

To the Chairman of the Scientific Jury  
At the Medical University - Varna  
Appointed by Order № P-109-263/ 15.05.2023  
The Rector of the Medical University - Varna by procedure  
for the protection of a dissertation for the acquisition of  
educational and scientific degree "DOCTOR"  
the Second Department of Internal Diseases of the Medical University - Varna  
With candidate Dr. Mirela Radkova Moneva-Petrova  
full-time doctoral student in the doctoral program "Gastroenterology", professional field 7.1.  
Medicine assigned by Order № P – 109-388/09.10.2020

## **REVIEW**

**From prof. Dr. Miglena Dimitrova Georgieva, MD, PhD**

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OF A DISSERTATION THESIS ON

### **OBESITY IN PATIENTS WITH CHRONIC INFLAMMATORY BOWEL DISEASES**

**Dr. Mirela Radkova Moneva-Petrova**

Scientific Director:

Assoc. Prof. Dr. Antonia Yordanova Atanassova, MD, PhD, DSc

For awarding the educational and scientific degree "DOCTOR" in the field of higher education  
7. Health and sport 7.1. Medicine and doctoral program "Gastroenterology".

## GENERAL PRESENTATION OF THE PROCEDURE AND THE DOCTORAL STUDENT

by order № P – 109-263/ 15.05.2023 Varna to the Rector of the Medical University – Varna, on the grounds of art. 4, para. 2 of the Law on the Development of the Academic Staff of the Republic of Bulgaria, art. 2, para. 2 of the Regulations for the Implementation of the Law on the Development of the Academic Staff of the Republic of Bulgaria and the Regulations on the Terms and Conditions for Acquiring Scientific Degrees and Holding Academic Degrees at the Medical University – Varna I have been appointed as a member of the scientific jury (review) in connection with the procedure for the defence of the dissertation "**Obesity in patients with chronic inflammatory bowel diseases**" of Dr. Mirela Radkova Moneva-Petrova.

Dr. Mirela Radkova Moneva – Petrova was born on May 9, 1991 in Varna. She graduated from primary and secondary education in Balchik with excellent grades. She graduated in "Medicine" in 2017 at the Medical University "Prof. Dr. Paraskev Stoyanov "-Varna. Since 2018 is a resident in "Gastroenterology" at the Clinic of Internal Diseases at the MHAT – Varna to the Military Medical Academy – Sofia. On 09.10.2020 is enrolled as a full-time PhD student at the Second Department of Internal Diseases of the Medical University - Varna. She is preparing the dissertation "Obesity in patients with chronic inflammatory bowel diseases" in conditions of the COVID-19 pandemic. She participated on 07–08 June 2021 with reports on topics: "Obesity in patients with chronic inflammatory bowel diseases" and "Metabolic syndrome in patients with chronic inflammatory bowel diseases" at the Third International Conference "Health Care – Contributing to Quality of Life". Participated on 01-02 April 2022 with a paper on "INFLUENCE OF OBESITY ON THE COURSE OF INFLAMMATORY BOWEL DISEASE" at the Jubilee Symposium "10 years "Alumni Club and Friends" at the Medical University – Varna". She participated on March 21, 2023 with reports on the topics: "Study of microribonucleic acid 146a-5p as a new biomarker for the diagnosis of obesity in patients with chronic inflammatory bowel diseases" and "Study of the expression of microribonucleic acid 17-5p in patients with chronic inflammatory bowel diseases" in the Jubilee Scientific Conference "Traditions and Future in Medical Education" of the Medical College "Yordanka Filaretova" - Sofia. Dr. Moneva – Petrova has interests in the field of inflammatory bowel diseases, ultrasound and endoscopic diagnostics of the gastrointestinal tract. She is fluent in English and Russian. She is a member of the BMA and the Bulgarian Society of Gastroenterology, Gastrointestinal Endoscopy and Abdominal Ultrasonography.

### Structure and technical implementation of the dissertation

The dissertation is technically sound and written in the correct Bulgarian language. The work of Dr. M. Moneva - Petrova consists of 180 standard printed pages, illustrated with 92 figures and 36 tables. The bibliographical reference contains 356 titles, of which 5 in Cyrillic and 351 in Latin.

In general, the requirements for the structure of the dissertation are met. The dissertation work covers 180 pages as follows: Abbreviations used - 2 pages; Introduction - 2 pages; Literature review - 40 pages; Purpose, tasks and hypothesis - 1 page; Own surveys - 1/ Material, methods and statistical analysis -7 pages. 2/ Results of own surveys - 78 pages, 3/ Discussion - 12 pages;

Conclusions - 2 pages; Conclusion — 2 pages; Contributions - 1 pages; Publications – 2 pages; Literature - 24 pages.

