

REVIEW

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External member of the Scientific Jury

Pursuant to Order No. RK-110-69 of 26.02.2024. of the Rector of the University of  
Varna

ON THE DISSERTATION OF  
IRINA IVANOVA MOMCHEVA

ON THE SUBJECT:

"STUDY OF THE PARTICIPATION OF HUMORAL FACTORS OF  
INNATIONAL IMMUNITY IN THE PATHOGENESIS OF ACTIVATED  
OSTEOARTHRITIS"

WITH SCIENTIFIC SUPERVISOR  
ASSOCIATE PROFESSOR ZHENYA RUSEVA PETROVA, DM, PhD

for awarding the educational and scientific degree "PhD"

field of higher education: 7. "Health and sports"

professional direction: 7.1. "Medicine"

doctoral program "General medicine"

The dissertation work of Irina Ivanova Momcheva is 120 standard pages long and is illustrated with 24 tables, 18 figures and 6 histograms. The list of cited literature includes 237 titles, of which 4 are in Cyrillic and 233 are in Latin.

Structured as follows: Abbreviations used; Literature review; Purpose, tasks; Materials and methods; Results of own research; Discussion; Conclusions; Contributions; Applications; Bibliography.

### 1. Evaluation of the topicality of the topic

The relevance of the chosen topic of the dissertation work is indisputable given the fact that worldwide scientific developments in the field of osteoarthritic disease, including therapeutic options, lag behind those for inflammatory joint diseases. In the introduction, Irina Ivanova Momcheva convincingly substantiates the relevance of the problem and the choice of the topic of the dissertation work.

Until recently, osteoarthritis was classified as a non-inflammatory disease, due to the absence of systemic inflammation and neutrophils in the synovial fluid, today it is considered that low-grade local inflammation is the main driver of the degenerative process. Cartilage degradation products released into synovial fluid are phagocytosed by synovial cells, maintaining synovial inflammation. In turn, activated synovial cells in the inflamed synovium produce catabolic and proinflammatory mediators that lead to excessive production of the proteolytic enzymes responsible for cartilage degradation, creating a positive feedback loop. The inflammatory response is enhanced by activated synovial T cells, B cells and infiltrating macrophages. Cartilage fragments may play the role of neoantigens inducing aseptic inflammation.

The conclusions reached by the PhD student regarding the involvement of innate immunity in the pathogenesis of osteoarthritis and the capabilities of the complement system for homeostatic regulation support the thesis that further research on complement in osteoarthritis is appropriate. The idea that complement proteins in synovial fluid could be used as biomarkers for disease activation on the one hand and illustrating the progression of structural damage on the other is applicable in daily clinical practice.

### 2. Evaluation of the objective, tasks and methodology

The purpose, tasks and methodology of the study are precisely and clearly presented. The objects and units of the observation were correctly defined - the observation covered 156 patients with activated arthrosis of the knee joint. Inclusion

and exclusion criteria are comprehensively defined. The methodology of scientific research is adequate to the purpose and tasks. Clinical, laboratory, imaging and statistical methods were used. The description of the methods used is thorough and detailed, which fully substantiates the validity of the results. The wide range of methods used to collect and process the material complement each other, which allows the information obtained to be evaluated in many ways. This shows that the doctoral student knows the methods of scientific research and can apply them correctly in practice.

### 3. Evaluation of results

The material presented in the literature review is rich, competently and critically analyzed by the author, and shows her broad awareness of the issues discussed.

The own research includes a competent and in-depth comparative analysis in several areas:

- After analysis of the results obtained in the studied group of 156 patients with activated arthrosis of the knee joint, it was found that the values of the three investigated proteins in the synovial fluid (CRP, C3 and C4) were higher than their values in the blood plasma in those cited in the introductory part norms of 10% for complement levels and up to 20% levels for CRP in a healthy joint. The relatively lower percentage of C4 values compared to C3 is explained by the fact that when arthrosis is activated, innate immunity plays a leading role in the inflammation, in particular the activation of complement through the alternative pathway, where C3 is involved.

- The observation regarding the strength of correlation between the above results and the radiological stage confirms a stronger correlation of the results obtained in the earlier stages of the disease, when the activity of the repair processes is more pronounced.

- There are no significant differences between the two sexes in all the investigated indicators.

- Based on the above results, the doctoral student developed a model of low-grade local inflammation in OA.

- The need to identify and quantify inflammation in the OA-joint before the onset of irreversible structural joint damage holds future therapeutic promise.

The general reading of the presented work leaves the impression of a consistent, extensive and competent view of Irina Ivanova Momcheva on an extremely serious and current problem - the modern understanding of the pathogenesis of the arthrosis disease and the possibilities for pathogenetic treatment based on this. The detailed analysis of the material included in the dissertation makes it possible to discover several of its indisputable advantages and merits. Treatment of key aspects of synovial inflammation holds promise for analgesia as well as structural modification. The question arises whether controlled balanced activation of complement could not be a future therapeutic strategy in the treatment of OA and prevent progression and?

#### 4. Evaluation of contributions

The work developed contains theoretical summaries and solutions to significant scientific problems that correspond to modern achievements and represent an enrichment of existing scientific knowledge.

The contribution nature of the dissertation work is scientific-theoretical, scientific-applied and confirmatory in nature and consists of:

- For the first time in Bulgaria, the leading role of innate immunity in the pathogenesis of activation of osteoarthritic disease has been proven quantitatively and statistically reliably;
- A pathogenetic model of low-grade inflammation in OA is proposed;
- The correlation between increased levels of CRP, C3 and C4 in synovial fluid and activation of the arthrosis disease is established with statistical reliability;
- The obtained results prove and support the concept of the pathways initiating and maintaining synovial inflammation in this cohort of patients;
- This type of analysis can be applied in clinical practice for the purpose of pathogenetic differentiation of the type of inflammatory process in hydrops of the knee joint;
- Controlled complement activation may be a therapeutic target in patients with OA and an inflammatory phenotype;
- The results argue for the need for the application of medicinal preparations with an effect on low-grade inflammation as a disease-modifying model of treatment behavior;

- The results of the study confirm the need for therapeutic control of inflammation in the arthritic joint at an early radiological stage of the disease.
- In this statistical sample from the Bulgarian population, the data from previous publications regarding the importance of elevated levels of CRP and complement fractions in the arthritic joint are confirmed - i.e. the role of humoral factors of innate immunity in the pathogenesis of OA,
  - The results of the study confirm the involvement of low-grade inflammation in disease progression.

#### 5. Abstract and publications on work

The abstract for the dissertation correctly reflects the structure of the work and contains the most important results and conclusions of the study.

In relation to the topic of the dissertation, there are 9 scientific publications and 3 scientific communications that reflect parts of the dissertation work. The presented publications reflect and are fully related to the issues of the dissertation work.

In conclusion, I believe that Irina Ivanova Momcheva's dissertation work on the topic: "Research on the involvement of the humoral factors of innate immunity in the pathogenesis of activated osteoarthritis" in terms of relevance, precision of the methodology, volume of the study, conclusions and recommendations is with specific scientific and scientific applied contributions, meets the requirements of the Law on the Development of Academic Staff and the Regulations of MU-Varna for its implementation.

In connection with everything stated above, I give my positive assessment and recommend the members of the Scientific Jury to award the doctoral student Irina Ivanova Momcheva the educational and scientific degree "PhD" in the doctoral program "General Medicine" in the professional direction: 7.1. "Medicine" and field of higher education: 7. "Health and sports".

27. 03.2024

REVIEWER:

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Prof. Vladimir Gonchev, MD, PhD