

To the Chairman of the Scientific Jury,
determined by Order No. R-109-100/ 28.01.2025
of the Rector of the Medical University - Varna
and on the basis of Protocol No. 1/07.02.2025

REVIEW

By Assoc. Prof. Dr. Boyan Nonchev, MD, PhD

Scientific specialties – Endocrinology and metabolic diseases, Internal diseases

Associate professor at the Department of Endocrinology, Medical University of Plovdiv

Clinic of Endocrinology and Metabolic Diseases – University Hospital “Kaspela” Plovdiv

Address and contacts: Postal address: 64 Sofia Str., 4001 Plovdiv

Email address: nonchev_md@abv.bg

Phone numbers: 0888 492828

On the dissertation work

of Dr. Gergana Tosheva Marinova, a full-time doctoral student, on the topic "Body composition, biochemical indicators, grip strength and gait speed in women with hyperthyroidism" for the award of the educational and scientific degree "doctor" in the professional field 7.1. Medicine, in the doctoral program "Endocrinology" with scientific supervisor: Assoc. Prof. Dr. Mira Valentinova Siderova, MD, PhD

1. General presentation of the procedure

The presented set of materials complies with the requirements of the procedure for acquiring the ONS "doctor" according to the Regulations of MU - Varna and includes all necessary documents.

2. Brief biographical data of the doctoral student

Dr. Gergana Tosheva was born in 1984 in Varna. She graduated with honors from the High School of Natural Sciences and Mathematics in 2003 and Medicine at MU-Varna in 2009. In the period until 2019, she was part of the team of the Clinic of Endocrinology and Metabolic Diseases at the University Hospital "St. Marina", Varna. From 2016 to 2018, she was a part-time assistant at the Department of Propaedeutics of Internal Medicine, and in 2018 she was appointed as a part-time assistant in Endocrinology and Metabolic Diseases, Department of Endocrinology.

In 2017, Dr. Tosheva acquired a specialty in Endocrinology and Metabolic Diseases, and from 2019 is a full-time doctoral student at the Second Department of Internal Medicine, Department of Endocrinology, MU-Varna.

Dr. Tosheva holds a certificate for cervical ultrasound.

3. Relevance of the topic

Hyperthyroidism is a problem affecting part of the working-age population. It is known that an excess of thyroid hormones leads to accelerated catabolic processes and weight reduction. By studying body composition among women with hyperthyroidism, we gain an idea of the change in the amount of muscle, bone and fat tissue by body region.

After the discovery of sarcopenia, medicine has paid increasing attention not only to the amount of muscle tissue in the body, but also to its "quality". It has been found that when weight loss is at the expense of muscle tissue, this has adverse consequences for the individual.

Hyperthyroidism affects muscle tissue, which is why it is important to assess whether there is a connection between it and sarcopenia. The combination of the two conditions poses an additional health risk. These data define the topic of the paper as interesting and relevant, especially in the context of scarce knowledge about the diseases causing secondary sarcopenia.

Grip strength is an important diagnostic indicator for the functional involvement of the muscles, but also an indicator of the overall health of the patient. Recently, it has emerged as a valuable biomarker for the risk of disability and impaired quality of life, with a much better predictive value than chronological age.

There are insufficient studies in the literature assessing the complex involvement of the body in hyperthyroidism, through simultaneous assessment of changes in body composition, grip strength and gait speed, and the results are contradictory.

4. Evaluation of the dissertation work

The dissertation work is written on 150 pages, illustrated with 38 tables and 53 figures and is well-structured in the following main sections: Title page (1 page); Table of contents (2 pages); Abbreviations used (2 pages); Introduction (2 pages); Literature review (47 pages); Aim and objectives (1 page); Materials and methods (6 pages); Results (45 pages); Discussion (15 pages); Conclusions (2 pages); Conclusion (1 page); Contributions (1 page); Publications related to the dissertation work (1 page); Sources used (23 pages). The bibliography contains 325 literary sources, of which 13 are in Cyrillic and 312 in Latin.

