

STATEMENT

By Professor Deian Tonev Jelev, MD, PhD, DSc

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On the dissertation for awarding of the educational and scientific degree "Doctor" in the field of higher education 7- Healthcare and sport, professional direction 7.1 - Medicine, Scientific Speciality – "Gastroenterology"

Candidate: Dr. Mirela Radkova Moneva – Petrova, full-time PhD student at the Second Department of "Internal Diseases", Medical University of Varna,

Title of the thesis: "Obesity in patients with chronic inflammatory bowel diseases"

Research supervisor: Assoc. Prof. Antonia Yordanova Atanassova, MD, PhD, DSc

By order № P-109-263/15.05.2023 of the Rector of the Medical University of Varna, I have been appointed as a **member of the Academic jury**. In compliance with a Decision took at the first meeting of the jury, I have been elected to prepare a **statement** on the aforementioned dissertation.

The submitted documents for review meet all requirements of the Law for development of the academic staff in the Republic of Bulgaria as well as the Regulations for development of the academic staff in the Medical University of Varna.

1. Biographical data and professional development of the PhD student

Dr. Mirela Moneva-Petrova graduated in Medicine at MU – Varna in 2017. Her professional development as a doctor began in 2017 at the Department of Neurology of the hospital "Dobrich". She has been a physician at the Center for Emergency Medical Care – Varna, Branch-Dolni Chiflik since February 2018. Since 01.10.2018 Dr. Moneva-Petrova has been a resident in "Gastroenterology" at the Clinic of Internal Diseases at the MHAT – Varna to the Military Academy-Sofia, and since 09.10.2020 she has been enrolled as a full-time PhD student in the doctoral program "Gastroenterology" at the Second Department "Internal diseases" of MU – Varna.

Dr. Moneva-Petrova has been constantly developing her knowledge and clinical skills. She has participated in a training course "Medical insurance in disasters and crises with a large number of victims", as well as in theoretical postgraduate basic course in the following five training modules: "Lower gastrointestinal endoscopy - PPC with biopsies"; "Upper gastrointestinal endoscopy - EGD with biopsy"; "Lower gastrointestinal endoscopy - fibrosigmoidoscopy with biopsy"; "Lower gastrointestinal endoscopy - FCS with biopsy"; "Enteroscopy/capsular endoscopy". She also received practical training in the "Emergency Medicine" module. She speaks English and Russian fluently.

2. Relevance of the problem

Inflammatory bowel diseases (IBD) are among the scientific challenges of modern medicine. Despite the progress in our knowledge, the etiology and a number of aspects of the pathogenesis of IBD remain unknown. In recent years, research interest has been growing on the role of obesity in clinical course of IBD as well as on the treatment response. New studies have shown that obesity increases the risk of developing Crohn's disease (CD). Adipocytic hypertrophy of intra-abdominal adipose tissue leads to metainflammation, which induces multiple pro-inflammatory mediators, including tumor necrosis factor alpha (TNF- α), interleukin-6 (IL-6), and leptin. Metainflammation may contribute to the progression of IBD, but data on the effect of obesity on the course of IBD are still quite limited and highly controversial. This also refers to studies of the impact of obesity on therapeutic response. The presented dissertation is dedicated to these important clinical problems. Actually it is the first in-depth study of this issue in our country.

3. Structure and content of the thesis

The dissertation contains 166 pages in total. It is properly and classically structured and contains the following parts: introduction; literary review; purpose, tasks and hypothesis; material and methods; results; discussion; conclusions and references.

The literary review is comprehensive and complete. It gives an overall description of the problem under consideration. Its content is well focused on the purpose and objectives of the dissertation. An in-depth analysis of the most significant studies on the topic in recent years has been performed. The leading trends that motivated the development of the present dissertation are clearly outlined.

The goal is correctly and clearly formulated: to evaluate obesity in patients with chronic inflammatory bowel diseases (Crohn's disease and ulcerative colitis). The author logically has set 5 specific and feasible tasks that are directly related to the achievement of the study goal.

