

REVIEW

By

Prof. Emil Paskalev Dimitrov, MD, DSc.

According to the Order No P-109-88/2Z.O2.2022 of the Rector of MU - Varna
of the dissertation on the topic:

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

Of

D-r Snezhana Atanasova Atanasova

Supervisor: Prof. Svetla Staykova, MD, DSc

for awarding the scientific and educational degree "Doctor"

Specialty "Nephrology"

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Dr. Snezhana Atanasova Atanasova was born in 1988 in Varna city. She graduated from Medical University "Prof. Dr. Paraskev Stoyanov", Varna in 2013, and has a recognized specialty in "Nephrology" and is currently an assistant and works in the clinic of nephrology and dialysis.

The dissertation was developed in the Department of Internal Medicine - Nephrology, Hemodialysis and Toxicology at the Faculty of Medicine, Medical University "Prof. Dr. Paraskev Stoyanov", Varna, discussed and directed for public defence at the Departmental Council in the same Department.

The dissertation is presented in 133 standard typewritten pages including 45 tables, 29 figures and one appendix. The PhD student has attached a list of cited literature from 206 sources, of which 8 in Bulgarian and 198 in English. A list of publications on the topic of the dissertation and an

abstract of 57 pages (A4 format) with a comprehensible summary of the main features of the dissertation are presented.

The dissertation is properly structured with a clear objective - to analyse the diagnostic, clinical and therapeutic aspects of bone mineral metabolism disorders in chronic kidney disease in the course of conservative and hemodialysis treatment. To accomplish it, six tasks were formulated precisely and clearly: To investigate the diagnostic and prognostic value of calcium, phosphorus and parathormone in the development and disorders of bone mineral metabolism in patients with chronic kidney disease in pre-dialysis stage and on hemodialysis treatment; to follow the dynamic influence of phosphorus-binding drugs - sevelamer hydrochloride and calcium carbonate on markers of bone-mineral metabolism in dialysis patients; to look for correlation between etelcalcetide and markers of bone-mineral metabolism in hemodialysis patients and to evaluate its effectiveness and safety in overcoming hyperphosphatemia; to compare serum sclerostin levels in pre-dialysis patients and patients undergoing haemodialysis treatment and to evaluate the effect of etelcalcetide (Parsabiv) treatment on serum sclerostin levels in haemodialysis patients; to analyse and compare the effect of conventional hemodialysis and hemodiafiltration on hyperphosphatemia in dialysis patients; to analyse the survival and quality of life in dialysis patients in relation to biochemical markers of BMD-CKD.

The material and methods are defined very precisely. The follow-up period of the patients is optimal - three years, with clear inclusion and exclusion criteria for patients - a total of 116 patients - M-75, W-41, sufficient as a population for statistical reliability. Methods include clinical examinations, anthropometry, laboratory and statistical methods, ensuring accurate and correct data processing.

The results of the first task were based on 86 patients on HD treatment and used a cohort of 30 pre-dialysis patients with CKD. From the studies and statistical analysis of the data, it is evident that patients on HDT have higher phosphorus and parathormone values and lower calcium values compared to pre-dialysis patients. In the analysis of the dynamic influence of phosphorus-binding drugs on markers of bone mineral metabolism, 43 HDT patients were studied, 18 on treatment with calcium carbonate and 25 with sevelamer hydrochloride (Renagel). In patients on sevelamer hydrochloride treatment, treatment with the calcimimetic cinacalcet was added to correlate the effect on parathyroid hormone values in patients on HDT. It was found that treatment with calcium carbonate and a combination of sevelamer and cinacalcet showed significant relevance with regard to hyperphosphatemia and secondary hyperparathyroidism.

