

REVIEW

Regarding the dissertation work of Dr. Vesselin Milkov Boyadzhiev, entitled:

"BONE HEALTH AND FRACTURE RISK AMONG CHILDREN IN PREPUBERTAL AND ADOLESCENT AGE – THE IMPORTANCE OF BODY WEIGHT, FAT TISSUE DISTRIBUTION, AND THE PRESENCE OF METABOLIC ABNORMALITIES"

for the award of the educational and scientific degree "Doctor" in the field of higher education 7. Health Care and Sports, professional direction 7.1. Medicine and scientific specialty "Pediatrics" of Dr. VESSELIN MILKOV BOYADZHIEV

Scientific Supervisors: Prof. Dr. Violeta Mihova Yotova, MD Prof. Dr. Borianna Borisova Varbanova, MD

Scientific Consultant: Prof. Dr. Dimitar Ivanov Raikov, MD

Reviewer: Assoc. Prof. Dr. Sonya Vasileva Galcheva, MD Pediatric Endocrinologist, Department of Pediatrics, Medical University "Prof. Dr. Paraskev Stoyanov" - Varna

In accordance with the order of the Vice-Rector for "Educational Activities" of the Medical University "Prof. Dr. Paraskev Stoyanov" - Varna № P-109-270/05.08.2024, based on Article 24, paragraph 6, and Article 30, paragraph 3 of the Law for the Development of the Academic Staff in the Republic of Bulgaria, and Article 68, paragraph 1 of the Regulations for the Development of Academic Staff at the Medical University – Varna, I have been designated as a member of the Scientific Jury in the procedure for obtaining the educational and scientific degree "Doctor" through the doctoral program "Pediatrics," professional direction 7.1 Medicine, field of higher education 7. Health Care and Sports, with candidate Dr. Veselin Milkov Boyadzhiev, a doctoral student in an independent form of study, enrolled by order № P-109-355/12.06.2018. According to protocol № 1/16.08.2024 from a meeting of the Scientific Jury, I present this review prepared in accordance with the requirements of the Law for the Development of Academic Staff in the Republic of Bulgaria and the Regulations for the Development of Academic Staff of MU – Varna.

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The review of Dr. Veselin Milkov Boyadzhiev's dissertation titled **"BONE HEALTH AND FRACTURE RISK AMONG CHILDREN IN PREPUBERTAL AND ADOLESCENT AGE – THE IMPORTANCE OF BODY WEIGHT, FAT TISSUE DISTRIBUTION, AND THE PRESENCE OF METABOLIC ABNORMALITIES"** and the materials presented for the competition is based on the requirements of the Law for the Development of Academic Staff in the Republic of Bulgaria and the Regulations for the Development of

Development of Academic Staff of MU – Varna. The stages of the doctoral training have been adhered to, and there has been no change to the initial topic or scientific supervisors.

Here's the translation of the provided text into English, maintaining an academic tone:

1. Brief Biographical and Professional Information about the Candidate.

Dr. Veselin Boyadzhiev was born on February 27, 1975. He graduated in 1999 with a Master of Medicine degree from the Medical University "Prof. Dr. Paraskev Stoyanov" in Varna. In 2005, he obtained a specialization in "Pediatric Diseases," followed by a specialization in "Pediatric Endocrinology and Metabolic Disorders" in 2009. Since 2001, he has been appointed as an assistant in the Department of Pediatrics and Medical Genetics at the Medical University – Varna. From 2011 to 2015, he served as a chief assistant in the Department of Pediatrics, and since 2014, he has also held the position of administrative assistant. Since 2001, he has been consistently working as a pediatrician and pediatric endocrinologist at UMHAT "St. Marina" EAD – Varna, in the First Pediatric Clinic. He has rapidly acquired competence for teaching activities and adequate professional skills necessary for conducting research related to his dissertation.

