



To
Head of the Department of Endocrinology,
MF, MU-Plovdiv

Opinion

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Regarding: Dissertation work for acquisition of the educational and scientific degree "Doctor" in the scientific specialty "Endocrinology" of Dr. Dimitar Manolov Troev, Department of Endocrinology, Medical Faculty of the Medical University - Plovdiv

1. Procedural requirements

Presented for opinion is a dissertation entitled "CHRONIC AUTOIMMUNE THYROIDITIS IN HASHIMOTO AND CO-MORBIDITIES" by Dr. Dimitar Manolov Troev, doctoral student of independent training at the Department of Endocrinology, Medical Faculty of the Medical University - Plovdiv, with scientific supervisors: Prof. Dr. Maria Orbetzova, MD, Department of Endocrinology and Prof. Dr. M. Geneva-Popova, MD, Department of "Propaedeutics of Internal Diseases "Anton Mitov", Faculty of Medicine, Medical University - Plovdiv

The provided set of materials on paper and electronic media is in accordance with the requirements for acquiring the educational and scientific degree "doctor" and the Regulations of MU-Plovdiv from 2021 and consists of all the required documents, incl. full-text publications and participations at scientific events.

2. Biographical data of the candidate

Dr. Dimitar Manolov Troev was born on 06.12.1964. He completed his secondary education at the "Dimitar Blagoev" secondary school - Plovdiv in 1982. He completed his higher education in medicine at the Higher Medical Institute - Plovdiv in 1990. Since 1991, he has been a doctor in the Clinic of Endocrinology and Metabolic Diseases at "Sv. Georgy" University Hospital - Plovdiv, and from the same year he became an assistant, after that senior and chief assistant at the Endocrinology Section of the Second Department of Internal Medicine, MF, MU - Plovdiv. After the separation of the Endocrinology Section into an independent department in 2020 and in connection with the legal requirements, Dr. Troev became an assistant, then a teacher, being enrolled for a doctoral program of independent training in 2022. He is also an administrative assistant of the Clinic.

Dr. Dimitar Troev has acquired clinical specialties - internal medicine, endocrinology and metabolic diseases. He has conducted a number of training courses related to different diagnostic and therapeutic activities, as well as additional highly specialized qualifications.

3. Actuality of the topic

Hashimoto's thyroiditis is the most common autoimmune thyroid disease in the world and its frequency continues to increase. Along with Graves' disease, they affect about 5% of the world's population, making them one of the most common autoimmune diseases. In addition, Hashimoto's thyroiditis is seen in one and the same patient with other autoimmune diseases (polyautoimmunity) - endocrine, non-endocrine (and malignant). Of interest is also the fluctuation in the function of the gland in autoimmune thyroid diseases, as well as the interaction between genetic and exogenous factors.

Most studies published in the scientific literature to date have focused on Hashimoto's thyroiditis with other autoimmune diseases, not the opposite.

Everything stated, as well as a number of research results, confirm the relevance of the topic of the dissertation work.

4. Structure of the dissertation; purpose and tasks, material and methods

The title fully reflects the topic of the dissertation work. Regarding the list of the most frequently used abbreviations, the PhD student quite rightly did not mention all those used (and explained) only once or rarely in the literature review and/or the dissertation, which is why they are labeled as "most frequently" used abbreviations. The content reflects the dissertation in detail, including the content of the literature review.

In the literature review, the problem set as the topic of the dissertation is considered in a purposeful, versatile and comprehensive way, and in some places the review is of an analytical nature. This proves that the doctoral student knows the scientific literature very well and in depth, even chronologically in time. The review is fascinatingly and expertly written.

As formulated, the aim concerns, on the one hand, an analysis of the type and frequency of diseases associated with Hashimoto's thyroiditis in a Bulgarian population of hospitalized patients, and on the other hand, the study of the influence of Hashimoto's thyroiditis on the clinical course of one of the most common concomitant non-thyroid autoimmune diseases, rheumatoid arthritis. Additionally, in the context of factors leading to combined pathology, zonulin was investigated as a new and reliable biomarker of increased intestinal permeability.