In a study to investigate the correlation between etelcalcetide and markers of bone mineral metabolism in hemodialysis patients and to monitor its efficacy and safety in overcoming hyperphosphatemia, 27 patients on etelcalcetide treatment were enrolled over a 12-month follow-up period. In this study, it was demonstrated for the first time in Bulgaria that more than half of the patients on HDT and etelcalcetide achieved more than 30% reduction in parathyroid hormone in the first quarter and more than 60% in the first year of treatment. These data prove the research significance of the PhD student and her scientific work.

Task 4 compared serum sclerostin levels in pre-dialysis patients and patients undergoing hemodialysis treatment and evaluated the effect of etelcalcetide treatment on serum sclerostin

levels in patients on HDT. A comparative analysis of serum sclerostin levels in pre-dialysis patients (control group) and patients undergoing dialysis treatment was performed. A total of 89 patients were studied, 59 on HDT and 30 control group. The role of etelcalcetide on serum sclerostin concentration was analysed in dialysis patients, who were divided into two groups, on treatment and no treatment with etelcalcetide. It is shown that patients on extracorporeal treatment have up to three times increased serum sclerostin level compared to the control group of pre-dialysis patients. The significance of serum sclerostin is determined by the fact that its levels are closely related to those of serum phosphate. There is evidence of a positive association between sclerostin levels and all-cause mortality. This predicts the significance of these studies for a dissertation. Results have been obtained that demonstrate that etelcalcetide controls secondary hyperparathyroidism and increases sclerostin levels in hemodialysis patients.

The effect of conventional hemodialysis and hemodiafiltration on hyperphosphatemia in dialysis patients was analysed and compared. Patients on hemodialysis and hemodiafiltration were studied over a period of 6 months. No statistical significance was found regarding serum calcium values. There was a statistically significant difference in serum phosphorus in patients on HDF during the periods studied. There was a significant decrease in serum phosphorus as early as the 3rd month of HDF. After 6 months, lower parathyroid hormone values were found in patients on HDF compared to those on HD.

The analysis of survival and quality of life in patients on dialysis treatment in terms of biochemical markers of bone mineral disorders in CKD (BMD-CKD) is of importance. Quality of life was assessed based on questionnaires. 86 patients on HDT were included and divided into three groups according to calcium, phosphorus and parathyroid hormone levels. The results showed that bone mineral disorders significantly affected quality of life in patients with CKD. Correction of abnormal calcium, phosphorus and intact parathyroid hormone levels improved quality of life in patients with CKD and those on dialysis treatment.

The conclusions of the dissertation are definite, significant, important and have practical relevance for clinical practice.

The theoretical contributions of the dissertation are five, of which the most significant are:

For the first time in Bulgaria, the serum marker sclerostin has been studied and interpreted in patients with CKD - pre-dialysis and dialysis stage with important diagnostic and prognostic significance.

Correlation between etelcalcetide and elevated concentrations of the serum biomarker sclerostin in patients on HD treatment demonstrated for the first time in our country.

The dissertation has contributions of practical and applied nature, of which the measurement and assessment of quality of life in patients with CKD and hyperphosphatemia is of great importance, allowing a more complete understanding of their specific needs and increasing the effectiveness of clinical management. For this purpose, a "Questionnaire" was formulated to assess the individual quality of life of patients with CKD on chronic hemodialysis treatment at UMHAT "St. Marina", Varna.

The PhD student has submitted three publications related to the dissertation, sufficient according to the regulated requirements.

In conclusion, I can point out that the dissertation is on a topic that has not been studied before in our country, significant from a theoretical and especially practical point of view, properly structured. The aim and objectives are precisely defined, logically consistent and solved with significant results. The contributions have an important practical orientation incl. "Questionnaire" for the assessment of individual quality of life of patients with CKD on chronic hemodialysis treatment at St. Marina", Varna. The dissertation meets the requirements of the Law On The Development Of The Academic Composition In The Republic Of Bulgaria and the Regulations of MU - Varna. This gives me reason to vote positively for the dissertation.



Prof. Emil Paskalev Dimitrov, MD, DSc.

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