He has participated in several significant national and international scientific schools, courses, and specializations, including the ESPE Winter School (Varna, 2006), ESPE Clinical Fellowship (Children's Bone Health, Sheffield, UK, 2008), the 2nd Joint Meeting of the Bone Research Society and the British Orthopaedic Research Society (UK, 2008), ISPAD Science School (USA, 2008), international conferences on pediatric bone health (2009, 2013, and 2015), the 11th International Conference on Osteogenesis Imperfecta (Croatia, 2011), and annual meetings of the European Society for Pediatric Endocrinology (2006-2023), VAPES (2011-2023), among others. He has attended training courses on bone dysplasia (Switzerland, 2018), growth and growth disorders (Sweden, 2011), and pediatric bone and calcium metabolism (United Kingdom, 2009). He has served as a principal investigator or co-investigator in several clinical trials involving children with Type 1 diabetes mellitus (BEGIN, 2012-2014; ONSET7, 2015-2017) and children with osteogenesis imperfecta (2015).

He is a member of several scientific societies and organizations, including the Bulgarian Medical Association, the Bulgarian Pediatric Association, the Bulgarian National Association of Pediatric Endocrinology, and the Varna Society for Pediatric Endocrinology (Chairman of the Management Board from 2017 to 2023).

2. Dissertation.

A. Introduction and Relevance of the Problem

In the past two decades, there has been a growing scientific interest and knowledge in the field of the biology of growing children's bones, transforming the topic of pediatric bone health into a well-recognized and significant medical issue. There is a notable accumulation of knowledge regarding various molecular-genetic mechanisms involved in the regulation of normal skeletogenesis, revealing the intricate stages in the processes of bone growth and maturation in children, as well as in the etiopathogenesis of various skeletal disorders. The

role of bone in the overall metabolism of the body is increasingly emphasized, and in recent years, the involvement of adipose tissue (AT) in the regulation of bone metabolism has been intensively studied, with the presence of obesity identified as a new and significant risk factor for impaired bone health even during childhood and adolescence.

At the time Dr. Boyadzhiev began this research, there were no other scientific works in our country focused on exploring the relationship between bone health and fracture risk in children and adolescents, body weight, the role of adipose tissue distribution, and the presence of metabolic abnormalities. For all these reasons, the selected topic of the dissertation is timely, innovative, and of exceptional significance not only for science but also for clinical practice.

B. Characteristics, Volume, and Structure of the Dissertation

Dr. Veselin Boyadzhiev's dissertation is composed of 147 pages and is illustrated with 50 tables and 75 figures. It is written in proficient Bulgarian, with a clear style that demonstrates a thorough command of specialized terminology, alongside precise discussions of the obtained results and the data in the scientific literature.

The dissertation consists of the following sections: content - 1 page; abbreviations used - 2 pages; introduction - 1 page; literature review - 36 pages; hypothesis, aim, and objectives - 1 page; design and methods - 9 pages; original results - 51 pages; discussion - 22 pages; conclusions - 2 pages; contributions - 1 page; publications and presentations related to the dissertation - 1 page; conclusion - 1 page; bibliography - 18 pages; appendix - 1 page. The reference list includes 463 titles in Latin script.

The content of the dissertation is well-structured and balanced across the various sections. The list of the candidate's scientific publications includes 3 full-text articles and 3 poster presentations at international scientific conferences. In all publications, Dr. Boyadzhiev is the first author. The scientific activity of the doctoral candidate aligns with regulatory requirements.

Here is a scholarly translation of the provided section into English:

B.1.) Literature Review

The literature review systematically organizes the results of studies found in the global literature, a significant portion of which (n=129 or 27.9%) have been published in the last five years. This serves as evidence of the candidate's solid theoretical foundation and extensive knowledge of the dissertation topic as well as the latest research in the field.

In the review, Dr. Boyadzhiev thoroughly examines the biology of growing children's bones, the biomechanical properties of bone, the processes of bone modeling, bone growth, and the accumulation of peak bone mass during childhood and adolescence. The candidate presents an in-depth overview of the methods utilized worldwide for assessing bone parameters (dual-energy X-ray absorptiometry, peripheral quantitative computed tomography (pQCT), high-resolution peripheral quantitative computed tomography (HR-pQCT), quantitative ultrasound (QUS), and bone biopsy) and for evaluating body composition (bioelectrical impedance

analysis, BIA), highlighting the advantages and disadvantages of their application in clinical practice. He demonstrates knowledge of approaches to overcoming the latter, drawing on global experience.

