

SOFIA UNIVERSITY
"ST. KLIMENT OHRIDSKI"
FACULTY OF MEDICINE

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1407, Sofia, BULGARIA
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Dear Mr. President,

Attached I am sending you an Opinion on the defense of a dissertation on "EVALUATION AND DYNAMIC MONITORING OF HYPERPHOSPHATEMIA - A PREDICTOR OF BONE-MINERAL DISORDERS IN DIALYSIS PATIENTS"

of Dr. SNEZHANA ATANASOVA ATANASOVA, Full-time assistant and PhD student of independent training at the Medical Faculty of MU - Varna, Nephrologist at the University Hospital "St. Marina" EAD

for awarding Educational and Scientific Degree "DOCTOR", Field of higher education - 7.0 Health and sports, Professional field - 7.1 Medicine, Scientific specialty - 03.01.15 Nephrology

with Supervisor: Prof. Dr. Svetla Vasileva Staykova, MD,

Prepared the opinion: External member of the Scientific Jury, appointed by the same Order of the Rector of MU, Varna, № P-109-88 of 23.02.2022.

Assoc. Prof. Dr. Velislava Dimitrova Dimitrova, Ph.D.

Scientific specialties: Internal Medicine, Nephrology, Clinical Pharmacology and Therapy
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The opinion was written in accordance with the requirements of the Higher Education Act, the Law on the Development of Academic Staff at the Medical University of Varna.

OPINION:

The opinion is part of the procedure for defense of the dissertation on "Assessment and dynamic monitoring of hyperphosphatemia - a predictor of bone and mineral disorders in dialysis patients" for the award of Educational and Scientific Degree "Doctor" and is made in accordance with the Rules the conditions and the order for acquiring scientific degrees and holding academic positions in the Medical University - Varna.

PROFESSIONAL DEVELOPMENT:

Dr. Snezhana Atanasova graduated in medicine in 2013 at the Medical University of Varna. He has acquired the specialty of Nephrology since the end of 2019. In 2017 she started her academic career initially as a part-time assistant, and from 2019 as a full-time assistant at the Medical University - Varna, Second Department of Internal Medicine: Nephrology, Dialysis and Toxicology. She is enrolled in full-time doctoral studies at the Medical University of Varna in 2019. Since the beginning of 2020 she has been working as a nephrologist at the Clinic of Nephrology and Dialysis at the University Hospital "St. Marina EAD, Varna. She attended a training course - theory and practice for "Working with hemodialysis machine 4008S V4.5 ONLINE plus". Fluent in English and German. Member of the BMA.

SCIENTIFIC ACTIVITY:

Dr. Atanasova presents a total of three scientific publications, one for 2019, 2020 and 2021. As the first author he has two publications on the topic of the dissertation, in the third publication he is the second author. The first is in the journal Nephrology, Dialysis and Transplantation, and the other two are published in the journal Current Nephrology. Dr. Atanasova has participated in national conferences on nephrology.

DISSERTATION WORK:

The dissertation is very well formed technically according to all requirements, it is written in very good language, it is precise in terms of terminology. The dissertation is written on 164 standard pages. It is richly illustrated with 29 figures, 45 tables and 1 appendix. The bibliographic reference is comprehensive. 206 literature sources were used, of which 8 in Cyrillic and 198 in Latin.

In recent years, there has been a growing worldwide interest of nephrologists, dialyzants and clinicians from various other fields in early diagnosis, timely adequate treatment and improving the prognosis of bone and mineral disorders in dialysis patients.

Calcium-free phosphate binders, new vitamin D analogues, and calcimimetic compounds offer new therapeutic alternatives for the management of CKD. Integrating these drugs into existing treatment regimens may provide safer and more effective methods of controlling secondary hyperparathyroidism and renal bone disease, while limiting the risk of vascular calcification in patients with CKD.

There are three approaches that work collectively to adequately control the 3 key laboratory indicators in CKD/Bone-Mineral Disorders (calcium, phosphorus, and PTH). They include diet, dialysis, and medication (phosphorus binders, vitamin D analogs, and/or calcimimetics). They are referred to as "3D - Diet, Dialysis and Drugs".

The topic of the dissertation is to develop a constellation of diagnostic and therapeutic methods that will contribute to elucidating the etiopathogenetic mechanisms of disorders of bone and mineral metabolism in patients with chronic kidney disease of conservative and

hemodialysis treatment, and to increase efficiency of the individualized approach to these patients.

The aim of the dissertation is to analyze the diagnostic, clinical and therapeutic aspects of disorders of bone and mineral metabolism in chronic kidney disease in the course of conservative and hemodialysis treatment. To achieve it, the dissertation and the team have set 6 specific tasks:

- To study the diagnostic and prognostic value of calcium, phosphorus and parathyroid hormone for the development and violation of bone and mineral metabolism in patients with chronic kidney disease in pre-dialysis and hemodialysis treatment.

