REVIEW

A dissertation on the topic:

„Obesity in patients with chronic inflammatory bowel diseases“

For acquiring the educational and scientific degree "Doctor"

doctoral program "Gastroenterology"

field of higher education

7. Health and sports, professional field

7.1 Medicine

Author: Dr. Mirela Radkova Moneva - Petrova

Reviewer: Professor Dr. Ivaylo Petrov Vazharov, MD, Professor of Gastroenterology, Specialist in Internal Medicine and Gastroenterology

I.Defence procedure

By Order № P -109-263/ 15.05.2023 the Rector of the Medical University "Prof. Dr. Paraskev Stoyanov" – Varna on the basis of a decision of the Faculty Council of the Faculty of Medicine at the Medical University "Prof. Dr. Paraskev Stoyanov" – Varna according to Protocol № 1 at it is first meeting, on the grounds of art. 71, para. 1, para. 2 and para. 4 of the Rules for the Development of Academic Staff at MU – Varna, I am determined to prepare a review of the dissertation of Dr. Mirela Radkova Moneva - Petrova on the topic: **"Obesity in patients with chronic inflammatory bowel diseases"** for acquiring the educational and scientific degree "Doctor" in the doctoral program "Gastroenterology" in the field of higher education. 7. Health and sports, professional field 7.1 Medicine. Dr. Moneva - Petrova is a doctor at the Center for Emergency Medical Care – Varna, Branch - Varna Dolni Chiflik, a doctor in a mobile emergency team and a resident physician in the specialty "Gastroenterology" at the Clinic of Internal Diseases at the MHAT – Varna to the Military Medical Academy – Sofia.

My review is consistent with the requirements for preparing a review for acquiring the educational and scientific degree "Doctor".

II. Short biographical data

Dr. Mirela Radkova Moneva – Petrova was born on May 9, 1991 in Varna. She completed primary and secondary education in Balchik with excellent success. 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.

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 and has a very good computer literacy. She is a member of the BMA and the Bulgarian Society of Gastroenterology, Gastrointestinal Endoscopy and Abdominal Ultrasonography.

III. Structure of the dissertation

The dissertation is written in 180 pages: introduction 2 pages, literature review 41 pages, purpose, tasks and hypothesis 1 page, material and methods 7 pages, results 78 pages, discussion of results 12 pages, conclusions 2 pages - 14 in number, conclusion 2 pages, contributions 6 in number, 2 of theoretical nature, 2 of practical nature and 2 of original nature, Bibliography 356 literary sources, of which 5 in Cyrillic and 351 in Latin. The work is illustrated with 92 figures and 36 tables. The clinical study was conducted after obtaining permission from the Research Ethics Committee at MU-Varna – Protocol/ Decision № 100, meeting on 25.02.2021. All participants in the study have signed informed consent. The study was funded by a project at the Science Fund at the Medical University – Varna, project № 20002 "Metabolic syndrome in patients with inflammatory bowel diseases".

IV. Relevance and significance of the dissertation

The topic of the dissertation is characterized by considerable relevance, both globally and in our country.

The prevalence of obesity worldwide has grown to epidemic proportions and is one of the leading public health problems of the 21st century. At the same time, an increasing incidence of obesity is also found in the patient population with chronic inflammatory bowel disease (IBD), in parallel with those among the general population. Data from various modern studies suggest that the prevalence of obesity in patients with IBD reaches about 40%, and this percentage increases further, adding overweight. What is the true role of this comorbidity in the pathogenesis, natural history, and treatment outcomes of IBD remains unclear, and data from available clinical trials are conflicting. The overwhelming majority of published studies use body mass index (BMI) as a measure of obesity assessment. But BMI does not accurately reflect fat stores, namely visceral adipose tissue, which has the unique metabolic and biochemical properties compared to subcutaneous fat. Visceral obesity stimulates intestinal inflammation. Only a few months ago, systematized recommendations to the gastroenterological community on the importance of complex assessment of obesity in patients with IBD at the first meeting with them were published for the first time, as well as recommendations covering the correction of the various aspects of the impact that this essential and until recently unappreciated comorbidity can have on quality of life, the progression of the disease as well as the response to the treatment concerned. The dissertation is the first detailed study in the country regarding the assessment of obesity in patients with chronic inflammatory bowel diseases (Crohn's disease and ulcerative colitis).

