REVIEW

of the PhD dissertation of **Dr. Miroslav Penev Markov**

on the topic:

"Biochemical and Ultrasound Markers of Early Cardiovascular Damage in Patients with Spondyloarthritis"

submitted for public defense before the Scientific Jury
for the acquisition of the educational and scientific degree **"Doctor"**
in the specialty **"Internal Medicine"**

Reviewer:
Assoc. Prof. Tanya Shivacheva, MD, PhD
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Biographical data of the doctoral candidate

Dr. Miroslav Penev Markov was born on April 28, 1995, in Yambol, Bulgaria. He graduated from the "Atanas Radev" Mathematics High School in Yambol in 2014, after which he continued his education at the Medical University "Prof. Dr. Paraskev Stoyanov" – Varna, where in 2020 he obtained the Master's degree in Medicine.

Since 2020, Dr. Markov has been working as a resident in Rheumatology at the Clinic of Internal Medicine, University Hospital "St. Marina" – Varna. In 2025, he successfully completed his specialization and obtained qualification as a **Specialist in Rheumatology**.

Alongside his clinical activity, he works as an **Assistant** at the Department of Propaedeutics of Internal Medicine at the Faculty of Medicine, Medical University of Varna, actively participating in teaching medical students in both Bulgarian and English. Since December 2021, Dr. Markov has been a full-time PhD student in the same department. He demonstrates excellent research skills, analytical thinking, and consistency in his scientific work.

General characteristics and relevance of the topic

The topic of the dissertation focuses on early cardiovascular alterations in patients with spondyloarthritis—a group of diseases increasingly recognized not only as rheumatologic but also as systemic inflammatory conditions with multi-organ involvement. It is well established that chronic inflammation in ankylosing spondylitis and psoriatic arthritis markedly increases cardiovascular morbidity and mortality. Therefore, identifying reliable, sensitive, and non-invasive markers of subclinical atherosclerosis is of significant scientific and clinical importance.

The topic's **relevance is unquestionable**, aligning with the growing interdisciplinary approach between rheumatology and cardiology, as well as with EULAR's priority to ensure early cardiovascular risk detection in chronic inflammatory arthropathies. The author adopts a comprehensive and innovative approach by combining **ultrasound markers of arterial stiffness** (CIMT, PWV, β-stiffness) with **serum levels of adhesion molecules** (VCAM-1 and ICAM-1), creating an integrated model for endothelial dysfunction assessment. The topic is fully consistent with current directions in rheumatology and meets the high academic standards required for a PhD dissertation.

Aims, objectives, and methodological justification

The main aim of the study—**to assess ultrasound and biochemical indicators as early markers of atherosclerosis in patients with ankylosing spondylitis and psoriatic arthritis**—is clearly and precisely defined. The set objectives are logically structured, coherent, and fully aligned with the main goal.

The study design is rigorous and consistent with good clinical practice. A total of **154 participants** were included, divided into three groups: patients with ankylosing spondylitis, patients with psoriatic arthritis, and healthy controls. Inclusion and exclusion criteria are clearly defined, ensuring representativeness and validity of results.

The applied methodology is concise and appropriate to the research goals:

- **Instrumental assessment** by echo-tracking of the common carotid artery, with measurement of local arterial elasticity indices;
- **Biochemical analysis** of adhesion molecules sICAM-1 and sVCAM-1 by ELISA method;
- **Disease activity assessment** using validated indices (ASDAS-CRP, BASDAI, DAS28);
- **Calculation of lipid fractions, atherogenic, and cardiovascular indices** (SCORE2, Framingham).

Statistical analysis was performed using **SPSS 27**, including correlation and multiple regression analyses, allowing for reliable interpretation of results and exclusion of random associations. The methodological precision and appropriate use of statistical tools are among the strong aspects of the work.

Main results and scientific contributions

The dissertation presents a comprehensive and well-structured scientific work (141 pages, 30 tables, 33 figures, and 363 references). The study is based on high-quality empirical data collected under real clinical conditions.

