

To the chairman of the scientific jury
Determined by order of the Rector of Medical University Varna

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and on the basis of protocol № 1/20.12.2022

Opinion

By assoc prof. Mira Valentinova Siderova MD, PhD

Scientific specialty – Endocrinology

Associated professor in “Endocrinology”, Second department of internal medicine,
Medical University Varna

Of the dissertation

Of d-r Savi Rinaldiev Shishkov, full time PhD student, with dissertation title

“Androgen levels in men with acute and chronic coronary syndrome” for awarding of
educational and scientific degree “doctor” in Area of higher education 7. Healthcare and sport
National classifier code: 7.1 Medicine, Scientific specialty “Endocrinology”

Scientific mentor: Prof. Dr. Kiril Hristov Hristozov, PhD.

1. General presentation of the procedure:

The submitted set of materials complies with the requirements of the procedure for obtaining PhD degree according to the Regulations of MU - Varna and includes all necessary documents.

2. Brief biographical data about the PhD student

Dr. Savi Shishkov was born in 1991 in Varna. He graduated from "Ioan Exarch" High School with German language degree in 2010 and subsequently medicine in Medical University Varna in 2017. From 2017 to 2021 he was a fellow in the department of Endocrinology and metabolic disease in UMHAT “St. Marina” Varna. In 2021 he acquired a specialty in endocrinology. Since 2018 after a competition he has been appointed as an assistant professor in Endocrinology in Medical University Varna in the second department of internal medicine, board of endocrinology. He teaches students in Bulgarian and English. Since 2019 he is a full time PhD student in the same department. In 2021, Dr. Shishkov completed an additional specialization

at Leiden University Medical Center, The Netherlands with a focus on growth hormone treatment, transition of patients from child to adult care. He is fluent in English and German and is a member of the Bulgarian and European Society of Endocrinology.

3. Relevance of the topic

Cardiovascular diseases, including acute and chronic coronary syndromes, are socially significant health problems worldwide. Little is known about the role of androgens in male survivors of acute and chronic coronary syndrome, which is the subject of the scientific research work of Dr. Savi Shishkov.

Despite the fact that men are more often affected than premenopausal women and the suggestion that androgens are one of the likely causes, there is no definitive scientific evidence for this and the question remains open. Regarding the effects of testosterone on the cardiovascular system in patients with coronary pathology, there are conflicting data, ranging from beneficial effects to evidence of a higher risk of cardiovascular events with testosterone substitution. On the other hand, testosterone levels are altered in certain conditions identified as risk factors for atherosclerosis - obesity, metabolic syndrome and diabetes mellitus. Other androgens (DHEAS) and estrogens have also been implicated in the pathogenesis of atherosclerotic cardiovascular disease. In this sense, the selected topic of the dissertation work is highly relevant.

4. Evaluation of the dissertation

The dissertation is written in 174 pages, illustrated with 58 tables and 16 figures and is well organized in the following main sections: Title page (1 page); Content (3 pages); Abbreviations used (2 pages); Introduction (2 pages); Literature review (35 pages); Aim and objectives (1 page); Methods (13 pages); Results (57 pages); Discussion (22 pages); Conclusion, conclusions and contributions (6 pages); References used (31 pages). The bibliography contains 400 titles, of which 4 in Cyrillic and 396 in Latin.

5. Structure of the dissertation

The literature review is very well structured and includes up-to-date information on the physiology and pathophysiology of the hypothalamic-pituitary-gonadal axis and the role of steroid hormones, including their effects on the myocardium. The epidemiology, etiology, and pathogenesis of arterial coronary disease and various aspects of the pathogenesis of CHD related to sex hormones are reviewed. The data accumulated to date on hormonal adaptation in acute coronary syndrome (ACS) are described in detail. The PhD student presents an in-depth analysis of the relationships: androgens and glucose metabolism, estrogens and CHD, sex hormone binding globulin (SHBG) and cardiometabolic syndrome, as well as of different hormone ratios. The PhD student has an excellent knowledge of the subject and has presented a creative assessment of the analyzed literary materials.

The aim of the thesis is clearly formulated, namely to investigate the role of androgen hormones in the adaptation to acute coronary syndrome, as well as in the development of cardiovascular disease in men with acute and chronic coronary syndrome. To accomplish the aim, 6 specific tasks were set, well formulated and feasible to perform.