V. Literature review

In the literature review, the epidemiology of obesity after IBD patients is discussed in detail and with competence. The types of adipose tissue, the compartment of mesenteric adipose tissue the main source of proinflammatory mediators. The role of metainflammation in pathogenesis, progression and response to conventional, biological and surgical treatment is also systematized. The main characteristics of the established and modern innovative biomarkers for assessment of immune-mediated inflammation both microribonucleic acids (miRNAs) and human Lipocalin-2/NGAL are discussed, with which both inflammation in IBD and obesity can be refined.

The aim is clearly formulated – to assess obesity in patients with chronic inflammatory bowel diseases (Crohn's disease and ulcerative colitis).

There are 5 tasks that explore the different aspects in the assessment of obesity and its role in the activity and effectiveness of treatment. The tasks are specific and realistic. They are well defined and adequate to solve the set goal.

VI. Clinical material used in the dissertation.

The study is prospective, but carried out entirely in the conditions of the COVID-19 pandemic. It included 78 patients with IBD divided into 2 groups, respectively with 40 with CD (20 with active CD and 20 in remission) and 38 with UC (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. The inclusion and exclusion criteria are clearly formulated.

VII. Methods

In order to achieve the research objective and to solve the pre-formulated tasks, data from patients with IBD who have undergone research according to the standard clinical approach have been studied and analyzed: history of the disease and concomitant diseases, physical examination, abdominal echoscopy, CT enterography or MR-enterography (for patients with CD and at the onset of IBD), ileocolonoscopy, with a view to assessing endoscopic activity and morphological examination. Based on these data, the diagnosis of CD or UC was made and these patients received therapy with mesalazine, corticosteroids, azathioprine or biological treatment.

50 IBD patients were prospectively examined in an activity or remission period for serum expression levels of miRNAs: hsa-miR-17-5p, hsa-miR-29a-5p, hsa-miR-146a5p, hsa-miR-142-3p, hsa-miR-155-5p, and control: cel-miR-39-3p. All 78 IBD patients were prospectively examined in an activity or remission period for serum expression levels of human Lipocalin-2/NGAL.

Each group of patients studied was detailed by gender, age, disease activity and treatment, presence of intestinal complications (UE – subileus, ileus, fistulation, abscession, stenosis) and extraintestinal manifestations (EEA – arthropathy, steatosis, hepatitis, cholelithiasis, iron deficiency anemia, B12 deficiency, malabsorption, erythema nodosum, pyoderma gangrenozum, aphthous stomatitis, ocular manifestations). In all patients, the disease was demonstrated by clinical,

endoscopic imaging (transversal – abdominal echoscopy and/or CT enterography, MR-enterography) and morphological criteria. The distribution according to localization (L/E) was carried out by the Montreal classification. Assessment of activity in patients with CD was performed by Crohn's Disease Activity Index (CDAI), in patients with UC by the Montreal severity, S, and Partial Mayo score (endoscopic Mayo score). The lipid profile was studied: triglycerides, total cholesterol, HDL-cholesterol, LDL-cholesterol, VLDL-cholesterol. Anthropometric measurements were also performed: BMI, waist circumference, waist/stature ratio and measurement of a skin fold of the abdomen with a caliperomer. The methodologies used of the studies are described in detail and in depth.

VIII. Results, discussion, findings, conclusions and contributions of the dissertation

Patients were distributed by gender, age, disease, anthropometric characteristics, lipid profile, serum expression of the panel of miRNAs, and human Lipocalin-2/NGAL. With an excellent knowledge of statistical survey methods, an in-depth analysis and comparison between the studied indicators has been carried out.

As there are no validated threshold values of miRNAs and serum human Lipocalin-2/NGAL in subjects of normal body weight, these have been calculated for the needs of this study.

