

**To the Chairman of the Scientific Jury,  
appointed by Order  
No. P-109 -270/05.08.2024  
of the Rector of MU-Varna**

**S T A T E M E N T**

**From: Assoc. Prof. Margarita Alexieva Archinkova, Ph.D  
Department of Pediatrics at Medical University - Sofia  
External Member of the Scientific Jury**

**Of dissertation "Bone health and fracture risk among peripubertal and adolescent children – the importance of body weight, adipose tissue distribution and the presence of metabolic abnormalities" for the educational and scientific degree "Doctor"**

**of Dr. Veselin Milkov Boyadzhiev**

**Field of higher education: 7. Health and Sport**

**7.1. Medicine**

**Scientific specialty "Paediatrics "**

**Form of doctoral studies: individual form of study**

**Medical University "Prof. Dr. Paraskev Stoyanov"- Varna**

**Scientific supervisors: Prof. Dr. Violeta Iotova, PhD, Prof. Dr. Boryana Varbanova, PhD.**

The submitted set of materials by Dr. Veselin Milkov Boyadzhiev is in accordance with the requirements of the Regulations for the Structure and Activities of MU-Varna, the Law for the Development of Academic Staff in the Republic of Bulgaria, as well as the Regulation for the Acquisition of the Doctoral Degree.

The dissertation has been discussed, accepted and directed for defense by the Head of the Department of Pediatrics of the Medical Faculty - Varna on the basis of the decision of the Departmental Council with protocol № 25/29.07.2024, and the decision of the Faculty Council of the Medical Faculty from the meeting held and report with registration № 103-3752/30.07.2024.

## **Biographical data**

Dr. Veselin Milkov Boyadzhiev graduated from the Medical University "Prof. Dr. Paraskev Stoyanov"- Varna, with a degree in Medicine and a Master's degree in 1999. In 2001 he became an assistant at the Department of Pediatrics of MU-Varna and was appointed as a doctor at the University Hospital "St. He was appointed as a doctor at the Pediatric Hospital "Marina" - First Children's Clinic, Varna, where he continues to work until now. The academic development of Dr. Veselin Boyadzhiev at the Department of Pediatric Diseases and Medical Genetics of Medical University - Varna includes his long-term work as an assistant, chief assistant 2011-2015 and administrative assistant since 2014. In 2005 he obtained the specialty "Pediatrics" and in 2009 - the specialty "Pediatric Endocrinology and Metabolic Diseases".

Dr. Veselin Milkov Boyadzhiev has numerous specializations, participation in conferences and trainings in Bulgaria and abroad in the field of pediatric endocrinology and especially in the field of bone diseases. He has also participated in 3 international clinical trials - in 2 of them related to the treatment of type 1 diabetes mellitus he is a sub-investigator and in 1 he is a principal investigator (treatment with Denosumab in children with osteogenesis imperfecta).

He is fluent in written and spoken English. He is a member of the Bulgarian Paediatric Association (BPA), the Bulgarian National Association of Paediatric Endocrinology (BNSDE), the Varna Society of Paediatric Endocrinology (Chairman of the Board).

## **Relevance and importance of the thesis**

In recent years, much new knowledge has accumulated about the biology of growing childhood bone, genetic and molecular mechanisms involved in the regulation of skeletogenesis have been revealed, and data from large epidemiological studies have shown that fractures in childhood are a particularly frequent problem.

The dissertation submitted for statement is devoted to bone health and fracture risk in peripubertal children and adolescents, a topic on which there are few publications abroad, and in Bulgaria there are no data on the epidemiology of fractures in childhood and adolescence. Another topical aspect of the thesis is the search for an association between metabolic disorders and fracture incidence in obese patients. Knowledge about the influence of adiposity on fracture risk is limited and the results of studies conducted in this regard are controversial.

The doctorand has thoroughly developed the topic of epidemiology of fractures in the pediatric population in the city of Varna. He selected the necessary clinical material for the analysis and

evaluation of metabolic abnormalities and their influence on bone parameters, he has organized and carried out the necessary studies in overweight and obese girls.

