Институт по биология и имунология на размножаването - БАН
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Attitude of Reviewer

By Professor Nina Atanassova, PhD, DSc,
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Re: defense of dissertation for acquisition of PhD degree of animal and human physiology, professional direction 4.3. "Biological Sciences" in the field of higher education 4. "Natural Sciences, Mathematics and Informatics" in the Department Molecular Immunology, IBIR - Sofia

Author: Georgi Lazarov
Title: Etiopathogenesis of partial testicular failure in young adult men

The dissertation thesis by Dr. Georgi Vladimirov Lazarov is addressed to the problems of male infertility and erectile dysfunction, which are not only of health and demographic importance, but also have a pronounced psycho-social aspect. The problem is particularly relevant in the context of the impact of lifestyle and related metabolic disorders on the reproductive and sexual function of young men. Despite the fact that androgen insufficiency in aging men is the subject of extensive research, Dr. Lazarov has found a niche for his studies, focused on young (35 - 45 year old) men, which convinces of the high usefulness of the work for the reproductive health care of men in active age. Valuable scientific results with high applied significance for clinical andrological and urological practice have been obtained, necessary for a correct therapeutic strategy in combination with an appropriate hygienic and dietary regimen. This inevitably outlines the prospects of the dissertation, having in mind the growing health problems associated with the modern unhealthy lifestyle.

The dissertation is written on 135 pages, illustrated with 22 graphic figures, 15 tables and 1 figure-scheme is attached in the conclusion. At the end of the dissertation, 40 tables with the initial results of the clinical examinations of all patients included in the study are given in the appendix. The dissertation is organized according to the generally accepted form for this type of work and is in a balanced ratio of the individual sections with a logical predominance of the own results. The concise literature review (25 pages) is specifically and purposefully addressed to the topic of the dissertation. The remarkable number of literary sources (249, of which 9 in Cyrillic) demonstrates the high competence of the author. The review ends with 4 conclusions, in which the Georgi Lazarov specifically addresses the unresolved issues related to the ambiguity of clinically significant testosterone (T) levels, below which specific symptoms of the genitourinary system appear (such as infertility, micturition disorders, and erectile dysfunction). In direct accordance, 4 tasks have been formulated to fulfill the goal of the dissertation, which is to establish the relationship between specific symptoms suspicious for androgen deficiency and T levels in young

men, in an attempt to determine whether there is a clear discrimination threshold below which they become clinically significant. The tasks are stated briefly and specifically, correspond to the chronology in the description of the results and convince of the fulfillment of the goal. They specifically target searching for a relationship/correlation between lower T levels (below 14.28 nmol/l, but still within the reference range) and unhealthy lifestyle; metabolic and hormonal profile and seminal pathology; testicular volume, prostate gland volume (PGV) and residual urine volume; erectile dysfunction (ED), measured with the blood flow of the deep penile artery.

The section "Patients and Methods" is presented concisely and clearly. The ethical issues was followed for research with patients, the number of whom is remarkable and allows to select a representative sample of 20 controls and 73 patients with specific symptoms suspicious of androgen deficiency. The proposed methodology is appropriately selected to ensure the successful implementation of the goal and objectives of the work. The author proposed three appropriate questionnaires for assessing unhealthy lifestyle (manifested by body mass index, BMI), micturition disorders and ED. Biochemical (lipid profile and glucose) and hormonal tests (sex steroids and gonadotropins) were performed correctly. The semen analysis is in accordance with WHO criteria from 2021. Modern color Doppler ultrasound of the reproductive system and uroflowmetry (determination of maximum urinary flow rate, MUF) were used. Professional statistics were applied with specialized software IBM SPSS STATISTICS Version 25 for parametric and non-parametric tests in data processing and correlation analysis.

The results are described clearly, specifically and with high clinical competence. They are presented systematically and consistently, in accordance with the tasks set. The graphic illustrations of the quantitative data are followed by tables with the correlation coefficients, proving the strength of the correlation (moderate, significant and strong). The finding of a moderate correlation between unhealthy life style (low physical activity, poor food hygiene, smoking and alcohol intake) and BMI is logical, and they in turn are significantly correlated with the reduced average T from the three-fold measurements (< 14.28 nmol/l). A significant correlation is established between T with the lipid profile (total cholesterol, LDL, HDL, triglycerides), with estradiol, (E2) and gonadotropic hormones (FSH and LH) and a strong one with SHBG (serum hormone-binding globulin). In normal and overweight men, an important prerequisite for seminal disorders (mild to moderate oligozoospermia and asthenozoospermia) is a T level below 14.28 nmol/L and an increased E2/T ratio, while in those with obesity the etiology is complex (together with FSH and LH).

The established significant correlations between PGV and MUF on the one hand and T and E2/T on the other demonstrate the primary role of endocrine abnormalities in the occurrence of micturition disorders and the initial enlargement of the prostate gland in young patients, and obesity and metabolic disorders remain an important, but not mandatory prerequisite. Comparison

of the correlation coefficients suggests that T and E2/T (significant correlation) are a primary prerequisite for ED than PGV and MUF (moderate correlation), and obesity is of less importance.

Based on the results, 4 conclusions have been drawn that correspond to the 4 tasks set and 5 original achievements have been formulated. The seeking for a constant interrelated analysis of the disorders based on an extensive professional correlation analysis is an important contribution of Dr. Lazarov to make a comparative assessment of the significance of each disorder (metabolic, hormonal, organ/functional) for the manifestation of the other ones. This allows him to develop a complex view of the significance of reduced T within the range of 8.60 – 14.28 nmol/l (although within reference range) in young men aged 37 to 45 years for the manifestation of symptoms originating from the genitourinary system (semen pathology, micturition disorders and erectile dysfunction), similar to those in aging men with hypogonadism. In perspective, he proposes that this association of specific symptoms with a T level of 8.60 – 14.28 nmol/l be referred to as "Lifestyle-related partial testicular failure syndrome in young men".

Three articles have been published on the topic of the dissertation, published in Proceedings of the Bulgarian Academy of Sciences (Q3), Folia Medica (Q4) Acta Medica Bulgarica (Q4), which give 39 points, exceeding the required 30 points.

In conclusion, The dissertation work of Georgi Lazarov is distinguished by its complex and systematic approach, applied purposefully and precisely, which allows him to define the reduced levels of testosterone, although in the reference range, for the manifestation of specific symptoms of the genitourinary system. This demonstrates the pronounced clinical potential of his research, which, conducted on young men, proves its originality and high social significance for the male reproductive health care in the context of the modern unhealthy lifestyle. The achievements of the dissertation can find direct application with a recommendation to medical specialists for a broad holistic view in solving problems related to internal medicine, psychology and urology.

The volume and quality of the conducted research and the successful implementation of the educational and scientific program fully meet the criteria of the IBIR-BAS for Regulations for acquiring scientific degrees and holding academic positions. Having in mind the above, with high conviction I give a positive assessment of the dissertation work on the topic "Etiopathogenesis of partial testicular failure in young men" and I recommend to the members of the esteemed Scientific Jury to vote "FOR" awarding the educational and scientific degree "Doctor" to Georgi Lazarov.

02.11.2025 Reviewer:

Professor Nina Atanassova, PhD, DSc