This section of the dissertation also provides a detailed and analytical discussion of the problem of osteoporosis in childhood—its causes and classification, the epidemiology of fractures in children and adolescents, and the prognostic osteometric indicators that can be used for risk assessment. Furthermore, it extensively analyzes the published scientific data regarding the relationship between childhood obesity and fracture risk in children, the roles of adipose tissue and lean body mass, and their influences on bone metabolism, as well as the impact of existing metabolic disorders on bone-molecular mechanisms.

B.2.) Aim, Objectives, and Working Hypothesis

The thorough and analytical review of the literature, along with a solid understanding of the scientific material, facilitated the formulation of the research hypothesis that overweight and obesity during childhood and adolescence are associated with deviations in proper skeletal development and a higher fracture incidence. This leads to a clear objective of the dissertation: to establish the epidemiological characteristics of fractures among the pediatric population in Varna and to investigate the bone densitometric parameters among girls with overweight and obesity, while determining the influence of body weight, body composition distribution, the amount of adipose tissue, and the presence of metabolic abnormalities on the processes of bone maturation and the achievement of optimal bone health by the end of childhood.

To achieve this objective, the dissertation outlines eight primary tasks, divided into two parts:

A) Epidemiological Section with 4 Tasks:

1. To determine the frequency of fractures among the pediatric population in Varna and their distribution by gender, age, and localization.
2. Among the children who have sustained fractures, to identify the percentage of those with normal weight, overweight, and obesity.
3. To ascertain the proportion of children with two or more fractures and to provide a percentage distribution based on the number of fractures.
4. To establish the percentage of children with fractures who also have additional musculoskeletal complaints and/or other chronic conditions.

B) Clinical Section with 4 Tasks:

1. To investigate osteometric parameters, including whole-body and lumbar bone mineral density (BMD), bone mineral content (BMC), and bone area (BA).
2. To analyze anthropometric data and the distribution of body composition, including the amount of adipose tissue, and their relationships with bone densitometric parameters.
3. To examine key laboratory biochemical and hormonal indicators, determining the percentage of girls with metabolic syndrome and assessing the impact of metabolic abnormalities on bone parameters.
4. To establish levels of vitamin D and the status of calcium-phosphorus metabolism and their relationship with bone parameters.

B.3.) Materials and Methods

To achieve the stated objectives and tasks, two sub-studies were conducted:

- **Epidemiological Study:** A questionnaire survey (available in both paper and online formats) was conducted among students aged 16-19 from 14 high schools in Varna during the period of 2021-2022. The questionnaire was approved in advance by the Ethics Committee of the Medical University of Varna and by the Department of Education and the Department of Health of Varna Municipality, and was coordinated with the management of the educational institutions. I commend Dr. Boyadzhiev for demonstrating good scientific and ethical practices!
- **Clinical Study:** This part encompassed a period of one year (2023), involving 41 hospitalized girls aged between 14 and 17, with clearly defined inclusion and exclusion criteria. The studies were conducted within the facilities of the University Hospital "St. Marina" EAD in Varna.

The study was approved by the Ethics Committee for Scientific Research at the Medical University of Varna. All parents signed an informed consent form for their child's participation.

The methods used included organizational methods (the basis and structure of the study), questionnaires, physical examinations, auxology/anthropometry, assessment of pubertal development according to Tanner, laboratory methods (hematological indicators, general biochemical and lipid panels, calcium-phosphorus metabolism, glycated hemoglobin, OGTT, hormonal tests, urine tests (chemical analysis, calciuria, and phosphaturia), and imaging studies (DXA densitometry, radiographs of the wrist, hand, and fingers, abdominal ultrasound, bioelectrical impedance analysis (BIA)).

The statistical methods were appropriately selected, allowing for reliable processing of the obtained data.

B.4.) Own Results

In this section, Dr. Boyadzhiev describes in detail and demonstrates the successful completion of each of the tasks related to the main objective of his scientific work. The results are well illustrated with a large number of figures and tables, organized into two subsections.

In the first subsection, the epidemiological data on the frequency of fractures among students are presented, categorized by sex, highlighting two age peaks—prepubertal and during the active years of pubertal maturation—most frequently affecting the upper extremity (72% in boys and 68% in girls). An interesting finding is that 36% of girls with overweight/obesity and 22% of boys have more than two and three fractures, respectively.

