic Staff Development at the Medical University of Varna. I recommend to the honorable members of the Scientific Jury to vote positively and to award Dr. Elena Stoyanova Marinova the educational and scientific degree "PhD".

12.11.2020

Varna

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/Prof. Kiril Hristov Hristozov, MD, PhD/