The main results and contributions can be summarized as follows:

1. **Objectification of early vascular changes in spondyloarthritis.**
   The author demonstrates significantly increased CIMT, β-stiffness, and PWV values in patients with ankylosing spondylitis and psoriatic arthritis compared to controls, confirming the presence of subclinical atherosclerosis even in early disease stages.
2. **Evidence of endothelial dysfunction through serum biomarkers.**
   Elevated sVCAM-1 levels in patients with psoriatic arthritis compared to those with ankylosing spondylitis and healthy controls highlight the inflammatory contribution of this molecule to the pathogenesis of atherosclerotic changes.
3. **Correlation between inflammation and vascular stiffness.**
   A statistically significant association is established between CRP and ultrasound markers of arterial stiffness, confirming that systemic inflammation is a key mechanism in early cardiovascular injury.

4. **Identification of demographic and clinical risk determinants.**
   Age, body mass index, and arterial hypertension are confirmed as independent predictors of arterial stiffness. However, even after controlling for these factors, inflammatory markers retain a significant effect.
5. **Comprehensive approach to early cardiovascular risk assessment.**
   Based on the findings, the author proposes an integrated diagnostic model combining ultrasound and biochemical parameters, potentially applicable in clinical practice for early risk stratification in patients with spondyloarthritis.

The dissertation includes both **theoretical contributions** (evidence of the link between inflammation and atherosclerosis in SpA) and **practical contributions**, related to the implementation of ultrasound techniques for arterial elasticity assessment in rheumatologic practice. Confirmatory contributions also strengthen the Bulgarian clinical evidence base in this field, harmonizing with international data.

Discussion, interpretation, and literature comparison

The discussion section is extensive and analytical. The author demonstrates deep familiarity with international literature and the ability to interpret his findings in the context of current scientific evidence.

The comparison with international studies (Eder et al., Mathieu et al., Gonzalez-Gay et al.) is precise and highlights both similarities and differences in observed trends. The discussion on adhesion molecules as potential therapeutic targets is particularly valuable, offering perspectives for future research.

The results are interpreted with a balanced view between clinical reality and statistical reliability. The presentation of figures and tables is clear, and conclusions logically follow from the data. The abstract is well structured, linguistically polished, and meets academic standards.

Critical remarks

The dissertation is remarkably complete and scientifically sound. However, several recommendations could enhance the applicability of the findings:

- A **longitudinal follow-up** of patients would be desirable to assess the dynamics of vascular changes under therapeutic influence;
- A more detailed **discussion of the effects of different biologic agents** (anti-TNF, anti-IL-17, JAK inhibitors) on arterial stiffness parameters would add value;
- Future studies might benefit from **expanding the control group** to increase statistical power.

These comments are **recommendatory rather than critical** and do not diminish the scientific value of the dissertation, which represents a comprehensive, original, and methodologically robust research work.

Conclusion

The PhD dissertation of **Dr. Miroslav Penev Markov**, titled *"Biochemical and Ultrasound Markers of Early Cardiovascular Damage in Patients with Spondyloarthritis,"* constitutes an

independent, original, and thoroughly completed scientific study distinguished by its high relevance, methodological rigor, and contributory significance.

The author demonstrates mature scientific reasoning, analytical skills, and competence in applying advanced methods for evaluating vascular risk in inflammatory joint diseases. The results possess real practical value and are applicable in both rheumatology and internal medicine practice. The presentation is clear, systematic, and fully compliant with the requirements for awarding the degree of Doctor.

Based on the presented results, scientific contributions, and full compliance with the **Law for the Development of Academic Staff in the Republic of Bulgaria** and the **Regulations of the Medical University "Prof. Dr. Paraskev Stoyanov" – Varna**,

I recommend that **Dr. Miroslav Penev Markov** be awarded the **educational and scientific degree "Doctor" in Internal Medicine**.

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