

REVIEW

by Assoc. Prof. Dr. Boyan Ivanov Nonchev, MD

Department of Endocrinology, Faculty of Medicine, MU-Plovdiv

of a dissertation for the award of the educational and scientific degree "Doctor", professional field "Medicine", doctoral program "Clinical Laboratory"

Author of the dissertation: Dr. Vania Miloucheva Peneva

Form of doctoral studies: independent preparation

Department: Department of Clinical Laboratory

Topic: "Serum melatonin in women with metabolic syndrome"

Scientific supervisors: Assoc. Prof. Dr. Dora Dimitrova Terzieva, MD; MU - Plovdiv

Prof. Dr. Mitko Dimitrov Mitkov, MD; Department of Endocrinology,
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1. General presentation of the procedure and the doctoral student

The presented set of materials on paper and electronic media is in accordance with Art. 70 (1) of the Procedure for acquiring the educational and scientific degree "doctor" at MU-Plovdiv and with the Regulations of MU-Plovdiv dated 28.01.2021.

The doctoral student has submitted all necessary documents in accordance with the existing requirements.

In relation to the topic of the dissertation, the doctoral student has three publications, one of which was published in a journal with an impact factor. Nine summaries of participation in world, European and national scientific forums are presented.

2. Brief biographical data about the doctoral student

Dr. Peneva graduated from medicine at MU-Plovdiv in 1994. Since 1995, she has specialized in clinical laboratory at the Department of Clinical Laboratory, MU-Plovdiv. She has a recognized specialty in clinical laboratory since 1999. From 1999 to 2004 she worked as a medical representative. In 2004 she was appointed as a doctor in the Central Clinical Laboratory of St. George University Hospital EAD, and from 2009 to 2011 she was a doctor in a clinical laboratory in the Department of Cardiac Surgery. From 2011 to 2014 she worked as a laboratory physician in France. After returning from France in 2014, she currently works as a clinical laboratory physician in the Department of Cardiac Surgery. Since 2004, she has been appointed as an assistant in the Department of Clinical Laboratory. She conducts exercises with 3rd year medical students, 2nd year pharmacy students, 1st year nurses and midwives.

Dr. Peneva builds her professional qualifications by participating in a number of courses and seminars on the problems of metabolic syndrome and hemostasis (Marseille, 2007), a training

course on the ISO 15189 quality system (MF Sofia, 2015), the latest developments in the field of hemostasis (NCSM "Pirogov", Sofia, 2017), mastering research tools and access to scientific documentation in the field of medicine (France, 2018), etc.

3. Relevance of the topic

The topic of the presented dissertation is relevant, since even today the metabolic syndrome (MetS) continues to be a significant socio-economic and medical problem. The continuously increasing consumption of foods with high fat content, rapidly absorbed sugars, a low-fiber diet, and increasingly reduced physical activity are important factors contributing to the increasing prevalence of MetS. It is believed that there are ethnic, racial, and gender differences in the prevalence and characteristics of MetS. According to some researchers, compared to men, in women the main characteristics of the syndrome (abdominal obesity, dyslipidemia, hyperglycemia, hypertension) are more pronounced and lead to higher morbidity and mortality from cardiovascular diseases. Data on the prevalence of MetS in both sexes are contradictory - according to some researchers, both sexes are equally affected, according to others, MetS occurs more often in women, and according to others, men are the more affected sex.

Currently, a number of scientific studies discuss the role of hormonal factors in the development of MetS, commenting on the involvement of melatonin in carbohydrate and lipid metabolism in experimental models. There is evidence that pinealectomy in animals leads to the development of a "diabetogenic syndrome", which includes impaired glucose tolerance, peripheral and central insulin resistance. It is also believed that melatonin is a key mediator between cyclical changes in the environment and circadian changes in the body, including for optimizing energy balance and body weight regulation. One of the main factors in body weight regulation is leptin, and it is assumed that leptin resistance and its subsequent hyperleptinemia are a significant factor in obesity. I believe that the complex study of the interrelationships between melatonin, leptin, ghrelin, cortisol and somatotrophic hormone (STH) on the one hand and the components of MetS on the other, will deepen knowledge about the mechanisms for the occurrence and maintenance of MetS.

