

Statement on the PhD Dissertation

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By order № P-109-581/December 17, 2021 of the Rector of the Medical University of Varna I was appointed as a member of the scientific Jury and to present an opinion regarding a dissertation work for acquisition of the educational and scientific degree "doctor of philosophy" in the field of higher education 7. "Health and Sports", professional field 7.1 "Medicine", doctoral programme "Endocrinology",

Topic: „Metabolic profile of patients with not-active adrenal incidentalomas”

Author: Evelina Boykova Zlatanova, MD, a PhD student in Second Department of Internal Diseases, MU - Varna

Scientific supervisor: assoc. professor Mira Siderova, MD, PhD

I. General presentation of the procedure and the doctoral student

The presented set of materials on paper and electronic format is in accordance with the "Requirements for a Dissertation for the Acquisition of a PhD" in MU - Varna and includes the following documents:

- Dissertation
- Abstract
- flash memory with publications and documents of the doctoral student: a copy of the publications related to the topic of the dissertation; CV; a copy of the diploma for completed Master's degree; enrollment order; doctoral minimum exam report; order with the right to defense a dissertation; protocol from the positive Department decision on the readiness for defense; declaration of originality.

Dr. Evelina Boykova Zlatanova was born in Sofia in 1987. She graduated National High School of Natural Sciences and Mathematics in Sofia with honors. In 2011 she graduated Medicine at the Medical University "Prof. Dr. Paraskev Stoyanov" - Varna and she was awarded the Golden Hippocrates. She acquired a degree in Endocrinology and Metabolic Diseases. During her medical practice she works at University Hospital "St. Marina" and is a member of the team of the clinic of "Endocrinology and metabolic diseases" from 2011 until present. Since 2013 she has

been an assistant in the Department of Internal Diseases at the Medical University "Prof. Dr. Paraskev Stoyanov" - Varna. Dr. Zlatanova has a master's degree in Health Management.

II. Significance of the problem and practical orientation of the topic

Adrenal incidentalomas (AI) are lesions found during imaging of the abdomen or lung for indications not associated with suspected adrenal disease. The incidence of those findings increases with the more frequent use of modern imaging methods with advanced equipment. According to recent publications, the overall prevalence of incidentaloma is over 4% and increases with age, with about 10% of patients over 70 years of age having computed tomography data for such a lesion. The adrenal incidentaloma should be further categorized after assessment of the hypothalamic-pituitary-adrenal axis. In general, and depending on the criteria used, the majority (70%) of AIs are classified as non-functioning. However, there is growing information about the link between adrenal incidentalomas and metabolic syndrome, a major factor in the development of cardiovascular events and associated mortality. Clinicians are faced with the difficult task of determining the nature of the adenoma, to identify high-risk patients in time, to decide what to do next in this group of patients. Even in this regard, the topic chosen by Dr. Zlatanova is extremely relevant, with prerequisites for contribution to research and clinical activities.

III. Structure of the dissertation

The dissertation contains 153 standard pages and is illustrated with 31 tables, 47 figures and 1 appendix.

The literature review has a volume of 48 pages, is built in 16 points, and in each of them it reflects purposefully and analytically the current data for the respective indicator. The good literary awareness of the doctoral student is evident, as well as her ability to systematize and summarize scientific data. I was very impressed by the two-way examination of the connection between adrenal incidentalomas - metabolic syndrome and the summary, which not only confirms the relevance, but also shows the need to develop a dissertation work.

Aim and tasks (on 1 page): The aim of the project is presented accurately and clearly. The set 6 specific tasks allow the fulfillment of the set goal.

Materials and methods: the design of the study presented on 4 pages is built according to the objectives of the work. The number of observation units 105 is sufficient for statistical analysis. The inclusion and exclusion criteria allow the

elimination of some interfering factors. In all subjects, the biological material was taken according to the standard requirements for patient preparation and venous blood collection for clinical and laboratory tests. All methods used in this study are described in detail: clinical, laboratory and statistical.

Results and discussion: cover 60 pages and follow the sequence of tasks. The results are presented systematically, illustrated with figures and tables, there is no overlap in the information. The author comments analytically the results and compares them to the data obtained by other Bulgarian and foreign researchers.

