

REVIEW

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Subject.

Author.

Topic: "Metabolic profile of patients with hormonally inactive adrenal adenomas" in the field of higher education 7. "Health and sport" in the professional field 7.1. "Medicine" and scientific specialty "Endocrinology"

Adrenal incidentalomas are defined as formations arising from the adrenal glands that are found incidentally during imaging in conditions unrelated to suspected adrenal disease.

The onset and natural course of adrenal incidentalomas are unknown. The cardiometabolic manifestations of these adrenal tumors are also unclear. A growing body of clinical and experimental evidence supports the idea of a fully or partially resolved metabolic syndrome in patients with adrenal incidentalomas. The latter are associated with cardiometabolic health, with an unresolved causal relationship to metabolic syndrome, hyperinsulinaemia and cardiovascular comorbidity. The emerging association between the presence of adrenal incidentalomas and metabolic syndrome raises the question of optimal clinical management of these patients, as well as the therapeutic benefit/risk ratio in the treatment of this indolent pathology.

The structure of the dissertation presented by Dr. Evelina Zlatanova fully corresponds to the submission for defense - introduction, literature review, aim and objectives, methodology of the dissertation, results, discussion, conclusions and contributions. It is written in 153 pages and illustrated with 31 tables and 47 figures.

The bibliography includes 250 references, of which 13 are in Cyrillic and 237 in Latin. The bibliography is extensive and well designed. About 10% of the authors cited are from the last 5-6 years.

The introduction stresses that the evidence from the literature remains quite controversial. Considering the opportunities provided by research in the field of modern medicine and the emerging link between the presence of adrenal incidentalomas and metabolic syndrome, the question is raised as to the optimal clinical management of these patients, i.e. should they be treated or only monitored.

The literature review presented in this thesis is very thorough and covers 15 sections in a logical sequence.

Dr. Zlatanova specifically and analytically presents the most important approaches published in the literature in relation to the diagnosis of metabolic syndrome in patients with adrenal incidentalomas and the interrelationship between the two diseases. Although metabolic syndrome is more commonly associated with functional adrenal adenomas, it seems that nonfunctional incidentalomas and subclinical Cushing's syndrome are also associated with an increased incidence of certain cardio-metabolic risk factors, such as impaired glucose tolerance, hypertension, atherogenic dyslipidaemia, diffuse and visceral obesity, hyperuricaemia, increased thrombogenicity, systemic inflammation and subclinical atherosclerosis, factors that are components of the metabolic syndrome.

After a thorough and analytical review of the literature and research on the issue at hand, Dr. Zlatanova concluded that accurate diagnosis of patients with adrenal incidentalomas, including non-functional ones, should include the evaluation of the components of the metabolic syndrome to identify patients at increased cardio-metabolic risk and prescribe appropriate lifestyle modifications and possibly therapeutic interventions.

The aim of this dissertation is very clearly and concretely stated - to analyze the diagnostic, metabolic, biochemical and hormonal aspects of patients with hormone-reactive adrenal adenomas and to make a contemporary assessment of some additional markers associated with metabolic syndrome, non-alcoholic steatohepatosis and cardiovascular risk.

To accomplish this goal, she set 6 objectives that also in logical sequence meet the goal.

The diagnostic, metabolic, biochemical and hormonal aspects of patients with hormone-reactive adrenal adenomas were studied and analyzed.

The subject of the study were 105 patients with hormonally inactive adrenal adenomas who underwent the Clinic of Endocrinology and Metabolic Diseases at St. Marina Hospital, Varna.

Patients were selected according to well-defined inclusion and exclusion criteria.

In order to achieve the research goal and to solve the formulated tasks, the data of the patients with hormonally inactive adrenal adenomas were studied and analyzed, who underwent the following examinations according to the standard protocol: history of the disease and concomitant diseases, physical examination, abdominal computed tomography with the consideration of the adenoma size and its CT characteristics, laboratory studies of biochemical and hormonal indicators. Patients were stratified by sex, age and risk factors.

