

POSTION STATEMENT

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about a dissertation

for the award of an educational and scientific degree "doctor" on the topic
"ANDROGEN LEVELS IN MEN WITH ACUTE AND CHRONIC CORONARY
SYNDROME"

of Dr. Savi Rinaldiev Shishkov

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I. Structure of the dissertation

The submitted dissertation covers 174 standard typewritten pages and is structured as follows:

1. Literature review – 38 pages.
2. Goals and objectives – 1 page.
3. Methods – 13 pages.
4. Results – 65 pages.
5. Discussion and main conclusions - 27 pages.
6. Contribution report - 2 pages.
7. Bibliography - 24 pages; covers 382 literary sources (4 in Cyrillic, 378 in Latin).

The content is presented correctly and in detail. The most frequently used abbreviations are listed. The individual chapters and sub-chapters are properly formatted, which gives clarity to the dissertation work. The material is illustrated with 58 tables and 17 figures.

The structure of the dissertation work and the independent participation of the PhD student in its preparation correspond to the requirements, according to the rules for the terms and conditions for acquiring scientific degrees and occupying academic positions of MU-Varna.

II. Actuality, significance and practical focus of the topic

Cardiovascular diseases are a major cause of morbidity and mortality worldwide. In recent years, a lot of data have been accumulated on the involvement of sex hormones in the pathogenesis of ischemic heart disease (IHD). Despite the empirical data that men suffer more often than premenopausal women and the assumptions that androgens are one of the possible causes, studies in this direction give ambiguous results. On the one hand, testosterone is associated with beneficial effects (reduction of infarct area size and vasodilation), but on the other hand, it is associated with the induction of inflammation and activation of signaling pathways associated with apoptosis. It has been suggested that the decline in testosterone levels during the acute period of acute coronary syndrome (ACS) is an adaptive mechanism providing better survival, but there is also evidence of increased mortality with low baseline testosterone during ACS. Hypogonadism is associated with increased cardiovascular risk, but studies on the effect of testosterone replacement therapy on CV risk in such patients have also yielded mixed results. These contradictions could partly be explained by the fact that many other hormones and binding proteins (DHEA-S, estrogens, cortisol, SHBG, etc.) are also related to the functioning of the cardiovascular system, which suggests their involvement in pathogenesis of atherosclerotic cardiovascular diseases. This necessitates a complex hormonal assessment and interpretation when studying the role of the endocrine system in cardiovascular diseases.

The problem of androgens in men with acute and chronic coronary syndrome is extremely relevant, as it turns out that major risk factors (arterial hypertension, dyslipidemia, dysglycemia, smoking) cannot fully explain the pathogenesis of CHD and its progression. In this sense, the search for other factors playing a role in the genesis of this socially significant disease can support both risk stratification and improvement of prevention strategies. This makes the topic of the dissertation chosen by Dr. Shishkov relevant from a scientific point of view and useful for clinical practice.

III. Components of the dissertation

The literature review is built purposefully, the emphasis is placed on the relevant aspects of the main topic, namely physiology and pathophysiology of the hypothalamic-pituitary-gonadal and - adrenal axis, as well as the interaction between them, systemic effects and role in the myocardium of steroid hormones, acute and

chronic coronary disease and aspects in the pathogenesis of ischemic heart disease related to sex hormones, hormonal adaptation in acute coronary syndrome, the role of testosterone-replacement therapy and the importance of different hormonal relationships (cortisol to DHEA-S, testosterone to estradiol and index of androgen sensitivity).

The wording of the aim and objectives is clear and precise and concerns the role of androgen hormones in the adaptation to acute coronary syndrome, as well as the development of cardiovascular disease in men with acute and chronic coronary syndrome.

In the "**Material and methods**" section, the following are detailed: the study design; patient recruitment method with inclusion and exclusion criteria; indicators studied. The strict selection of the covered contingent according to standardized criteria guarantees the reliability of the obtained results. The methods of the individual clinical and laboratory indicators, as well as the definitions used, are precisely described.

The "**Results**" section contains the individual aspects of the dissertation development. The results of the comparison of the hormonal indicators between the groups with acute and chronic coronary syndrome and controls are reflected, and it was established that the controls had a significantly higher value of totalT and freeT, bioT and DHEA-S; lower cortisol/DHEA-S ratio compared to the other two groups (chronic and acute coronary syndrome); while ACS patients had higher serum cortisol and lower totalT/totalE and freeT/freeE ratios compared to controls.