5. Structure of the dissertation

The literature review is very well structured and includes up-to-date information on the epidemiology, etiology and pathogenesis of hyperthyroidism and sarcopenia. The data accumulated to date on the relationship between the two conditions are examined in detail. The doctoral student presents an in-depth analysis of the following issues: the importance of body composition in the norm, the importance of thyroid hormones for body composition in the norm and pathology, methods for examining body composition, as well as a detailed review and significance of the diagnostic criteria for sarcopenia - grip strength, index of the amount of muscle tissue in the limbs and gait speed.

The review of the review demonstrates excellent knowledge of the state of the problem with creative evaluation of the analyzed literary material.

The aim of the dissertation work is clearly formulated, namely to assess the relationship of hyperthyroidism with body composition, grip strength and gait speed (diagnostic components for sarcopenia), as well as with some biochemical indicators (vitamin D, creatinine, creatine phosphokinase, albumin). To achieve the goal, 8 precisely formulated tasks have been set, which allow the achievement of the set goal:

1. To compare anthropometric and biochemical parameters between women with hyperthyroidism and healthy controls.
2. To compare the body composition of the two groups (healthy controls and women with hyperthyroidism).

3. To compare grip strength, appendicular skeletal muscle mass (ASM/m², ASMI) and walking speed in women with hyperthyroidism and healthy controls.
4. To search for a relationship between anthropometric indicators and body composition, as well as between anthropometric indicators and diagnostic criteria for sarcopenia - ASMI, grip strength and gait speed.
5. To search for a relationship between hormonal and biochemical indicators and body composition, as well as between hormonal and biochemical indicators and diagnostic components of sarcopenia - grip strength, appendicular skeletal muscle mass/m² and gait speed.
6. To establish the risk of developing secondary sarcopenia, to determine its frequency among the studied individuals and the threshold age above which the risk of secondary sarcopenia increases.
7. Among individuals with identified sarcopenia, to search for correlations between anthropometric, hormonal and biochemical indicators, on the one hand, and the diagnostic components for sarcopenia - ASMI, grip strength and walking speed - on the other.
8. Comparison and search for correlations between the studied parameters among women with hyperthyroidism, compared to those with hyperthyroidism and established sarcopenia.

Participants and methods:

For the purposes of this dissertation, Dr. Tosheva selected 90 women aged ≥ 18 years, affected by hyperthyroidism (N=45), as well as healthy controls (N=45). A cross-sectional study was conducted among outpatients selected in the period 2020-2022.

The inclusion and exclusion criteria were adequate to the purpose and design of the study. The research methods were also optimally selected: anthropometric, physical, laboratory and bioelectrical impedance. Adequate statistical analysis was used - a method for statistical grouping of data; descriptive methods; for testing statistical hypotheses, correctly selected T-test for dependent and independent variables with Levene's test for equality of variations; correlation analysis; a method for determining threshold values.

The results of the study are presented correctly in 9 sections, well illustrated in tabular and graphical form, accompanied by adequate and objective commentary. The sections strictly follow the set objectives, 8 tasks are the implementation of the goal, and the last one is additional results of correlation analyses of individuals affected by thyrotoxicosis and sarcopenia.

Results of task 1:

The statistical analyses conducted revealed that both groups were correctly selected so that the women were comparable in age and height.

The majority of patients in both groups had a normal BMI (BMI 18.5-24.9 kg/m²), with group A accounting for 46.63% of cases, while group B accounting for 42.11% of the included individuals.

The values of the thyroid parameters studied reflect the sample of women included in the study - those with hyperthyroidism, mainly of autoimmune origin, and healthy controls.

The mean values of the immunological parameters - TPO Ab and TRAb are significantly higher in hyperthyroid individuals, while in women from group B they are lower and below the reference laboratory values diagnostic of autoimmune disease.

