

R E V I E W

by **Prof. Dr. Valentina Christova Madjova, PhD.**

Head of the Department of General Medicine,

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of the dissertation on the topic

"ASSESSMENT AND DYNAMIC MONITORING OF HYPERPHOSPHATEMIA - PREDICTOR OF BONE MINERAL DISORDERS IN DIALYSIS PATIENTS"

of **Dr. Snezhana Atanasova Atanasova**

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and

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for awarding the educational and scientific degree "DOCTOR"

1. General presentation of the procedure and the PhD student

According to the Order of the Rector of the Medical University - Varna № P-109-88/23.02.2022, Protocol of the Faculty Council № 60/14.02.2022 and Protocol №1 of the meeting of the Scientific Jury, I have been elected as its Chairman and reviewer of the scientific work of Dr. Snezhana Atanasova Atanasova.

The set of materials provided to me on paper/electronic media fully complies with the requirements of the Procedure for acquiring an educational and scientific degree "Doctor" according to the Regulations of MU- Varna.

I did not find any violations of the procedure for awarding the scientific degree "Doctor".

2. Brief biographical data about the PhD student

Dr. Snezhana Atanasova Atanasova graduated from the III Natural-Mathematical High School in Varna and after graduating as a Master of Medicine in 2013 at the Medical University - Varna, she started specialization at the University Hospital "St. Marina" - Clinic of Nephrology.

Since 2018 she has been an assistant in Department of Nephrology, Dialysis and Toxicology at MU - Varna, one year later she acquired a specialty in nephrology, and since 2020 she has been appointed a resident at the Clinic of Nephrology and Dialysis.

3. Relevance of the topic and expediency of the set goals and objectives

The dissertation of Dr. Snezhana Atanasova treats a topical and important practical problem in nephrology related to the study and dynamic monitoring of hyperphosphatemia as a predictor of bone mineral disorders (BMD) in dialysis patients. These are severe systemic complications of increasing medico-social importance worldwide, associated with the risk of fractures, cardiovascular disease and death of patients.

I highly appreciate the chosen topic of the dissertation of Dr. Snezhana Atanasova as a relevant and important for the clinical nephrology practice due to the increasing prevalence of CKD among the elderly population in our country and the unfavorable fact that 90% of patients are found to have advanced renal impairment, which requires dialysis treatment and management of subsequent bone mineral disorders as complications of hyperphosphatemia in patients on hemodialysis (HD).

An important circumstance that directs Dr. Snezhana Atanasova to develop her dissertation is the fact that at this time in Bulgaria there is no serious study on the assessment and dynamic monitoring of hyperphosphatemia as a predictor of bone mineral disorders in dialysis patients.

4. Knowledge of the problem

Dr. Snezhana Atanasova knows very well the material she treats in her dissertation. Proper treatment of hyperphosphatemia not only improves the quality of life of dialysis patients, but also reduces the BMD that is common in the group of patients with end-stage renal disease (ESRD).

The PhD student extensively analyzed the systemic disorders of mineral and bone metabolism, namely calcium, phosphorus, parathyroid hormone, vitamin D, mineralization, volume, linear growth or bone strength, and vascular or other soft tissue calcifications. These are associated with risk of fractures, cardiovascular disease and death, so regular monitoring is recommended.

Dr. Snezhana Atanasova has a detailed knowledge of the changes in the body of patients with end stage renal disease on HD treatment and points out a number of other complications such as anemia, electrolyte disturbances (e.g., hyperkalemia, hyperphosphatemia), secondary hyperparathyroidism, changes in vitamin D activation and renal osteodystrophy that also need to be assessed and dynamically monitored.

She discusses important aspects of current management of these complications, namely that by controlling elevated serum phosphorus, calcium levels, restoring vitamin D levels and suppressing PTH production, it is possible to reduce the rate of these injuries.

Dr. Snezhana Atanasova has been actively researching the scientific literature, which identifies multiple classes of drugs, including phosphate binders, vitamin D analogues and calcimimetics to directly or indirectly influence BMD markers in CKD, and in particular the class of calcimimetics - Cinacalcet (Sensipar, Amgen, Inc.) and etelcalcetide (Parsabiv, Amgen, Inc.), which are approved for use in the EU.

5. Research methodology

The larger section of the dissertation is a study in which Dr. Snezhana Atanasova actively participates as a researcher. The complex diagnostic-therapeutic study was conducted between 1.02.2019 and 31.01.2022, in which a total of 116 patients - 75 men (65 %) and 41 women (35 %) with CKD, admitted to the Clinic of Nephrology and Dialysis of the University Hospital "St. Marina"- Varna, were studied.

The age distribution of the patients was as follows: 17 patients (15%) in young age (18 - 44 years), 51 patients (44%) in middle age (45 - 59 years), 39 patients were elderly (60 - 59 years). 74 years) and 9 patients (7%) were elderly (75 - 89 years).

Of these, 86 were on hemodialysis treatment and 30 - pre-dialysis. The mean age was 63.55 ± 9.69 years, and according to the Kolmogorov-Smirnov test there was no statistically significant difference between the mean age of men and women ($p = 0.228$).

In her dissertation Dr. Snezhana Atanasova uses the following methods:

1. Clinical examinations: anamnesis and physical status.
2. Anthropometric methods: blood pressure under standard conditions
3. Laboratory tests: parathyroid hormone (PTH), Ca, P, alkaline phosphatase, vitamin D and sclerostin.
4. Statistical methods:
 - 1) non-parametric: Kolmogorov-Smirnov test; chi-square test (X^2); Fieldman test and Wilcoxon test
 - 2) parametric methods - Independent t-test and Paired Samples t-test
 - 3) analysis of variance - ANOVA test
 - 4) graphical analysis - to visualize the results obtained.