A strong direct relationship was found between BMI, waist circumference, abdominal fold size and waist/height ratio in IBD patients. There is also a different correlation between anthropometric indicators (BMI, waist circumference, skin abdominal fold size and waist/height ratio) and laboratory indicators of the full lipid profile (total cholesterol, LDL – cholesterol, HDL – cholesterol, VLDL – cholesterol, triglycerides). The expression of the panel of considered miRNAs according to anthropometric indicators for assessing obesity differed in patients with CD and UC. In patients with a BMI $\geq$ 25 kg/m2, increased expression of hsa-miR17-5p, hsa-miR-146a-5p, and hsa-miR-155-5p was detected, while hsa-miR-29a-5p, hsa-miR-142-3p, and human Lipocalin-2/NGAL had downregulated expression. Overexpression of hsa-miR-17-5p is associated with the patient's age > 40, obesity, waist circumference above normal for both sexes, waist circumference/height ratio > 0.5, disease activity and UC. Decreased expression of hsa-miR-29a-5p is associated with male, obesity, patients with UC and achieved remission. Decreased expression of hsa-miR-142-3p was observed in ages > 40, male and CD patients. Increased expression of hsa-miR-146a-5p was found at the age of < 40, obesity, waist circumference above the norm for both sexes, active disease and UC. Overexpression of hsa-miR-155-5p was observed in female, obese, patients with CD and achieved remission. Decreased human Lipocalin-2/NGAL expression was associated with obesity, above-normal waist circumference, skin abdominal fold size, patients with UC and achieved remission.

The discussion covers 12 pages. The dissertant compares his own results with those of other authors.

The conclusions are 14 in number, which are mainly of practical importance.

The conclusion summarises the most important results of the study.

The dissertation work ends with six concrete well-formulated contributions 2 of a theoretical nature, 2 of a practical application and 2 contributions of an original nature.

Contributions of a theoretical nature

1. For the first time in Bulgaria, anthropometric characterization of patients with IBD and obesity is performed. 2. For the first time in Bulgaria, the application of miRNAs and human Lipocalin-2/NGAL in patients with IBD and obesity is reflected in detail and comprehensively.

Contributions of a practic-applied nature

1. Threshold values were determined to discriminate the expression of miRNAs and human Lipocalin-2/NGAL according to BMI, CRP, FCP, CDAI, Mayo score. 2. A specific profile of patients with obesity CD and UC based on the expression of miRNAs and human Lipocalin-2/NGAL was prepared.

Contributions of an original nature

1. For the first time in Bulgaria, a panel of miRNAs and human Lipocalin-2/NGAL was studied to evaluate IBD obese patients. 2. For the first time in Bulgaria, the expression of miRNAs and human Lipocalin-2/NGAL has been described in relation to the applied therapy and BMI in patients with IBD.

The autoreferencing is structured according to the requirements. The content corresponds to the dissertation.

IX. Publications and scientific activity.

The dissertation of Dr. Mirela Radkova Moneva - Petrova includes 4 scientific publications related to the topic of the dissertation – in national journals as the first author, 5 participations in national forums also as the first author. The publications are from 2021 and 2022, and the participations in scientific conferences are from 2021, 2022 and 2023 and reflect the topicality of the topic.

X. Conclusion

In conclusion, **Dr. Mirela Radkova Moneva - Petrova** managed to produce a thorough and comprehensive scientific work on **"Obesity in patients with chronic inflammatory bowel diseases"**. The topic is relevant for our country, the research is excellently organized and executed. She has managed to achieve this due to the magnificent literary awareness, as well as the very good combination of her competent knowledge and skills.

All this gives me reason to propose to the members of the Scientific Jury at the Medical University "Prof. Dr. Paraskev Stoyanov"-Varna, **Dr. Mirela Radkova Moneva - Petrova** for awarding the educational and scientific degree "Doctor" in the doctoral program "Gastroenterology".

14.06.2023

Varna

Reviewer: _____

Prof. Ivaylo Vazharov, MD, PhD