A total of 12 biochemical indicators were studied, 8 of which were used to identify individuals with exclusion criteria. The focus for comparison was on the remaining 4 (creatinine, CPK, albumin and vitamin D), which were analyzed for research purposes due to the relationship described in the literature with the distribution of body composition and the presence of sarcopenia.

Of the target indicators, two stand out with a significant difference in values between the two groups. These are creatine phosphokinase (CPK) - mean value for group A 75.23 ± 35.06 U/L and 98.11 ± 45.13 U/L for group B (p 0.021), as well as vitamin D - mean value for group A 19.30 ± 6.45 ng/mL versus mean 23.56 ± 11.11 ng/mL for group B (p 0.04). Creatinine shows a borderline significant difference (p 0.056).

Although within reference values, serum levels of total protein and albumin were lower in group A compared to group B, with the difference not reaching statistical significance.

The results of task 2 establish statistically significantly lower bone mass and muscle tissue among women affected by hyperthyroidism.

Of interest is the weaker involvement of subcutaneous adipose tissue in conditions of hyperthyroidism.

Valuable from a scientific point of view are **the results of task 3**, where a significant impact is established not only on the amount of muscle tissue in hyperthyroidism, expressed by the ASMI index, but also on grip strength and walking speed.

Dr. Tosheva found that a total of 17 of the 90 individuals studied were also affected by another disease process - sarcopenia. The fact that 16 of these women suffered from hyperthyroidism raises the question of whether this condition could be a cause of secondary sarcopenia. This is an important issue given the severe sarcopenia recorded in 3 of the affected patients.

The relationships between anthropometric indicators and body composition, as well as between anthropometric indicators and diagnostic criteria for sarcopenia - ASMI, grip strength and walking speed, presented in **the results of task 4**, are discussed in detail and in a structured manner, as well as well illustrated with tables and figures.

The dissertation is unique in that it is one of the few that examines the correlations between anthropometric indicators and each of the diagnostic components for sarcopenia in hyperthyroidism.

The focus in **task 5** is on establishing relationships between laboratory indicators (hormonal and biochemical) - on the one hand, and body composition and diagnostic components for sarcopenia - on the other.

Supporting the assumption that hyperthyroidism may be a prerequisite for the development of secondary sarcopenia, regardless of the woman's age, are the data on a decrease in muscle mass in each of the limbs, as well as a decrease in bone mass, which are observed in parallel with the decrease in TSH.

In the literature, various laboratory indicators have been combined as probable biochemical markers for muscle tissue involvement in various processes to the extent of sarcopenia development. In this dissertation, this possibility has been rejected, because none of the target biochemical indicators (25(OH)D, creatinine, CPK and albumin) showed significant correlations with body composition distribution.

The correlation analysis revealed that the decrease in serum TSH was accompanied by a decrease in ASMI, grip strength and a slowdown in gait speed, which would encourage the use of some of these studies in the routine examination of individuals with hyperthyroidism.

Of particular interest are **the results of task 6**. They not only prove that individuals suffering from hyperthyroidism are often affected by sarcopenia, but most importantly, that this occurs much earlier in the years compared to the development of primary sarcopenia.

From the statistical model made based on the construction of the ROC curve, the age above which screening for the presence of secondary sarcopenia should be

carried out among women with newly diagnosed hyperthyroidism is 54 years (AUC 0.656 (0.519- 0.793)).

Similarly and clearly presented are **the results of task 7** - to search for correlations between anthropometric, hormonal and biochemical indicators, on the one hand, and the diagnostic components for sarcopenia - ASMI, grip strength and gait speed - on the other, among individuals affected by sarcopenia.

Results of task 8 - comparison and discovery of correlations between the studied parameters among women with hyperthyroidism, compared to those with hyperthyroidism and established sarcopenia.