- To monitor the dynamic effect of phosphorus-binding drugs - sevelamer hydrochloride and calcium carbonate on markers of bone and mineral metabolism in dialysis patients.

- To look for a correlation between etelcalcetide and markers of bone and mineral metabolism in hemodialysis patients and to monitor its effectiveness and safety in overcoming hyperphosphatemia.

- To compare serum sclerostin levels in predialysis patients and hemodialysis patients and to evaluate the effect of etelcalcetide (Parsabiv) treatment on serum sclerostin levels in hemodialysis patients.

- To analyze and compare the effect of convection hemodialysis and hemodiafiltration on hyperphosphatemia in dialysis patients.

- To analyze the survival and quality of life in dialysis patients with respect to the biochemical markers of CKD.

The tasks are very well structured, clear and precise and correspond to the topic of the dissertation. The material and methods also correspond to the topic of the dissertation, the goal and the tasks.

The dissertation is based on the observations and evaluation of the results of a serious clinical study in 30 pre-dialysis patients and 50 patients enrolled in chronic hemodialysis treatment. The work on these tasks includes the use of various modern methods of diagnosis and in-depth analysis of basic clinical, laboratory, immunological and other indicators in patients with CKD. Of particular interest is the survey conducted with them. Dr. Atanasova makes a very thorough analysis of the results and facts, summarizes the data and draws relevant conclusions.

Dr. Atanasova uses many different statistical methods and analyzes to process the data from her dissertation, compare and evaluate the indicators. The widespread use of a unique questionnaire is related not only to its universal applicability to various diseases, but also to the general understanding of certain aspects of health in general - physical, mental and social.

The presentation of the results of the conducted research follows the set tasks.

The obtained results are subject to in-depth discussion, which deserves high praise. They are described and illustrated very well. Impressive in quantity and quality are all 29 figures and 45 tables.

The discussion made at the end of the paper follows the results. It is comprehensive and up-to-date, very rich literary reference, the result of the dissertation's knowledge and work and her ability to handle scientific facts. It highlights the scientific merits, the indisputable qualities of the dissertation, finalized in the generalized Conclusions and Contributions. Their significance as such with scientific-theoretical and practical-applied character is evident.

Dr. Atanasova points out 6 main conclusions. Of particular interest are her findings on the timing of the reduction in PTH levels with etelcalcetide (Parsabiv). The dissertation student draws interesting conclusions about the marked positive trend in the use of calcium carbonate therapy and the combination of sevelamer and cinacalcet, showing significant significance in terms of hyperphosphatemia and secondary parathyroidism.

Her conclusion that the correction of abnormal values of serum phosphorus, serum calcium and iPTH are crucial for improving the quality of life in patients with CKD-Bone-Mineral Disorders on dialysis is also convincing.

The main conclusions made in the dissertation and the outstanding contributions from it will undoubtedly find their inalienable place in the field of nephrological clinical practice. They mark the new directions in the successful fight against bone and mineral disorders, will bring additional clarity in terms of timely diagnosis, prevention, preservation and prolongation of the life of dialysis patients. They will also help to significantly increase the success of hemodialysis treatment.

The dissertation clearly shows that dr. Atanasova has in-depth theoretical knowledge and professional skills in the scientific specialty of nephrology, demonstrating qualities and skills for independent and team research.

The dissertation, in the way it is presented, is completely dissertable, very relevant, valuable with a significant contribution to the theory and clinical practice. Meets the requirements of the Academic Staff Development Act, the Regulations for the implementation of the Academic Staff Development Act and the Regulations on the terms and conditions for acquiring scientific degrees and holding academic positions at MU - Varna.

I believe that the work on the presented dissertation on "EVALUATION AND DYNAMIC MONITORING OF HYPERPHOSPHATEMIA - A PREDICTOR OF BONE-MINERAL DISORDERS IN DIALYSIS ACTIVITIES" and the data on the overall scientific activity of Dr. Snezhana Atanasova show that she has all the necessary qualities to acquire the Educational and Scientific Degree "Doctor" .

Given the relevance of the topic, the original results obtained with scientific and applied contributions, as well as published scientific articles, I confidently give my POSITIVE assessment and propose to the esteemed Jury to award the Educational and Scientific Degree "Doctor" in professional field 7.1. Medicine, Field of Higher Education - Health and Sports, Scientific specialty - Nephrology of Dr. SNEZHANA ATANASOVA ATANASOVA.

Sofia, March 2022



Assoc. Prof. Dr. Velislava Dimitrova, Ph.D.