The tasks derive from the goal and are 8 in total. They are clearly and precisely formulated

Patients and methods: The doctoral student describes in detail the research methods - clinical, instrumental, clinical-laboratory and statistical. The individual studies, which cover a large number of patients and whose design fully corresponds to their aims and objectives, are presented in detail:

1. Randomized cross-sectional study on a sample of hospitalized patients with proven Hashimoto's thyroiditis (n=447) in the Clinic of Endocrinology and Metabolic Diseases with analysis of anamnestic, clinical-anthropometric, clinical-laboratory data, incl. hormonal and immunological indicators and imaging studies of the thyroid gland with an emphasis on comorbidities.
2. Randomized cross-sectional study on a sample of patients with type 1 diabetes mellitus (n=67), admitted to the Clinic for Endocrinology and Metabolic Diseases in order to assess the prevalence of Hashimoto's thyroiditis, resp. APS type 3 compared to a control group of age- and sex-matched clinically healthy individuals (n=124)
3. Retrospective analysis of data in a randomized representative sample of patients with early rheumatoid arthritis (n=180) hospitalized in the Clinic of Rheumatology regarding association with Hashimoto's thyroiditis and follow-up of the latter's influence on the clinical course of the disease.
4. Study of zonulin levels in patients with newly diagnosed Hashimoto's thyroiditis (n=106), comparative analysis of clinical and laboratory indicators in different functional states of the thyroid gland – hypothyroidism, euthyroidism and hyperthyroidism.

5. Results, discussion and conclusions

The PhD student has in practice combined the results with the discussion, doing the latter when describing the different studies. This brings greater clarity to the obtained results and allows for "extended" conclusions to be made in the relevant section. The doctoral student freely makes comments on his own results, compared with those from the literature, and in addition to the data indicated in the review, he also analyzes many new and modern studies related specifically to the different aspects of dissertation work.

The description of the characteristics of a large sample of hospitalized patients with Hashimoto's thyroiditis is important for practice, since there is no such generalized study of this most widespread autoimmune disease of the thyroid gland in our country. The female sex predilection is proven - the female:male ratio is about 5:1 - 372 females and 75 males. The findings about the functional status of the thyroid gland in hospitalized patients are important - almost 3/4 (72.1%) of the patients were euthyroid, and the frequency of Hashitoxicosis in 3.4% fully confirms the average one reported in the literature.

The doctoral student examines in detail and systematically the all autoimmune and non-autoimmune diseases associated with Hashimoto's thyroiditis, including diabetes mellitus,

rheumatoid arthritis, systemic lupus erythematosus, megaloblastic anemia, vitiligo, carbohydrate and lipid disorders, etc. Thus, developed metabolic syndrome is detected in 26.85%, diabetes mellitus type 2 in 20.13%, separate components of metabolic syndrome - dysglycemia in 0.89%, dyslipidemia in 2.01%, leading to the conclusion that about half of patients with Hashimoto's thyroiditis are at high cardiovascular risk. In addition, almost half of the patients had arterial hypertension and ischemic heart disease - 38.26% and 11.86% respectively. The incidence of a number of other comorbidities in Hashimoto's thyroiditis has also been reported in detail. Regarding gastroenterological diseases, it can be noted that the diagnosis "chronic colitis" should not be used in the scientific literature - colitis can be ulcerative, granulomatous (Crohn's disease, tuberculosis), enterocolitis, etc. It is better to write "irritable colon" not in Bulgarian but in Latin (colon irritable) or Irritable Bowel Syndrome (IBS), as it is popular in gastroenterological literature. Data for "chronic colitis" are mostly anamnestic and most probably mean IBS in these cases.

Special attention is paid to the autoimmune polyglandular syndromes (APS), especially the combination of Hashimoto's thyroiditis with type 1 diabetes mellitus within the APS type 3A, which is the main subject of the second study in a sample of hospitalized type 1 diabetics. In this study, the family history of diabetes mellitus on the one hand, and of autoimmune thyroid diseases on the other was analyzed in diabetic patients in comparison with the healthy controls.

The combination of Hashimoto's thyroiditis with rheumatoid arthritis was purposefully examined in 180 patients with early rheumatoid arthritis. The results of the third study in a hospitalized cohort of patients in the Clinic of Rheumatology are valuable in terms of development of the autoimmune process of the thyroid gland - progression from presence only of antibodies to clinically manifested disease. The author makes important conclusions of a contributing nature about the presence of antithyroid autoantibodies (in the absence or subclinical manifestation of a thyroid disease) in early rheumatoid arthritis and their increased frequency in the years of follow-up, as well as a lack of correlation between these antibodies and the activity of the rheumatoid arthritis but not with the joint impairment objectified radiologically.