Statistical processing of the obtained data was carried out using the following software products: BM SPSS v.25 and Jamovi v.2.1.1. descriptive indicators for quantitative and qualitative variables were used and presented in tabular and graphical form. The values of specific variables at $p \leq 0.05$ are considered statistically significant.

To assess the individual quality of life of 86 hemodialysis patients, a specialized questionnaire for quality of life in patients with kidney disease with 36 questions (Kidney Disease Quality of Life - Short Form-36, KDQOL-36) was used after modification by S. Staykova (2018) in order to adapt it to the conditions in our country, which uses direct questionnaires.

6. Characteristics and evaluation of the dissertation

The dissertation contains 134 standard pages and is illustrated with 45 tables, 29 figures and 1 appendix. The reference list includes 206 literary sources, of which 8 in Cyrillic and 198 in Latin.

In the literature review, Dr. Snezhana Atanasova discusses the problem of CKD, which is increasing rapidly every year and is one of the main significant health problems affecting society, especially important for nephrological practice are its complications - anemia and secondary hyperparathyroidism. It provides an important analysis of the scientific evidence on the metabolic changes that occur in patients with CKD and their impact on mineral and bone metabolism in HD patients.

The main aim of Dr. Snezhana Atanasova's dissertation is to evaluate the diagnostic, clinical and therapeutic aspects of BMD in chronic kidney disease during conservative and hemodialysis treatment.

To achieve it, 6 main tasks were identified:

1. To investigate the diagnostic and prognostic value of calcium, phosphorus and parathyroid hormone in the development and disturbance of bone-mineral metabolism in patients with chronic kidney disease in the pre-dialysis stage and on hemodialysis treatment.
2. To investigate the dynamic influence of phosphorus-binding drugs sevelamer hydrochloride and calcium carbonate on markers of bone-mineral metabolism in dialysis patients.
3. To look for a correlation between etelcalcetide and markers of bone mineral metabolism in hemodialysis patients and to monitor its effectiveness and safety in overcoming hyperphosphatemia.
4. To compare serum sclerostin levels in pre-dialysis patients and patients undergoing hemodialysis treatment and to evaluate the effect of etelcalcetide (Parsabiv) treatment on serum sclerostin levels in hemodialysis patients.
5. To analyze and compare the effect of convection hemodialysis and hemodiafiltration on hyperphosphatemia in dialysis patients.
6. To analyze the survival and quality of life in dialysis patients in terms of biochemical markers of BMD-CKD.

Dr. Snezhana Atanasova defines the following hypothesis in her thesis: " The constellation of diagnostic and therapeutic methods that we have developed contributes both to elucidating etiopathogenetic mechanisms of bone mineral metabolism disorders in patients with chronic kidney disease on conservative and hemodialysis treatment and to increasing the effectiveness of the individualized approach to these patients".

The PhD student formulates 6 main conclusions, all of them correspond to the aim and the objectives. They have important implications for nephrology practice.

7. Contributions and significance of the development for science and practice

Dr. Snezhana Atanasova has indicated in her dissertation 8 contributions - 5 are of theoretical nature and 3 of practical-applied nature, which I fully support.

In the data of her study, she summarizes that "the treatment of BMD in HD patients is a multifaceted, integrative approach including control of hyperphosphatemia, serial tests of Ca, P and PTH, analysis of the relationships between these markers, their absorption and release from the gut and bone, and fluctuations with disease progression requiring adequate treatment", which is important for nephrology practice.

8. Assessment of the dissertation publications

3 publications related to the dissertation are attached to the documentation, which fully meets the requirements for acquiring an educational and scientific degree "Doctor".

9. Personal participation of the doctoral student

The conducted research, the formulated contributions and obtained results are the merit of Dr. Snezhana Atanasova and are supported by her supervisor Prof. Dr. Svetla Staykova, DSc

10. Abstract

The abstract is completely sufficient in content and quality to present the main results achieved in the dissertation. It meets the requirements of the Regulations of MU - Varna.

11. Critical remarks and recommendations

I have no critical remarks and recommendations to the conducted research and the materials provided to me.

12. Personal impressions

I know Dr. Snezhana Atanasova from her work as a doctor in the Clinic of Nephrology and I have very good impressions of her as a serious and responsible young nephrologist.

The dissertation and abstract proposed for evaluation are made precisely and thoroughly and are characterized by well-formulated conclusions and contributions.

Conclusion

In general, I evaluate the dissertation of Dr. Snezhana Atanasova Atanasova as relevant and valuable for nephrology practice.

The dissertation contains important scientific and applied results and meets all the requirements of the Law on the Development of the Academic Composition in the Republic of Bulgaria, the Regulations for its application and that Medical University - Varna.

The presented materials and dissertation results fully comply with the specific requirements of the Regulations of MU - Varna.

The dissertation shows in-depth theoretical knowledge and professional skills of the PhD student in the scientific specialty of "nephrology" and demonstrates her qualities and skills for independent scientific research.

As a reviewer, I confidently give my *positive* assessment of the research, dissertation, abstract, results and contributions and *propose to the esteemed scientific jury to award the educational and scientific degree "Doctor"* of Dr. Snezhana Atanasova Atanasova in the scientific specialty "Nephrology".

11.03.2022

Reviewer. Prof. Valentina Madjova, PhD.
Nephrologist, Head of the Department of General Medicine
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A handwritten signature in dark ink, appearing to read 'VM', is written on a light-colored rectangular background.