### **Actuality of the dissertation topic**

The dissertation paper is dedicated to a topical problem – Obesity in patients with chronic inflammatory bowel diseases (IBD). Does this problem exist at all? Traditionally, many gastroenterologists associate IBD with low or underweight bodyweight. In recent years, there has been a clearly emerging trend: an increase in the incidence of IBS, and at the same time overweight and obesity among these patients are increasing. There is evidence in the literature that an increase in the incidence of obesity among the general population increases the risk of developing Crohn's disease (CD). On the other hand, about 15–40% of patients with IBD are obese. Metainflammation may contribute to the progression of the disease. Various clinical studies in this area present conflicting data on the effect of obesity on the natural history and course of IBD. Adipocyte hypertrophy of intra-abdominal adipose tissue leads to metainflammation that induces multiple pro-inflammatory mediators, including tumor necrosis factor alpha (TNF- $\alpha$ ), interleukin-6 (IL-6) and leptin and others. The increase in these inflammatory mediators may be reflected in elevated levels of C-reactive protein (CRP) and fecal calprotectin (FCP). The impact of obesity on the efficacy of IBS-related therapy remains a poorly researched area, although data from other autoimmune diseases suggest that obesity leads to a suboptimal response to therapy, rapid clearance of biologic agents, and low plasma concentrations, respectively. Therefore, the need has emerged to give modern characteristics of obesity in patients with IBD by comparing classical methods of assessment and new biomarkers, as well as to determine the activity of the disease, the response to conventional therapy and new biologics in patients with IBD who are overweight and obese.

### **Characterization and evaluation of dissertation and contributions**

**1. The literature review** is made up of 6 parts – starting from 1/ the essence of obesity and metabolic syndrome; 2/ the relationship between obesity and IBD; 3/ the essence and role in the assessment and prognosis of the inflammatory process of microribonucleic acids (miRNAs); 4/ the role of microribonucleic acids as biomarkers in the assessment of inflammatory bowel diseases and obesity; 5/ expression of lipocalin 2 in patients with IBD; 6/ summary of the literature review. From the summary of the review, it is clear that the prevalence of obesity in patients with IBD is significant and consistent with the incidence among the general population, contrary to the generally accepted notion that these patients are underweight. Although from a pathophysiological point of view, obesity, and visceral obesity in particular, appears to stimulate intestinal inflammation, epidemiological studies suggesting obesity in the development of IBD are limited. Based on pharmacokinetic data, obesity is found to stabilize the rapid clearance of biological agents, regardless of the dose of the drug. The effect of obesity on response to therapy remains to be studied. On the other hand, miRNAs have been extensively studied in many diseases due to their diagnostic value as a factor that reflects and controls various elements of immuno-mediated inflammation. Further definition of the complex networks of miRNAs and the genes they regulate will have tremendous relevance to advances in therapy for induction and maintenance of remission. The desire of clinicians to look for newer biomarkers that in an

elegant and indisputable way to reflect the activity of the disease (ulcerative colitis (UC) or CD), as well as the effectiveness of the treatment as a continuation of the efforts for a personalized approach in patients with IBD is also justified. On the other hand, circulating levels of human Lipocalin-2/NGAL have recently been successfully associated as a tool for monitoring activity and response to treatment in patients with immune-mediated diseases.

The review is written thoroughly, a little more extensive than necessary. The well-unresolved problems in this topic are highlighted, especially for our country.

**2. The objective** shall be clearly formulated.

**3. The 5 tasks** set follow the goal, allowing good performance of the planned study. The hypothesis is refined well – the expression of a panel of miRNAs and human Lipocalin-2/NGAL can serve as a sure and reliable marker for assessing the activity and treatment carried out in patients with CD and UC with overweight and obesity.

**4. Material and methods.** The study included 78 patients with IBD, divided into 2 groups, respectively with CD 40 (20 with active CD and 20 in remission) and with UC 38 (16 with active UC and 22 in remission), who went through the Clinic of Gastroenterology at the University Multiprofessional Hospital for active treatment "Sv. Marina" – Varna from 02.2021 to 11.2022. A panel of miRNAs (hsa-miR-17-5p, hsa-miR-29a-5p, hsa-miR-146a-5p, hsa-miR-142-3p, hsa-miR-155-5p, cel-miR-39-3p) and human Lipocalin-2/NGAL in serum was studied in patients with proven CD and UC in the stage of disease activity and in the stage of remission achieved with medication.