### **Structure of the dissertation**

The dissertation submitted for my statement is structured in accordance with the Academic Staff Development Act in the Republic of Bulgaria (ASDA). The dissertation is written in 202 standard pages and is illustrated with 50 tables, 80 figures, and 1 appendix. The bibliographic reference contains 463 titles. The dissertation introduction is 1 page, literature review is 50 pages, hypothesis, aims and objectives - 2 pages, research methodology -11 pages, results - 65 pages, discussion - 22 pages, conclusions - 3 pages, contributions - 1 page, publications related to the dissertation - 1 page, conclusion - 1 page.

**The literature review** is extensive and reveals an in-depth knowledge of the topic and a good awareness of the research done to date on bone health and the epidemiology of fractures in childhood. It includes current knowledge of the biology of growing bone and bone fractures in children and adolescents, the concept of "Peak Bone Mass", methods of assessing bone parameters, osteoporosis in childhood and the impact of obesity, as well as other factors in increasing fracture risk.

Of particular note is the increased fracture incidence among overweight and obese children. Available data suggest that adipose tissue (AT) is an active participant in the regulation of bone homeostasis, and obesity is a potential risk factor for bone strength disorders. Obesity is a mechanical stimulus for increased bone mass, and visceral adipose tissue, through its production of cytokines and hormone-like substances, predisposes to the development of insulin resistance, dyslipidemia and metabolic abnormalities, which in turn have a negative effect on bone.

**The aims of the thesis** are clearly stated:

- To establish the epidemiological characteristics of fractures in the paediatric population of the city of Varna
- To investigate bone densitometric indices among overweight and obese girls by determining the influence of body weight, body composition distribution, amount of BMD (visceral adipose tissue) and presence of metabolic abnormalities on bone maturation processes and achievement of optimal bone strength in late childhood.

In order to fulfill the objectives, a total of 8 tasks were formulated- 4 for the epidemiological part of the thesis and 4 for the clinical part.



## **Study design and methods**

In order to meet the research aims and objectives thus defined, the study was conducted in two distinct phases.

In the first stage, an epidemiological study was conducted for the period 2021-2022 in 14 secondary schools in the city of Varna. 415 surveys were completed remotely in the electronic format (Google form), and 2098 on paper. The questions in the questionnaire were mainly related to the number and location of fractures sustained so far, family burden, presence of other concomitant skeletal or chronic diseases and/or complaints, possible medication intake.

In the second stage, the clinical part of the study was conducted on the territory of the First Children's Clinic, the Clinic of Imaging Diagnostics and the Clinical and Immunological Laboratory of the University Hospital "St. Marina"-Varna in the period January 2023 - January 2024. It involved 41 girls aged between 14 and 17 years who were hospitalized in connection with overweight, deviations in carbohydrate metabolism, menstrual disorders or the presence of bone and joint complaints. Patients were categorized according to the degree of obesity, for which the American Association of Pediatrics Expanded Classification for Childhood Obesity was used.

Modern clinical, laboratory, imaging, densitometric and statistical methods were used. Statistical package Graph Prism version 10.2.2. for Windows 64-bit was used, and differences with  $p < 0.05$  were considered statistically significant.

The chosen research methods allowed achieving statistically reliable results in response to the aim and objectives set in the thesis, as well as subsequent formulation of scientific conclusions.

## **Results and discussion**

The results in this thesis are presented in 65 pages and are very well illustrated with 80 figures and 50 tables, the discussion is 22 pages.

In the epidemiological part of the dissertation, a total of 2513 students participated (completed the questionnaire correctly), out of which 1291 girls - 54% and 1106 boys - 46%, 116 (4.6%) did not indicate gender. A total of 612 students or 24% of all respondents reported having sustained fractures to date, an overall incidence of 13.1/1000.

The number of boys with fractures is 30% of all boys, and the number of girls with fractures is less - 20%. There were two peaks in fracture incidence, one earlier and less pronounced in the prepubertal period and a true peak with a 3- to 5-fold increase in fracture incidence occurring in

the years of active pubertal growth. The most common localization of fractures in both sexes is in the upper extremity.

