

## REVIEW

**by Professor Dr. Mihail Angelov Boyanov, Doctor of Medical Sciences,  
Department of Internal Medicine, Faculty of Medicine, Medical University - Sofia**

*Member of the scientific jury according to Order № P-109-585 / 17.12.2021 of the Rector of the Medical University "Prof. Dr. Paraskev Stoyanov" - Varna*

of the PhD dissertation for the award of the educational and scientific degree 'Doctor' in the professional field of Medicine and Sports; PhD program Endocrinology (03.01.16)

Author: **Dr. Radina Stoyanova Dimitrova**; Form of doctoral studies: full-time

Department: Second Department of Internal Medicine; Board of Endocrinology, Faculty of Medicine, Medical University - Varna.

Title: *COMPARATIVE CHARACTERISTICS OF METABOLIC MARKERS IN THE ASSESSMENT OF POSTMENOPAUSEAL BONE HEALTH*

Scientific adviser: **Professor Dr. Kiril Hristov Hristozov**, doctor of medicine, Head of Clinic of Endocrinology and Metabolic Diseases, Faculty of Medicine, Medical University - Varna.

### **1. General presentation of the procedure and the PhD student**

Dr. Radina Stoyanova Dimitrova presented a set of materials on electronic media, which is in accordance with Article 69 (1) of SECTION III. EXECUTION OF DOCTORAL STUDENTS from the Regulations for the development of the academic staff at MU-Varna. The set includes all the necessary documents: administrative ones as well as the essence of the dissertation - abstract, dissertation, publications.

The PhD student has submitted 5 (five) publications.

I have no remarks or comments on the documents.

### **2. Brief biographical data about the PhD student**

Dr. Radina Stoyanova Dimitrova graduated from the High School of Natural Sciences and Mathematics in Shumen and afterwards in 2010 - the 6-year training course in medicine at MU-Varna with a master's degree and excellent scores. From Oct. 2010 she started working as a physician at the Eurohospital in Varna, where she worked until Dec. 2013. Since March 2011 she has been working at the University Hospital "St. Marina" - 2 years at the Emergency department, and since 2013 - in the Clinic of Endocrinology and Metabolic

Diseases. In the period 2014-2018 she specialized in the field of endocrinology and metabolic diseases and received her specialty diploma in 2018. Since July 2018 she has been a full-time PhD student in endocrinology. In 2019 she obtained a qualification for highly-specialized examinations: "Ultrasound of the cervical region" and "Fine-needle aspiration biopsy under ultrasound control ...". Her main interests are in the field of the thyroid gland and diabetology. She has publications in Bulgarian journals and 1 participation in a textbook of internal medicine. Dr. Dimitrova is a member of the Bulgarian Society of Endocrinology and the Bulgarian Union of Physicians. Fluent in German and English.

### **3. Relevance of the topic and respective aims and objectives**

The topic of the dissertation is the relationship between calcium-phosphorus metabolism, bone metabolic and mineral status and a number of components of the metabolic syndrome. The relevance of this topic is indisputable for 2 reasons. First, the frequency of diagnosed cases of metabolic syndrome has increased significantly in recent decades, as shown by data from the National Epidemiological Study of the Bulgarian Society of Endocrinology under the leadership of Prof. A-M Borissova. Second, the same increasing trend is observed with respect to the bones. The influence of anthropometric parameters on bone density and biochemistry (such as serum calcium and phosphates) is quite well studied. With advanced knowledge of bone biology, other important bone molecules were discovered. They complemented the classic concept of the osteoblast / osteoclast antagonism. It is the changes in these recently described molecules that are not so clearly defined in the context of the metabolic syndrome. The evidence on the components of the metabolic syndrome, in turn, has experienced a great rise in the last 2 decades. The aforementioned study under the auspice of the Bulgarian Society of Endocrinology also found a high prevalence of hypertension and dyslipidemia in the Bulgarian population. Of particular interest is the question which patients are at highest risk for combined pathology (metabolic and bone pathology). All these incompletely resolved issues make the current PhD study relevant, with potential scientific and practical contributions to clinical practice.

### **4. Knowledge of the problem**

The literature review covers 40 pages of the dissertation (approx. 30%). Introductory data on osteoporosis and metabolic syndrome are discussed in detail. Special attention is paid to the relationships between them - through adipose tissue, insulin resistance, lipids and hypertension. Data on the influence of metabolic dysfunction on bone biology are

presented. The text is clear, concrete and up-to-date. By presenting the problem in depth, the PhD student has shown excellent knowledge of previous scientific evidence, on which she builds her hypotheses and scientific research. The literary review ends with a kind of creative summary, which is a major advantage of the text.

The literature review cited 411 sources, at least half of which are from the last decade. Important and relevant sources have been included, and a balance has been achieved between publications confirming and rejecting the hypothesis under study. As a certain weakness I consider the fact that only 6 Bulgarian articles were cited. The impact of anthropometric parameters, body weight, body composition, adipose / non-adipose tissue, etc. on the BMD have been extensively studied by Bulgarian authors, and publications on the subject are available also in international journals. Nevertheless, the PhD student showed good knowledge of the topic and did creatively assess the scientific background of the problem under study.

## **5. Research methodology**

Based on the literature review and the summary, Dr. Radina Dimitrova formulated as aim of her research "To establish a possible association between bone health in postmenopausal women and their metabolic profile by comparing certain metabolic parameters and inflammatory markers and to assess the relationship between metabolic syndrome and bone integrity'. For this purpose, she formulated logically 6 tasks. 5 hypotheses have been formulated, however, the 1st and 2nd of which are repetitions of well-known facts and might be dropped.

