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Review of the Doctoral dissertation
of Paulina Samczuk, Msc
entitled: "Application of untargeted metabolomics to study metabolic effects of bariatric surgerics"

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Obesity is one of the diseases of civilization of the XXI century, leading to serious metabolic disorders and opening the way for many coexisting diseases, among which should be mentioned e.g.: type 2 diabetes, arterial hypertension, cardiovascular diseases, depression and cancer. Epidemiological studies indicate a steady increase in obesity in many countries around the world, including Poland. Non-invasive treatment of obesity is a huge challenge for clinicians and specialists in dietetics or the patient himself and requires determination and steady consistency from the patient. On the other hand, the most effective form of treatment of pathological obesity remain bariatric procedures, which were initiated in the 1950s and since then, along with the development of surgical techniques, have become significantly more common.

Paulina Samczuk's doctoral dissertation is a part of this interesting aspect of research into surgical treatment of obesity. It should be emphasized that the thesis was written in English, which proves that the Doctoral student has a very good knowledge of this language.

The doctoral dissertation submitted to me for a review is 125 pages long and has an innovative character, consisting of a cycle of 3 publications, two of which - a review and an original paper with a total IF index of 5.973 points and a total of 60 points of the Ministry of Sciences and Higher Education - have already been published.

The list of publications included in the dissertation is at the beginning of the dissertation. The detailed description of the three publications is preceded by a short Introduction, the Aims of the study and the Material and methods. After the

description of 3 publications, the results are discussed, followed by Conclusions, a Summary in Polish and English, References, a list of abbreviations and statements of the co-authors.

In the Introduction, the Doctoral student presents the definition and epidemiology of obesity, as well as the criteria for its diagnosis, and then discusses metabolic disorders related to obesity and coexisting diseases, demonstrating great knowledge in this area. She also discusses the treatment of obesity, with particular emphasis on bariatric surgery methods. In this chapter the Author also takes into account the metabolic effects of bariatric procedures in patients with type 2 diabetes, thus justifying the need to undertake research in this area. The chapter Introduction ends with a description of the development of metabolomics as a relatively young branch of science but dynamically developing and quickly finding recognition and wide application in various fields of medicine.

In the next chapter the Doctoral student formulates the aims of the study in an understandable and substantial way.

The next chapter entitled Material and Methods is dedicated to the process of patient recruitment for research and a general description of metabolomics and statistical methods and analyses used. Although it is assumed to be a general description rather than a detailed one, the way in which the Doctoral student presents a number of actions taken to identify compounds obtained from non-targeted analyses and the ability to use platforms and modules to link the obtained metabomic data with potential biochemical pathways must be admired. This proves the excellent knowledge of the research workshop of Doctoral candidate.

This chapter also contains information that the Bioethics Commission of the Medical University of Białystok (R-I-002/531//2013) has given its consent to conduct the research. This chapter ends with the information that a detailed description of the research methods can be found in each of the discussed publications.

The next chapter entitled Publications opens with a description of the review of the application of metabolomics in the study of the effects of bariatric surgery. On the background of the history of the development of bariatric methods and the possibility of a comprehensive study of dynamic alterations of the metabolome, the Author presents the possibility of using metabomics not only for cognitive purposes in the field of obesity, but also to modify the techniques of bariatric surgery and the possibility of developing in the future the non-surgical methods of treatment of

pathological obesity. This work is a comprehensive analysis of available modern literature and confirms the ability of the Doctoral student to evaluate the value of data coming from literature to formulate objective conclusions.

The aim of the next publication discussed in the dissertation, this time the original publication and the supplement attached to it, was to evaluate metabolic changes during the six months observation period after laparoscopic Roux-en-Y gastric bypass or laparoscopic sleeve gastrectomy. A group of 54 patients included in the study was selected from among obese patients with type 2 diabetes who underwent one of the mentioned bariatric procedures. As a result of metabolic fingerprinting analysis 49 statistically significant and identified metabolites were obtained. Based on the detected metabolites and pathways on which they act, a "gear mechanism" showing molecular changes induced by both bariatric procedures was proposed. Based on the obtained metabolomic results, it was concluded that the two procedures are very similar in terms of general clinical outcome, but they differ significantly in molecular mechanisms leading to the final result. This work is the first description of the metabolic effect of the bariatric procedures. New hypotheses presented by Doctoral student et al. concern molecular mechanisms induced by bariatric interventions and new gut microbiota modulations in patients undergoing bariatric surgery. The choice of reliable research techniques made by the Doctoral student, a detailed description of the methodology and the obtained results, as well as their innovative character are the main points of this paper. All of this indicates a high degree of scientific independence of the Doctoral candidate.

The aim of the last publication attached to the dissertation, not yet published but being under review, was to analyze metabolic profiles related to different remission rates of type 2 diabetes after a bariatric procedure in 20 patients who did not receive anti-diabetic treatment. The rate of remission in type 2 diabetes was determined in relation to the HOMA-IR index. In different metabolic profiles obtained for patients with type 2 diabetes "quickly" and "slowly" entering remission of the disease, a significant increase of acylcarnitines levels was also observed in patients with a faster remission rate of type 2 diabetes. Summarizing the obtained results, Doctoral student et al. conclude that it may indicate the importance of beta-oxidation process in remission of type 2 diabetes after bariatric procedure. This work is also an

example of a well-planned and consistently conducted research hypothesis by the Doctoral student based on the use of modern research methods.

In the next chapter Results and Discussion, the Author on the background of the presented results obtained in the study group, fully describes the reports of the world literature concerning the effects of bariatric procedures and metabolic disorders found in patients with type 2 diabetes. Wording this chapter indicates a comprehensive knowledge of the literature of the Doctoral student and proves her high scientific maturity.

The results presented in the dissertation allowed the Doctoral candidate to formulate 5 conclusions, which in a transparent way respond to the aims of the work.

The quoted literature includes 60 English-language publications from recent years.

Concluding, I believe that Paulina Samczuk's doctoral thesis deals with a very important aspect of the metabolic effects of bariatric procedures in patients with obesity and the accompanying type 2 diabetes. It is an innovative approach to explain molecular mechanisms related to the observed metabolic results. The dissertation is carefully written and its editorial form does not raise any objections.

I fully appreciate Paulina Samczuk's doctoral dissertation. The Doctoral student showed great theoretical knowledge and the ability to solve a scientific problem on her own.

Taking into account the entire doctoral dissertation, I conclude that it meets the conditions set out in Article 13 of the Act of 14 March 2003 on Academic Degrees and Academic Title and Degrees and Title in Art (Journal of Laws 2016, item 882, as amended). Based on the opinion presented above, I have the honour to ask the High Council of the Faculty of Medicine of the Medical University of Białystok to accept this doctoral dissertation and to admit Ms Paulina Samczuk to further stages of the doctoral thesis.

Moreover, due to the high scientific value of Paulina Samczuk's dissertation, which was also reflected in the publication of her results in peer-reviewed English-language scientific journals from the Philadelphia list with a total IF score of 5.973 points, I ask the High Council of the Faculty of Medicine at the Medical University of Białystok to award the dissertation.

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Lodz, 2nd November 2018 Agnieszka Zmysłowska, MD, PhD., Assoc. Prof.