In the clinical part of the thesis 41 girls were included, distributed according to the degree of obesity: 8 girls with overweight (weight between P85 - P95), 17 girls with mild obesity (weight P95 - 120% of P95), 9 girls with severe obesity (weight 120% of P95 - 140% of P95) and 7 girls with extreme obesity (weight > 140% of P95). For the purpose of analysis, the patients were grouped into 2 groups: the BMI-1 (overweight and mildly obese) group with a total of 25 participants and the BMI-2 (severely and extremely obese) group with a total of 16 girls.

An interesting result was found in the analysis of the relationship between FM/LM (fat mass/muscle mass) and BMD (bone mineral content), that while in the general group and the BMI-1 group of girls, the increase in fat mass had a positive effect and led to some increase in BMD, conversely, in the more obese girls of the BMI-2 group, the same correlation now takes on a negative character.

Moderate hypovitaminosis D was found with mean 25(OH) vit D levels in the suboptimal range - 17.77 ng/ml. There was a marked decline in levels in parallel with increasing degrees of obesity - borderline values of 15.86 ng/mL in the BMI-2 group.

**The discussion** is 22 pages and is a logical extension of the results presented. In it, the PhD student compares her own results with data from the literature, skillfully analyzing, comparing and interpreting the scientific information.

In his discussions, Dr. Veselin Milkov Boyadzhiev demonstrates creative maturity, excellent use of methodology and the ability to interpret scientific results thoroughly and objectively.

Dr. Veselin Boyadzhiev formulated a total of **16 conclusions** for the two parts, which correspond to the set tasks and are a consequence of the formulated aim of the present work.

The contributions are 8, arising from the results obtained and conclusions drawn. The present dissertation is the first Bulgarian study on the epidemiology of fractures in childhood. The results of the epidemiological analysis confirm the accepted practice in the world that children sustaining more than 2 fractures are indicated for further investigations in order to clarify the presence of underlying bone pathology.

For the first time in our country, a detailed analysis of body parameters and their relationship to metabolic abnormalities was performed, demonstrating the leading influence of fat and muscle mass on bone growth during adolescence. For the first time in this country, DXA densitometric



indices of BMD quantity were investigated and analyzed, and correlations of BMD (visceral adipose tissue) with bone health among adolescent children were determined. The results of the present study, indicate a worsening of bone deficiency with advancing degree of obesity, necessitating the introduction of routine screening osteometric examinations into clinical practice, especially in extreme obesity. Bioelectrical impedance analysis to determine body composition is proving to be a useful highly informative method for clinical practice in the diagnosis and follow-up of overweight and obese children and adolescents.

### **Assessment of publications and personal contribution of Dr. Boyadzhiev**

The results of the dissertation work are reflected in 3 articles, and in all three Dr. Boyadzhiev is the first author. The doctoral candidate has participated in 2 scientific international forums related to the dissertation. The presented publications and participations meet the necessary requirements of MU-Varna.

The layout of the dissertation is clear, the terms are used correctly, the text is structured logically correct, the figures and tables are precisely explained.

The dissertation and the contributions are without doubt the work of Dr. Boyadzhiev. The work reflected in the dissertation was carried out personally by Dr. Veselin Boyadzhiev.

### **Conclusion**

The dissertation contains scientific and applied results that represent an original contribution to science and meet the requirements of the Academic Staff Development Act in the Republic of Bulgaria (ASDA), the Regulations for the Implementation of the ASDA and the internal criteria of MU - Varna.

The dissertation work shows that Dr. Veselin Milkov Boyadzhiev possesses in-depth theoretical knowledge, high professionalism and demonstrates qualities and skills for independent scientific research.

Due to the above, I give my positive evaluation for the conducted research, presented by the above reviewed dissertation, abstract, achieved results and contributions, and I propose to the honorable scientific jury to award the educational and scientific degree "Doctor" to Dr. Veselin Milkov Boyadzhiev in the scientific specialty "Pediatrics".

29.10.2024

Sofia

Assoc.Prof. Margarita Archinkova, PhD

Заличено на основание чл. 5,  
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