Differences in hormonal parameters between ACS and controls, on the one hand, and STEMI and controls, on the other hand, are largely overlapped, with both controls having higher levels of totalT, bioT, DHEA-S, and totalT/totalE and lower cortisol and cortisol/DHEA-S ratio. No difference in SHBG levels was observed, suggesting that differences in freeT and bioT are entirely due to total testosterone. On the other hand, the levels of totalT, freeT, bioT and the totalT/total E ratio were lower in the subgroup of patients with ST-elevation, while those of DHEA-S were higher. Total testosterone correlated with the type of incident and the presence of ST-elevation, as well as with the sequence of the incident, which, however, lost statistical significance after adjustment for the presence of ST-elevation. DHEA-S appears to be

the best predictor of the presence of ST-elevation in a patient with ACS.

No difference was found in testosterone and DHEA-S levels between patients with and without diabetes mellitus in the ACS group, but patients with diabetes had a lower T/LH ratio and higher cortisol/DHEA-S compared to non-DM patients.

In the follow-up of some patients, no significant change in hormonal indicators was found, despite the tendency for a slight increase in the levels of total testosterone, while in the modeling of the results, a statistically significant increase in freeT% and a decrease in DHEA-S was found over time.

The discussion is structured logically and examines the results related to the levels of testosterone and its fractions in patients with ACS, the relationship with diabetes mellitus and with disorders in glucose metabolism in general, as well as with body weight. The tracking of testosterone in dynamics makes it possible to make the assumption that the drop in freeT is related to the physiological stress caused by the acute cardiovascular incident, given the tendency of T to increase over time, and the lack of correlation of freeT with a correlation between BMI and age.

Of interest are the results of the DHEA-S study in the different groups of patients and their interpretation, with threshold values that completely exclude the presence of STEMI and those that correspond in 95% to ST-elevation. On the other hand, DHEA-S levels below the lower reference limit do not reliably predict the presence of ST-elevation as data show for cortisol, further suggesting that low DHEA-S levels are the result of a chronic condition rather than consequence of ACS.

The analysis of the obtained results for SHBG levels outline it as an additional risk factor for cardiovascular diseases in men both in the period immediately after the onset of ACS and in stable CAD.

The different hormonal ratios (freeT/LH, totalT/LH, totalT/totalE; freeT/freeE; cortisol/DHEA-S) were examined as a method to assess the balance between two hormonal systems in the context of acute coronary syndrome. Due to the fact that both absolute hormone values and hormone ratios demonstrate correlations with clinical and biochemical indicators on the one hand, and on the other hand, the aromatization index expressed by the freeT/freeE ratio is better associated with cardiovascular risk factors, than each of the indicators separately, the hypothesis is confirmed that the study of hormonal axes in their interaction with each other brings more information than each indicator alone. Based on this, it has been proposed to add the ratio

freeT/LH, freeT/freeE, as well as the albumin value to the usual risk characteristics, given the associations of these indicators with the lipid profile and the GRACE score.

The conclusions are presented separately for the different tasks and concretely and precisely reflect in a summary the results related to the main and most important aspects of the development.

The contributions are divided into those of a scientific-practical nature and of a confirmatory nature. Most of the contributions are original and contribute to the enrichment of the overall knowledge in the field of the role of androgens in acute coronary syndrome.

The bibliography covers 382 literary sources and meets the requirements while being sufficiently comprehensive and up-to-date.

The dissertation student has 3 **publications** related to the dissertation, of which 2 in refereed journals, 1 participation in a scientific forum and 1 participation in a scientific project.

CONCLUSION: Dr. Savi Rinaldiev Shishkov's dissertation "ANDROGEN LEVELS IN MEN WITH ACUTE AND CHRONIC CORONARY SYNDROME" is up-to-date and properly structured. The design of the individual studies and the overall setting of the development correspond to the goals and objectives. The dissertation meets all the requirements of the Law on the Development of the Academic Staff in the Republic of Bulgaria, the Regulations for its Implementation and the Regulations for the Conditions and Procedures for Acquiring Scientific Degrees and Occupying Academic Positions at MU-Varna for the Acquisition of the Educational and Scientific degree "Doctor" in the doctoral program "Endocrinology".

I give a positive review and strongly recommend to the members of the respected scientific jury to give a positive vote for awarding the educational and scientific degree "Doctor" to Dr. Savi Rinaldiev Shishkov.

15.01.2023

Sofia

Signature :

/ass. prof. A. Gateval/