4. Knowledge of the problem

The literature review is sufficient in volume and shows a very good knowledge of the problem. It presents in great detail and consistently the current understanding of MetS and the role of hormonal factors in the development of the syndrome, blood glucose homeostasis and the role of the pineal gland in glucose metabolism. There are detailed data on the synthesis and secretion of melatonin and the regulation of melatonin synthesis, as well as on the mechanisms by which melatonin exerts its biological effects. The metabolic and chronobiological action of melatonin under physiological conditions is presented, which affects the regulation of energy metabolism, energy balance and body weight. The relationships of melatonin with ghrelin, leptin, cortisol and HGH are examined. Attention is paid to the close relationship between melatonin, cortisol, leptin, ghrelin and HGH and sleep and circadian rhythmicity. Data on desynchronization of the circadian rhythm of melatonin and cortisol in women with MetS were analyzed, for certain contradictions in the reported results on the relationship of melatonin with metabolic disorders, for example, in type 2 diabetes. It is noted that the role of melatonin in insulin secretion is increasingly being studied, but

the question of the probable regulatory role of melatonin on glucose homeostasis through its influence on other islet hormones, for example, glucagon, is rarely considered. The need for a more detailed clarification of the relationship between melatonin and carbohydrate and lipid metabolism in individuals with MetS is justified. This leads to the correct formulation of the goal and objectives of the dissertation work.

5. Research methodology

The research methodology allows solving the tasks set and achieving the goal of the dissertation work. The dissertation included 66 women with MetS aged 18 to 66 years, divided into two groups: women with MetS with dysglycemia and women with MetS without dysglycemia. The inclusion and exclusion criteria for patients from both groups are clearly formulated. Data on the principles of the methods used for determining melatonin, ghrelin, leptin, HGH and cortisol and their analytical characteristics are presented very clearly and correctly. Appropriate statistical methods have been selected, which create a good basis for discussing the obtained data and for drawing correct conclusions (variation analysis, alternative analysis, t-criterion for testing hypotheses for the presence of a statistically significant difference, correlation analysis, non-parametric methods, etc.). Graphical methods have been used to visually present the results.

6. Characteristics and evaluation of the dissertation work

The dissertation work is written on 150 pages, of which the title page is 1 page, the table of contents is 2 pages, abbreviations used are 2 pages, introduction is 3 pages, literature review is 33 pages, aim and objectives are 1 page, material and methods are 7 pages, results are 38 pages, discussion and conclusions are 33 pages, literature is 18 pages. The literature contains 316 literary sources, of which 41% are from the last ten years, and 19% are from the last 5 years. There are 9 pages of appendices, which present questionnaires, informed consent for the patient, data on the clinical-chemical and hormonal indicators used. The dissertation work is illustrated with 40 tables and 39 figures. The goal and tasks are structured clearly and logically follow the problems posed in the scientific review. The tasks are 6 and are sufficient to fulfil the set goal.

After the general characteristics of the studied contingent of individuals, the results obtained by Dr. Peneva are presented, which logically follow the tasks posed in the dissertation work. I highly appreciate the idea of Dr. Peneva to analyse the daytime and nighttime concentrations of melatonin, leptin, ghrelin, cortisol and HGH not only in women with MetS in the group as a whole, but also depending on whether the women have a preserved physiological melatonin rhythm (44% of the women included in the study) or have an inverted rhythm of melatonin secretion (56% of the women). The study shows that in all women with MetS there is a tendency towards lower nocturnal and higher daytime leptin, which is important from a pathophysiological point of view. The study, which analysed the daytime and nighttime concentrations of melatonin, leptin, ghrelin, cortisol and CTX in women with MetS with and without dysglycemia, deserves a very high rating. A statistically significantly lower nocturnal melatonin in combination with higher daytime leptin was found in women with dysglycemia, who had a higher BMI and a larger waist circumference than women without dysglycemia. The third task was developed very carefully and thoroughly, in which an intergroup comparative analysis of hormonal indicators was performed when subdividing

women with MetS according to the anthropometric and metabolic components of the syndrome. In addition, for a more detailed assessment of the changes in hormonal indicators, an intragroup analysis was also performed, comparing the average daytime and nighttime values of the indicators in the newly obtained groups. The analyses performed show that BMI is not associated with deviations in day-night melatonin concentrations; women with waist circumference ≥ 80 cm. have lower night-time serum melatonin than women with waist circumference ≤ 80 cm.; there is no change in day-night melatonin concentrations depending on triglycerides and HDL-cholesterol.