Material and methods: a total of 78 patients with IBD were studied. All of them were treated and followed-up at the clinic of Gastroenterology, University Hospital „St. Marina" - Varna during the time periode: Feb 2021 – Nov 2022. Subjects were divided into two groups: CD 40 pts. (20 with active CD and 20 in remission) and UC 38 pts. (16 with active UC and 22 in remission). Complex and precise characterization of patients was carried out by appropriately selected modern methods of examination – clinical, laboratory, imaging endoscopic and morphological. Each of the groups is detailed by gender, age, disease activity and treatment, as well as the presence of intestinal complications and extrinsic manifestations. The expression level in miRNAs serum was studied in all participants: hsa-miR-17-5p, hsa-miR-29A-5p, hsa-miR-146a-5p, hsa-miR-142-3p, hsa-miR-155-5p and control of cel-miR-39-3p and Human Lipocalin-2/NGAL. The specific working protocols are described in detail, as well as the type of whales used with quoted catalog numbers. A lipid profile was also examined and anthropometric studies were carried out.

The data are processed using adequate and reliable statistical methods, ensuring the reliability of the results obtained and the conclusions drawn.

The results of the own studies are presented in detail and appropriately illustrated with tables and figures. Due to the lack of validated threshold values for miRNAs and human Lipocalin-2/NGAL in subjects with normal body weight, they were calculated by the author for the needs of her study. Dr. Moneva-Petrova found that the espressiveness of the panel from the considered miRNAs according to anthropometric indicators for assessing obesity differs in patients with CD and UC. Overexpression of hsa-miR-17-5p is associated with UC, disease activity, as well as obesity and age of the patient over 40. The decreased expression of hsa-miR-29a-5p is associated with UC and achieved remission, obesity, and male gender. The author observed a decreased expression of hsa-miR-142-3p in patients with CD over the age of 40 and male sex, as well as overexpression of hsa-miR-155-5p patients with CD and achieved remission, obesity and female sex. Decreased expression of human Lipocalin-2/NGAL in UC is associated with obesity. Dr. Moneva - Petrova shows that neutralization of patients with IBD during treatment with biological drugs is a risk factor for failure to achieve remission, assessed by the expression of hsa-miR-29a-5p and hsa-miR-155-5p. In addition, obesity in patients with CD is a risk factor for failure to achieve remission, assessed by the expression of hsa-miR-146a-5p and hsa-miR-155-5p. In patients with UC of biological treatment, a BMI of more than 25 kg/m² and a Mayo score below 2 are a prerequisite for achieving remission, assessed by serum expression of hsa-miR-17-5p, hsa-miR-29A-5p, hsa-miR-146a-5p and hsa-miR-155-5p. In addition, the assessment of obesity and the activity of both diseases under conventional therapy with 5-ASA, immunosuppressants and/or corticosteroids did not show a significant correlation with the research panel of miRNAs and the level of human Lipocalin-2/NGAL.

In the "discussion" section, the results are discussed and compared with the data available in the medical literature. The author handles the scientific facts freely and skillfully, showing high awareness and competence in the matter.

The dissertation concludes with 14 conclusions, which are a logical consequence of the results. I accept the conclusions and contributions made. For the first time in Bulgaria, an anthropometric characterization of patients with IBD and obesity was carried out and a panel of miRNAs and human Lipocalin-2/NGAL was examined for evaluation of patients with IBD with obesity, describing the expression of these indicators in relation to the applied therapy and BMI in Bulgarian patients with IBD.

In connection with the dissertation a research project was developed, which was adopted and funded by The "Science" Fund at the Medical University-Varna. A total of 4 publications have been realized: 2 - in Bulgarian and 2 – in English. Some of the results are presented at national and international scientific forums.

In all of the above scientific developments, the PhD student is the first author, which shows her leading role in the realization of the research and the results obtained, which are her work.

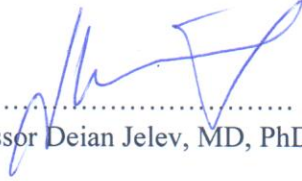
4. Conclusion

The dissertation work of Dr. Mirela Moneva - Petrova is a well-planned scientific study dedicated to a current Gastroenterological problem. A sufficient number of patients have been studied. Modern and adequate research methods are used, which is a prerequisite for data reliability. The results obtained are well summarized and analyzed. They lead to important conclusions and significant contributions. Some of the results are pioneering for our country. They definitely enrich our current knowledge in this interesting and still insufficiently studied field of medical science.

I strongly believe that the discussed thesis meets all requirements of the Law for development of the academic staff in the Republic of Bulgaria, as well as the relevant inner Regulation for development of the academic staff in the Medical University of Varna.

I grant my positive assessment and I recommend that the academic jury awards Dr. Mirela Radkova Moneva - Petrova the academic degree “Doctor” in Gastroenterology.

30/Jun/2023
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/Professor Deian Jelev, MD, PhD, DSc/