The values of the anthropometric indicators among women from subgroup A2 are lower than those from subgroup A1, but these differences do not reach statistical significance, probably due to the small number of individuals falling into both subgroups.

As expected, the differences in the amount of bone and muscle tissue are significant, which also results in the functional indicator grip strength among women affected by both hyperthyroidism and sarcopenia.

The discussion is well structured, with the doctoral student critically analyzing the results obtained in the context of the available literature on the problem.

The twenty-one conclusions drawn are in accordance with the results obtained and follow the tasks set in the dissertation.

Contributions:

For the first time in Bulgaria:

- an analysis of the body composition of women with newly diagnosed and untreated hyperthyroidism is performed;
- the presence of sarcopenia among women with untreated hyperthyroidism is investigated;
- grip strength and gait speed are used as valuable, informative and easy-to-perform studies among hyperthyroid women;
- a comparison is made simultaneously between anthropometric and biochemical indicators, body composition, grip strength and gait speed in women with newly diagnosed hyperthyroidism;

- the relationships between thyroid and biochemical indicators (on the one hand) and body composition, grip strength and gait speed (on the other hand) in women with newly diagnosed hyperthyroidism.

In addition to being a pilot study in Bulgaria, this study is one of the few **worldwide** that:

- makes a comprehensive assessment of muscle health in women with hyperthyroidism, taking into account both the amount of skeletal muscle as an absolute value and through the ASMI, as well as its functional state;
- analyzes grip strength and gait speed within the framework of hyperthyroidism;
- marks hyperthyroidism as a risk factor for the development and earlier onset of sarcopenia.

The doctoral student has a total of 4 publications on the topic, the work was presented at the XII National Congress of Endocrinology in Plovdiv in 2023, as well as in the poster sessions of 3 international congresses and symposia.

The attached list of publications meets the requirements for awarding educational and scientific degree "PhD".

6. Thesis summary

The abstract is fully sufficient in content and quality to present the main results achieved in the dissertation.

7. Critical remarks and recommendations.

It is recommended that when citing literary sources in the text, the corresponding publication number be indicated in the bibliography. I recommend that the dissertation candidate expand his publication activity and popularize the obtained results in national and international scientific publications. To continue the follow-up of the included group of patients with a reassessment of the registered changes after restoration of the euthyroid state.

8. Conclusion

The dissertation submitted for review is written in clear and precise Bulgarian and contains clinically significant scientific and applied scientific results, some of which represent an original contribution to science. The dissertation shows that Dr. Gergana Tosheva Marinova possesses the necessary theoretical knowledge and professional skills in the scientific specialty "Endocrinology and Metabolic Diseases", clearly demonstrating qualities and abilities for independent scientific research.

In connection with the above, I give my positive assessment of the conducted scientific research, which is dedicated to a current and socially significant problem. It represents a thorough and valuable work and meets the requirements of the Act on the Development of the Academic Staff in the Republic of Bulgaria, the Regulations for its implementation and the Regulations for the Development of the Academic Staff at MU-Varna for the acquisition of the scientific and educational degree "PhD". I confidently vote for the award of the scientific and educational degree "PhD" to Dr. Gergana Tosheva Marinova.

26.02.2025

Reviewer:

Заличено на основание чл. 5,
§1, б. „В“ от Регламент (ЕС)
2016/679

Assoc. prof. Boyan Ivanov Nonchev, MD, PhD

In connection with the above I give my positive assessment of the conducted scientific research, which is dedicated to a current and socially significant problem. It represents a thorough and valuable work and meets the requirements of the Act on the Development of the Academic Staff in the Republic of Bulgaria, the Regulations for its implementation and the Regulations for the Development of the Academic Staff at IMU-Varna for the acquisition of the scientific and educational degree "PhD". I confidently vote for the award of the scientific and educational degree "PhD" to Dr. Gergana Toshova Marinova.

Reviewer:

Assoc. Prof. Boyan Vassilov Petrov, PhD

06.02.2022