An important merit of the dissertation work are the correlation studies between hormonal indicators and indicators of carbohydrate and lipid metabolism in women with MetS both in the group as a whole and in the subgroups with preserved and inverted melatonin rhythm. Dr. Peneva found a wide variety of correlations depending on the group studied. For example, in the general group with MetS, lower night-time melatonin correlates positively with indicators of carbohydrate metabolism (IRI and HOMA-IR), and in the subgroup with preserved rhythm with HDL-cholesterol. In the subgroup with an inverted rhythm, higher daytime melatonin correlated positively with IRI. The relationship between hormonal indicators and indicators of carbohydrate and lipid metabolism in women with MetS with and without dysglycemia was also analyzed. Dr. Peneva's study shows that in women with MetS and dysglycemia, low nocturnal melatonin and high daytime and nocturnal leptin correlate positively with indicators of insulin resistance. Daytime CTX values correlate negatively with indicators of insulin resistance, and cortisol with glucose. However, these correlations are not observed in women with MetS without dysglycemia. In them, the trend towards higher nocturnal ghrelin correlates with lower triglycerides.

The last sixth task, Dr. Peneva, has dedicated to the analysis of changes in the night-day secretion of melatonin, leptin, ghrelin, cortisol and CTH depending on the number of clinically manifested components of MetS. It can be seen that melatonin concentrations vary depending on the number of clinically manifested components of the syndrome. The physiological rhythm is preserved in women without or with one component of MetS. With an increase in the number of clinically manifested components of MetS, changes in melatonin secretion are observed with higher daytime and lower nighttime values.

The dissertation work ends with eight conclusions made on the basis of the results obtained from the own studies, which are formulated accurately and comprehensively.

7. Contributions and significance of the work for science and practice

I accept the original contributions that Dr. Peneva has indicated. For the first time, a comprehensive clinical study has been conducted on the circadian rhythm of melatonin, leptin, ghrelin, cortisol and CTX in women with MetS from the Bulgarian population. For the first time in our country, changes in the circadian rhythm of melatonin, leptin, ghrelin, cortisol and HGH in women with MetS are analysed depending on glycemia. For the first time in our country, the relationship between melatonin, leptin, ghrelin, cortisol and HGH with indicators of carbohydrate and lipid metabolism in women with MetS is studied. The conducted clinical study contributes to clarifying the relationship between the observed hormonal indicators with indicators of carbohydrate and lipid metabolism in women with MetS with and without dysglycemia. For the first time in our

country, the relationship between the individual components of MetS and melatonin secretion has been analysed. For the first time in a Bulgarian population, the relationship between the melatonin rhythm and the clinically manifested components of MetS has been analysed. Some of the contributions have a confirmatory and scientifically applied nature. The role of disturbed rhythm of melatonin secretion in women with MetS in the development of insulin resistance is confirmed. The relationship between leptin, ghrelin and cortisol with visceral obesity is also confirmed. An analysis of the modern view of the role and place of melatonin, leptin, ghrelin, cortisol and CTX in the clinical manifestation of MetS has been performed.

8. Evaluation of the publications on the dissertation work

Dr. Peneva has presented 3 scientific articles in relation to the topic of the dissertation work, the first of which was published in an international journal with $IF_{2023} = 3.9$, the second in a Bulgarian journal indexed in Scopus, and the third was published in a paper at an international scientific conference. 9 scientific communications were presented, seven of which were from international firms, and five were printed in a journal with an impact factor. In all articles and scientific communications, Dr. Peneva is the first author.

9. Personal participation of the doctoral student and recommendations

During the development of the dissertation work, Dr. Peneva shows in-depth theoretical knowledge and practical skills, the ability to analyze the results obtained and draw correct conclusions. She works with literary sources with great desire and selects appropriate clinical cases.

I have no comments on the materials presented. I have a recommendation to Dr. Peneva to expand her scientific research on the involvement of melatonin in the complex and intricate pathogenesis of metabolic syndrome in men. Also, a monograph could be prepared that would have theoretical and practical significance.

10. Abstract – prepared on 63 pages, well structured, reflects the main results of the conducted studies.

CONCLUSION

Dr. Peneva's dissertation "Serum melatonin in women with metabolic syndrome" is the result of her own research and fully meets the requirements for awarding the educational and scientific degree "doctor" under the ZRASRB and the Regulations of the Medical University-Plovdiv. The dissertation shows that the doctoral student possesses professional skills, in-depth theoretical knowledge and skills for conducting independent scientific research. Therefore, I convincingly give my positive assessment of Dr. Peneva's dissertation work and recommend to the esteemed members of the Scientific Jury to award the educational and scientific degree "Doctor" to Dr. Vanya Milusheva Peneva.

19. 10. 2025

Plovdiv

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Заличено на основание
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