Conclusions (2 pages): based on the results obtained, Dr. Zlatanova makes 14 conclusions, mostly confirmatory ones, which are not clearly formulated, and some of them are quite debatable. I have noted my remarks below, but I will mention here that conclusion 14 is neither a conclusion, nor an algorithm. Easily feasible and inexpensive indicators are presented that should not be missed in the treatment and follow-up of patients with AI, for which I fully support the PhD student.

The bibliography is presented in 34 pages. It contains 250 literary sources, 13 of which are in Cyrillic and 237 in Latin. It includes basic and recent literature sources, thus meeting the requirements.

IV. Contributions

The research target of the present study is to analyze the relationships between hormonally inactive adrenal adenomas and metabolic parameters and in the pathogenesis of both insulin resistance is involved. In her self-assessment, the PhD student indicated 9 contributions, most of which I agree with. I fully support the opinion of Dr. Zlatanova that the current work can become the basis for building a register for tracking patients with hormonally inactive adrenal adenomas.

V. Assessment of the doctoral student's publications and personal contribution

Dr. Zlatanova has presented 3 publications in Bulgarian scientific journals and 4 participations in scientific forums related to the dissertation, and she is the first author of all of them. The articles are overviews, and original data is presented only in one of the forums.

VI. Abstract

The content and quality of the abstract corresponds to the developed work and is made according to the requirements of MU-Varna. It reflects the main results obtained in the dissertation, the conclusions and contributions.

VII. Remarks and recommendations

This is my first reading of Dr. Zlatanova's work, which is why I consider it appropriate to present my critical remarks without belittling the the dissertation work. Criteria for inclusion and exclusion of patients contain mutually exclusive criteria. Exclusion criteria could be supplemented by the absence of chronic diseases or the intake of other drugs affecting metabolic status, e.g. antihyperlipemic, HRT, nutritional supplements, etc.

The conclusions contain elements of reasoning, clarification and data already mentioned in the chapter "Results and discussion". Conclusion 9 and the corresponding contribution do not explain the five-fold increase in insulin per 120 minutes. Stimulated insulin secretion is influenced by many factors and has been the subject of discussions since the 1960s without a common opinion. I cannot understand the meaning of conclusion 10. The first sentence is imposed by the basic knowledge of medicine, and the second by the basic knowledge of statistics.

I believe that the main disadvantage of the work is the lack of a control group, and when it comes to metabolic parameters, the correspondance in age and BMI is highly recommended. The comparison of original data (selected population) with those of Borisova et al. (unselected population) sounds convincing only in terms of epidemiological data. Many of the obtained results are presented independently, without comparison to age and BMI matched controls. Perhaps additional stratification of some of the analyzed parameters by age with subsequent intergroup and intragroup analyzes, would lead to more significant relationships than the correlation analysis of the whole group.

All of the remarks I made are related to my main recommendation, which is: to increase publishing activity. Each point in the "Results and Discussion" chapter is almost a finished publication.

In her conclusion, Dr. Zlatanova mentions that further prospective studies are needed to clarify whether patients with hormonally inactive adenomas and altered metabolic profile have increased cardiovascular morbidity and mortality, which is my other recommendation. If at least half of the studied patients are followed up, a very valuable prospective study would be obtained, as a well-deserved reward for the work invested in the dissertation!

IIIX. Conclusion

The dissertation submitted to me for review meets all the requirements of the Regulations for the Development of the Academic Staff in the Republic of Bulgaria, the and the Requirements for a Dissertation for the Acquisition of a PhD of MU - Varna.

Despite these remarks, the presented dissertation is an original analytical study and shows that the goal and objectives have been achieved. The PhD student has a deep knowledge of the problem and has the necessary knowledge and skills for independent research, so I give a positive assessment of the work "**Metabolic profile of patients with hormonally inactive adrenal adenomas**" and suggest esteemed members of the Scientific Jury to award positively Dr. Evelina Boykova Zlatanova with educational and scientific degree " DOCTOR" in the scientific specialty "Endocrinology", professional field 7.1. Medicine.

07-Feb-2022 r.
Plovdiv

Signature:
/Assoc. Prof. M. Mitkov, MD, PhD/