The research methodology is a sectional, observational, study in a Bulgarian population of postmenopausal women. This methodology allows achieving the goals and objectives and obtaining an adequate answer to the formulated hypotheses.

## **6. Characteristics and evaluation of the dissertation**

The Materials and Methods are presented in 4 pages. The inclusion and exclusion criteria were well selected. All requirements from the point of view of the ethical norms for participation of humans in research were also met. The clinical part was performed in the Clinic of Endocrinology and Metabolic Diseases, and the laboratory panels - in the Central Clinical Laboratory at the University Hospital "St. Marina - Varna. This has ensured the necessary quality control and the conformity of the used laboratory kits.

It would be appropriate to indicate which software version and reference database were used in the X-ray osteodensitometry. It is also important to note exactly which FRAX formula was applied (specific to Bulgaria or another country).

The study included 84 postmenopausal women over the age of 45, in which all the planned parameters were examined.

The Results and the Discussion are presented on a total of 80 pages. I consider their merging in one section as a certain weakness, but it also improves the clarity of the discussed results and their comparison with the already published data.

Briefly, the data from the dissertation show an unexpectedly low frequency of normal bone mineral density among the studied women. Serum phosphates and estimated glomerular filtration are generally lower in women with osteoporosis, while TNF- $\alpha$  is elevated.

The analysis of the relationship between bone markers and BMD (very weak or missing) are not surprising, as the markers reflect both bone metabolism and BMD - long-term processes. It is no coincidence that only osteocalcin levels to some extent helps to distinguish people with osteoporosis.

The relationship of serum calcium and phosphate with BMD is also not direct and it is not surprising that real correlations are almost missing. Serum phosphates correlated with BMD only.

The relationships of BMD with anthropometric indicators are also weak or very weak (if at all), which has already been proven in numerous publications from the last 2-3 decades.

Of interest are the analyses of the relationships between BMD and the lipid profile. The relationship with triglycerides and HDL-C is directly proportional, while with LDL-C it is inverse. No association with C-reactive protein has been established, but there is one with TNF- $\alpha$ .

The analyses on arterial hypertension are intriguing, however the number of participants in the subgroups (e.g. degrees of hypertension) is too low to allow significant conclusions.

The PhD student found that BMD increased in parallel with the increasing number of components of the metabolic syndrome, however no data on fracture risk were presented.

The algorithm for complex assessment of bone and metabolic health proposed at the end is useful from a practical point of view. It reflects the author's view of the need for a holistic approach in medicine and represents a significant contribution of this work.

The Conclusions correspond to the pre-defined objectives and reflect the essence of the work. Conclusions 1 to 4 reaffirm alphabetical truths in osteology.

## **7. Critical comments and recommendations**

They are noted in the text above in the relevant sections. Additionally, the following can be noted:

- Weakness of the study is that the participants do not have osteoporotic fractures, which would allow, apart from the purely theoretical calculation of fracture risk, a comparison with real events;
- It is not necessary to draw conclusions for individual vertebrae (eg page 91); they apply only to the sum L1-L4;
- When discussing the differences between subgroups of women with different parameters, the respective number of participants should always be indicated.

## **8. Contributions and significance for science and practice**

The dissertation contains several scientific and applied scientific achievements. New analyses proved significant aspects of existing scientific evidence; confirmatory facts were also obtained.

The original contributions arise from the fact that this is one of the first studies in our country exploring the relationship between the metabolic profile and the parameters of calcium-phosphorus metabolism, BMD and fracture risk. The other contributions are rather confirmatory and only a few of them are original for the country.

Contributions should be listed after the conclusion and the bibliography - not before them.

## **9. Evaluation of the related publications**

The PhD student presented 5 full-text publications related to the scientific work - 4 reviews and 1 original article, reflecting an aspect of the dissertation. In all publications Dr. Radina Dimitrova is the leading author. Thus, her PhD thesis meets the minimum national requirements for the degree "doctor in medicine" and, accordingly, those of Section IV, Chapter II (acquisition of scientific degrees) of the Regulations for the development of the academic staff at the Medical University "Prof. Dr. P. Stoyanov" - Varna.

The PhD student also presented 1 participation in a research grant from MU-Varna, which supported the dissertation.

#### **10. Personal contribution of the PhD student**

The presented work was created with the personal participation of the PhD student, and the results and contributions are entirely a result of her personal efforts.

#### **11. Abstract (Synopsis)**

The abstract (synopsis) covers 87 pages and in terms of content and quality meets the requirements of the regulations. It synthesizes in sufficient detail, the main results of the dissertation. So it corresponds well to the full-text.

#### **CONCLUSION**

The dissertation contains scientific and practice-oriented results, which represent a major contribution and meet the requirements of the Academic Staff Development Act in the Republic of Bulgaria (ZRASRB), the Regulations for implementation of ZRASRB and the relevant Regulations of MU - Varna. The presented materials and dissertation fully comply with the specific requirements of MU - Varna.

The dissertation shows that the PhD student Dr. Radina Stoyanova Dimitrova has in-depth theoretical knowledge and professional skills in the medical specialty Endocrinology by demonstrating qualities and skills for formulating hypotheses, goals and objectives and for independent research.

Due to the above, I confidently give my positive assessment of the present study, and I propose to the esteemed scientific jury to award the educational and scientific degree "Doctor" to Dr. Radina Stoyanova Dimitrova in the doctoral program in Endocrinology (03.01.16).

February 8, 2022.

Reviewer:



Prof. Dr. Mihail Boyanov, DMSc