The specific studies, the methods applied to realize the purpose and tasks of the study, the statistical methodologies are described in detail.

The contingent of patients covered is more than sufficient to obtain reliable results, which have been analysed with appropriately selected statistical methods and illustrated with tables and figures.

## **5. Results and discussion**

The author's results are presented in detail:

1/ the groups studied were characterized and the threshold values of miRNAs and human Lipocalin-2/NGAL were determined

2/ anthropometric characteristics of patients with obesity CD and UC have been determined

3/ the expression of a panel of miRNAs in patients with CD and UC according to BMI was studied

4/ the expression of human Lipocalin-2/NGAL in patients with CD and UC was studied

5/ an assessment of inflammation in IBD in obese patients was made by comparing some anthropometric indicators, levels of a panel of circulating miRNAs and serum expression of human Lipocalin-2/NGAL.

6/ the circulating levels of the panel of miRNAs studied and serum expression of human Lipocalin-2/NGAL according to the activity of CD and UC and the conventional or biological treatment carried out was evaluated.

It is extremely impressive the detailed presentation of the results, starting from anthropometric data, passing through the levels of miRNA's and human Lipocalin-2/NGAL at different clinical and therapeutic givens, the functionalism of statistical methods.

**The dicussion** is directed and competent, following on points the basis of the results obtained. The skill of Dr. M. Moneva - Petrova is evident and analyzes her own results in the context of the data known in the literature. The author compares his results with the results of the international database. The last 4 figures, showing the direction of expression of the studied markers, are particularly impressive compared to patients with normal BMI. At the end of the discussion there is no conclusion formed.

## **6. Findings**

On the basis of the results obtained, 14 conclusions are formulated, which follow the logically set goal and tasks of the study.

## **7. Conclusion**

The dissertant makes the general conclusion that the use of classical anthropometric assessment scales is not sufficient to convey the complex clinical map of overweight and obesity in these patients, nor can they reveal the diverse impact on the phenotypic expression of CD and UC, the activity of both diseases, as well as the impact on classical assessment scales such as CDAI, Mayo index and/or non-invasive biomarkers to assess the achieved remission and the Treatment.

The application of a selected panel of miRNAs, which are involved in both immune system control, barrier epithelial function in CD and UC, as well as human Lipocalin-2/NGAL levels that change in the course of activity and remission of both diseases in different therapeutic regimens, are proving to be innovative, more modalities that open new perspectives in personalized therapy and monitoring in these diseases. As a first study in this area, the present study gives the current picture of the expressions of the selected miRNAs and human Lipocalin-2/NGAL and their correlation with the classical anthropometric assessment scales, lipid status, CRP, FCP, CDAI and Mayo score.

**8. The scientific contributions** are formed in 3 and groups: scientific contributions of a theoretical nature, contributions of a practical-applied nature and contributions of an original nature, namely - for the first time in Bulgaria a panel of miRNAs and human Lipocalin-2/NGAL has been studied for the evaluation of IBD obese patients; for the first time in Bulgaria the

expression of the studied miRNAs and human Lipocalin-2/NGAL compared to the applied therapy and BMI in patients with IBD has been described.

**9. The bibliography** is extensive, well formed, with few Bulgarian authors present, probably due to the innovativeness of the dissertation topic

**10. Publications and participations** are sufficient.

### **Autoreferat**

The presented autoreferat has a volume of 116 pages and reflects the content of the dissertation.

### **Conclusion**

The dissertation submitted to me for evaluation shows good professional qualities of Dr. Mirela Radkova Moneva - Petrova and her ability to carry out scientific research, as well as to make an adequate analysis of the results obtained and to draw the relevant conclusions. The work is the personal work of the dissertant and is the result of several years of labor.

The dissertation works meet the qualitative and quantitative criteria for acquiring the educational and scientific degree "Doctor", according to the regulations on the terms and conditions for acquiring scientific degrees and academic positions of MU Varna, as well as the Law on the Development of Academic Staff in the Republic of Bulgaria and the Regulations for its implementation.

I recommend to the honorable scientific jury to vote positively for awarding Dr. Mirela Radkova Moneva - Petrova the educational and scientific degree "Doctor".

16.06.2023

Varna

Sincerely:

Dr. Miglena Georgieva, MD, PhD