The second subsection presents the classification of participants based on the degree of obesity according to BMI and the presence of risk factors for metabolic syndrome, comparing them across osteometric parameters. It demonstrates that total bone mineral content (t-BMC) significantly increases with rising body mass, BMI, waist circumference, central distribution of fat mass, and indicators of visceral fat mass (VFM). In contrast to the results obtained for t-BMC without adjustments for weight and for fat-free mass (FFM), there is a well-expressed tendency for a "decline" in total bone mineral density (t-BMD) in the examined girls when

adjusted for FFM, corresponding to an increase in the degree of obesity and the quantity of VFM. The dissertation shows a strong positive relationship between t-BMC and FFM indicators, including those primarily reflecting skeletal muscle mass (SMI, SMM), particularly in the upper extremities. It is demonstrated that bone area significantly decreases with BMI, waist circumference, and the amount of VFM among participants with obesity; however, a positive significant relationship is established between bone mineral content (BMC) and height and %FFM. This suggests that as weight increases and fat progressively accumulates, the influence of VFM on BMC begins to diminish, eventually disappearing after a certain degree of obesity.

When analyzing the relationship between obesity indicators and the osteometric DXA parameters, no correlation is found between lumbar BMC and body weight, BMI, waist circumference, or percentage of body fat.

An analysis of the relationship between metabolic and bone parameters shows a positive correlation between serum insulin, triglycerides (TG), uric acid, and t-BMC, while sex hormone-binding globulin (SHBG) negatively correlates with BMC.

The study of calcium-phosphorus metabolism reveals significantly lower levels of 25(OH) vitamin D with increasing obesity (% Ob), the amount of muscle mass, visceral fat index (VFI), and levels of visceral fat.

B.5.) Discussion, Conclusions, and Contributions

In this section of the dissertation, Dr. Veselin Boyadzhiev demonstrates a very good understanding of the global scientific literature concerning the discussed problem, adequately commenting on and comparing the obtained results with those from other national and international scientific sources. This thorough approach makes the successful formulation of conclusions, in line with the results obtained, entirely justified, highlighting the applied scientific nature of the work and summarizing the significance of the dissertation.

A total of five conclusions are drawn from the epidemiological sub-study, with two particularly interesting ones: Conclusion 1.3 states that among children with fractures, 42% of boys and 31% of girls had more than one fracture, which is a higher percentage than reported in the existing literature. Conclusion 1.4 indicates that among children with more than one fracture, there is an observed increase in the percentage of those with overweight/obesity, with this trend being more pronounced among girls. Analyzing the results from the clinical sub-study, the dissertation presents clearly justified 11 conclusions that evoke significant scientific interest and should be published.

I accept the outlined contributions of this work, which total eight. These contributions have both scientific-theoretical (numbers 1, 3, 4) and scientific-applied (numbers 2, 5, 6, 7, 8) characteristics.

Publications and Scientific Activity

Dr. Boyadzhiev has provided a list of three full-text publications and three participations in international scientific events, where part of the results of this dissertation work is presented. This meets the normative requirements for the dissertation candidate.

Author's Summary

The author's summary is developed over 104 pages, structured according to the requirements, and its content fully corresponds to the dissertation.

Critical Remarks

There are none.

CONCLUSION

The dissertation submitted for review is the author's original work, characterized by originality, relevance, depth, and a serious understanding of the scientific subject matter, as well as an important scientific-applied character.

Dr. Veselin Boyadzhiev is an excellent pediatric endocrinologist and educator, fully dedicated to his work with children. Throughout his research work, he invested a significant amount of personal effort, resources, patience, and perseverance, which, despite numerous obstacles and difficulties (including the COVID-19 pandemic), allowed him to successfully conduct and complete his work. All of this, along with the aforementioned, provides me with ample grounds to give a fully convinced positive opinion and to recommend to the esteemed Scientific Jury to confer the scientific degree of "Doctor" to Dr. Veselin Milkov Boyadzhiev.

Varna, 04.11.2024

Reviewer:

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

Assoc. Prof. Sonya Galcheva, MD, PhD