Very interesting are the results for increased serum levels of zonulin (a marker for intestinal permeability) in patients with Hashimoto's thyroiditis, a study that has not been conducted so far in our country and is still the subject of studies in the world. Also interesting are the relationship of zonulin to the "tight junction" not only in autoimmune diseases of the thyroid gland, but also in insulin resistance, overweight and obesity, its interrelationship with liver enzymes (resp. non-alcoholic steatohepatitis), and in general the role of the microbiota in increased intestinal permeability and malignant diseases. The data of the study are pioneering and shed light on a number of still unsolved pathogenetic processes of the relationship between intestinal microbiota, autoimmunity and even malignancy. According to the results of the dissertation, patients with Hashimoto's thyroiditis and hypothyroid status have higher serum zonulin levels, although the difference was not statistically significant – possibly due to the heterogeneity of the groups and the relatively small number of patients with hyperthyroidism. The hypothyroid state (low FT4 levels, high FT3/FT4 ratio), overweight and obesity, as well as HOMA-index correlate with high levels of serum zonulin. The study of zonulin in this doctoral thesis is a pilot one, but the author states that it is being expanded with a new targeted project with additional variables and formation of a control group of healthy subjects.

In the interpretation of the results in several places, the author emphasizes the limiting factors of the study, which was conducted in a hospitalized population with Hashimoto's thyroiditis. It differs from the general population with this disease due to various reasons for hospitalization, which are related either to diagnostic and therapeutic problems, or to complications and concomitant pathology. This is also related to the regulatory requirements of the health care system in our country. But quite correctly, the results of the present study have been compared with international studies in both general and hospitalized populations. Again, it should be emphasized that in the world literature in general, studies on co-morbidity in Hashimoto's thyroiditis are scarce and significantly less than those considering it as a concomitant pathology. This increases the merits of the doctoral thesis for clinical practice.

The doctoral student drew 16 summarizing conclusions, ending with purely practical messages about the need for a precise study of thyroid function and autoimmunity already at the diagnosis of the corresponding autoimmune disease, as well as strict follow-up in the direction of the appearance of thyroid pathology in the course of the latter, in order to clarify the diagnosis and, if necessary, to include timely treatment. Conversely, when diagnosing Hashimoto's thyroiditis, in case of clinical suspicion it is necessary to look purposefully for other autoimmune manifestations from various organs and systems through functional and immunological biomarkers, taking into account the possibility of their appearance over time.

The bibliography is comprehensive, meets the requirements - it covers 460 basic and modern literary sources (8 in Cyrillic, 452 in Latin).

6. Contributions

I accept the self-assessment of the dissertation's contributions as original and confirmatory, with a predominantly scientific-theoretical and scientific-applied nature. The study is a pioneer for the country in a number of aspects of studying Hashimoto's thyroiditis, and with regard to zonulin - also on a global scale.

7. Publication activity

In connection with the dissertation, the following have been presented: 1 participation in a monograph, 8 full-text publications, of which 2 in international journals, 1 with an impact factor and 2 publications in Folia Medica - journal of an international character; 7 participations in scientific conferences (3 international) and participation in 2 research projects.

8. Summary of the dissertation

The presented summary is properly structured, contains all the required details and reflects the most important aspects of the doctoral thesis, which fully meets the requirements of the Regulations of the MU-Plovdiv in terms of content and layout.

9. Conclusion

Based on the above, I consider that the developed topic "CHRONIC AUTOIMMUNE THYROIDITIS OF HASHIMO AND CO-MORBIDITIES" is up-to-date and dissertable, meets all the requirements of the Law on the Development of the Academic Staff in the Republic of Bulgaria, the Regulations for the Implementation of the latter and the Regulations for the organization and activities of the MU-Plovdiv for the acquisition of the educational and scientific degree "Doctor" in the doctoral program "Endocrinology".

I give a positive opinion and strongly recommend to the members of the respected Scientific Jury to give a positive vote for the implementation of the procedure for awarding a doctorate degree to Dr. Dimitar Manolov Troev on the basis of the dissertation work presented by him. The doctoral student shows high professionalism and established skills of a researcher, which gives good opportunities for further academic development.

24.01.2024
Plovdiv

Signature:
/Assoc.prof. Dr. N. Krastev/

Заличено на основание
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