Participants and methods:

For the purpose of this dissertation Dr. Shishkov selected 105 men, mean age 56.75 years (36-70 years), hospitalized in the cardiology clinics of University Hospital "St. Marina" Varna. Inclusion and exclusion criteria were adequate for the purpose and design of the study. Clinical, laboratory, instrumental and survey methods were optimally selected. Adequate statistical analysis was used - analysis of variance (ANOVA); analysis of variance and correlation, parametric analysis - to compare means of dependent and independent samples with normal distribution, and non-parametric analysis to compare medians.

Results and discussion:

The results of the study are correctly presented in 6 sections, well-illustrated in tabular and graphical form, accompanied by adequate and objective commentary.

The first section presents the clinical characteristics of different patient groups and intergroup differences related to cardiovascular disease and cardiovascular risk. Data, including tabulated data from clinical and laboratory studies, are presented in detail and a comparative analysis of the parameters between the different patient groups is performed. A statistically significant higher BMI was found in the chronic coronary syndrome (CCS) group compared to the other two groups. The populations of patients with ACS and CCS differed in terms of the relative proportion of diabetics and the relative number of those with known arterial hypertension or CHD at admission. Differences in biochemical and blood count indices are also presented with significantly higher LDL-cholesterol, total cholesterol and leukocyte levels in ACS.

The second section discusses hormonal indices in individuals with ACS, CCS and controls. Significantly higher values of total T and free T, bioavailable T and DHEA-S were reported in controls compared to the other two groups (CCS and ACS). Men with ACS had significantly lower values of total T/ total E and free T/ free E ratios compared to controls, as well as higher morning serum cortisol and lower total T/LH ratio.

The third section is devoted to the analysis of hormonal indicators in men of the OCS group. The PhD student found a significantly lower level of total T, free T and bioavailable T in the STEMI group compared to NSTEMI and UAP. The aromatization index was significantly lower in the STEMI group compared to the NSTEMI and UAP groups. When comparing STEMI with controls, Dr. Shishkov found additional differences besides those already mentioned, namely in

free T levels and free T/free E ratio. In the group of diabetic patients with ACS, a lower total T/LH ratio and a higher C/D were recorded compared to patients without DM. The results of dynamic monitoring of androgens in ACS are interesting. There was a tendency for total T value increase without reaching statistical significance, but such was found in an increase in free T% with time and decreases in DHEA-S.

The fourth section presents the results of the hormonal analysis in men with CCS, which showed a statistically significant difference in the levels of total, free and bioavailable T, SHBG and free E% between patients with and without diabetes mellitus.

The fifth section analyses the hormone levels and their differences between the control group and all patients with arterial coronary artery disease - CHD (ACS+CCS). Significantly lower androgen levels and higher cortisol levels were reported in the ACS group compared to controls. From the correlation analysis, the correlation between total T and the presence of DM, SHBG and DM, and the negative association between free T and BMI were of interest.

The sixth section discusses the results of hormones, clinical and biochemical parameters studied in the controls. In this group of healthy men, a positive association was found between estradiol and age, and a negative one between some androgens (DHEA-S, bioT%) and age.

The discussion is thorough, summarizes the findings in the context of current understanding of the problem, and compares them with results from other research teams. The self-criticism of the PhD student is noteworthy, pointing out some limitations/flaws of the thesis.

The twenty-three **conclusions** drawn are consistent with the results obtained and follow the objectives set in the thesis.

The **contributions** of the dissertation are divided into two categories: of a scientific-practical and of a confirmatory nature. Some of the contributions are definitely innovative for Bulgaria.

Thesis summary and publications related to the thesis

The thesis summary is fully sufficient in content and in quality to represent the main results achieved in the thesis. The doctoral candidate has attached to the documentation 3 full-text publications related to the dissertation. The attached list meets the requirements to be awarded the PhD degree. The dissertation work was supported by the scientific project "Dynamics in serum levels of male sex steroids in men after acute coronary syndrome" - funded by the Science Fund of MU - Varna in 2020.

6. Critical comments and recommendations.

I have no critical comments or recommendations regarding the research and materials provided.

In **conclusion**, the thesis, reviewed by me, which addresses an up-to-date and socially relevant topic, reflects a thorough and valuable work, impressive for its precise statistical analyses. I consider that the thesis meets the requirements of the Law for the Development of Academic Staff in the Republic of Bulgaria (LADRB), the Regulations for its implementation and the Regulations for the Development of Academic Staff at MU-Varna for the acquisition of the scientific and educational degree "Doctor" and I vote positively for the awarding of this degree to Dr. Savi Rinaldiev Shishkov.

11.01.2023r.

Varna



assoc. prof. Mira Siderova MD, PhD