These data are indicative of Dr. Evelina Zlatanova's drive not only to achieve new directions in diagnosis, control and treatment outcome, but also to derive reliable scientifically based results and conclusions that will support and improve clinical practice and treatment approach in patients with metabolic syndrome and hormone-reactive adrenal adenomas.

The mentioned statistical methods allow to illustrate the set tasks in detail.

The results obtained on the individual tasks confirm the thorough analysis of the clinical material. Despite the specificity of processing this clinical material, Dr. Zlatanova presents it very clearly in tables and figures. The doctoral student discusses his results and discussion on each individual task, which gives a very accurate assessment of the clinical material by comparing it with the available results of other authors who have performed similar studies among different groups of patients.

The discussion is focused and competent. Dr. Zlatanova ability to analyze her own results in the context of what is known in the literature is evident, comparing her results with results from international and national databases.

The paucity of publications and information in the literature suggests that her study appears timely, enabling the application of new non-invasive advanced and complex indices for the assessment of metabolic syndrome in patients with adrenal incidentalomas.

On the basis of the results, 14 conclusions were formulated that follow the logical aim and objectives of the study. Among them I would highlight the following:

1. Glycemic disorders were present in 89.5% of the studied patients, a high frequency of carbohydrate disorders was found: newly diagnosed DM (38.1%), NGG (5.7%), NGT (45.7%), which requires an active search for carbohydrate disorders among patients with hormonally inactive adenomas.
2. A prevalence of 67.60% of patients with NI were found to have more than a 5-fold increase in insulin levels at 120 min.
3. Adenoma size does not correlate with carbohydrate indices. Determine a cutoff value for HOMA-IR and QUICKI above which an increase in adenoma size is expected
4. Visceral obesity (demonstrated by increased waist circumference) is a risk factor in patients with adrenal hormone-reactive adenoma. BMI and waist circumference correlate with insulin at 0' and 120', HOMA-IR and QUICKI.
5. 46.7% of NI patients had a high risk of developing hepatic steatosis assessed by FLI screening. We determined a threshold FLI value of 57.5 above which adenoma growth could be expected. This value may serve as a noninvasive method to develop screening programs in this group of patients.
6. Propose an algorithm for monitoring metabolic parameters in patients with adrenal hormone-inactive adenomas.

Adrenal hormone-inactive adenomas may be a public health problem even if only because of the proportion of carbohydrate abnormalities. Early diagnosis is important, not only with a single fasting blood glucose value, but also by performing an OGTT with blood glucose and insulin testing at 0 and 120 min. Only in this way will there be a complete picture of carbohydrate metabolism and patients can be properly interpreted, monitored and treated. Increasing carbohydrate metabolism testing would have a positive effect in order to search for hidden morbidity and timely prevention of associated complications, for which a diagnostic algorithm

has been proposed to search for metabolic disorders in patients with hormone-reactive adrenal adenomas.

Further prospective studies are needed to elucidate whether patients with hormone-reactive adenomas and altered metabolic profiles have increased cardiovascular morbidity and mortality as has been demonstrated in the general population. Such data and comprehensive evaluation will be critical in selecting optimal treatment for these patients, which currently remains largely empirical.

The contributions presented by Dr. Zlatanova are given very accurately and correctly and are defined as contributions of a scientific and theoretical nature.

Dr. Evelina Zlatanova presents 3 publications in periodicals. In all publications she is first author. The publications reflect different aspects of the results obtained and the literature reviews performed investigating the association between metabolic syndrome and adrenal incidentalomas.

The abstract is written in 61 pages and fully presents the thesis work.

In conclusion, I would like to reiterate my high appreciation for the clinical and research work presented in Dr. Zlatanova dissertation and I will confidently vote "YES" for the award of the scientific and educational degree "Doctor" to Dr. Evelina Boykova Zlatanova.

26.01.2022 Prof. Dr. Kiril Hristov Hristozov, Ph.

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