

REVIEW

by Prof. Dr. Dimitrichka D. Bliznakova, PhD

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Member of the scientific jury appointed by Order of the Rector of MU - Varna

P 109-88/23.02.2022 and Protocol of Faculty Council 60/14.02.2022.

Subject: the dissertation of Dr. Snezhana Atanasova Atanasova "Assessment and dynamic monitoring of hyperphosphatemia - a predictor of bone mineral disorders in dialysis patients"

Dr. Snezhana Atanasova Atanasova was born on 25.01.1988 in Varna. She graduated from IIIrd natural-mathematical high school „Accad. Metodiy Popov” – Varna. In 2013 she graduated from MU - Varna.

Professional Development:

From 2015 to 2019 - doctor in the clinic of nephrology and dialysis.

From 01.01.2020 - nephrologist in the clinic of nephrology and dialysis

Academic Development:

Since 2018 full-time assistant at MU-Varna in IInd Department of Internal Medicine, Nephrology, Dialysis and Toxicology. Since 2019 full-time PhD student at MU-Varna.

Publications related to dissertation: 3 pcs.

2017 co-author of an English-language practical handbook to nephrology.

2018 - Co-author of Handbook of nephrology and renal replacement therapy.

Membership in professional organizations: 2

Fluent in: German and English

Personal skills and competences: 2019 training course - Therapy and practice for "Operation of the 4008S V4.5 ONLINE plus hemodialysis machine".

The dissertation contains 134 pages, illustrated with 45 tables, 22 figures and 1 appendix. The reference list includes 206 references, of which 8 in Cyrillic and 198 in Latin.

Chronic kidney disease (CKD) debilitates the patient with many complications, one of which are bone and mineral disorders, which are of increasing medical and social importance worldwide. They are associated with disturbances in calcium-phosphorus metabolism, parathyroid hormone (PTH), vit. D mineralization volume, linear growth or bone health as well as vascular or other soft-tissue calcifications. Patients with CKD on hemodialysis also have a risk of complications such as anaemia, electrolyte disturbances (hyperkalaemia, hyperphosphatemia, secondary hyperparathyroidism, renal osteodystrophy). With the progression of CKD and loss of nephron mass, absolute calcitriol deficiency occurs, phosphate retention (hypocalcaemia with hyperphosphatemia), which enhances the production of PTH and leads to the development of secondary hyperparathyroidism with hyperplasia of the parathyroid glands and a disturbance in bone metabolism. Many classes of drugs have been developed, including phosphate binders, vit. D and calcimimetics to directly or indirectly influence markers of CKD.

The aim of this dissertation is clear and specific: analysis of diagnostic, clinical and diagnostic aspects of bone mineral metabolism disorders in CKD, in the course of conservative and hemodialysis treatment.

The tasks are property structured:

- To investigate the diagnostic and prognostic value of calcium, phosphorus and PTH on the development and disturbance of bone mineral metabolism in patients with CKD in the pre-dialysis stage and on hemodialysis treatment.
- To investigate the dynamic influence of phosphorus-binding drugs - Sevelamer, Hydrochloride and Calcium Carbonate on markers of bone mineral metabolism in dialysis patients.
- Search for correlation between Etelcalcetide and markers of bone mineral metabolism in hemodialysis patients and monitor its effectiveness and safety in overcoming hyperphosphstemia.
- 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.
- To analyse and compare the effect of convection hemodialysis and hemodiafiltration on hyperphosphatemia in dialysis patients.
- Analysis of survival and quality of life in hemodialysis patients in relation to biochemical markers.

Material methods:

A comprehensive diagnostic study was carried out in the period 01.02.2019 and 31.01.2022, with the permission of REC at MU - Varna, with Protocol α Decision N: 110/11.01.2022. Included are persons over 18 years of age, signed Informed Consent, with proven CKD in pre-dialysis stage and on hemodialysis.

A total of 116 patients - 75 males and 41 females with CKD - were studied. There were 86 patients undergoing dialysis treatment and 30 in pre-dialysis stage.

Methods:

- Clinical examinations, detailed anamnesis and objective physical status of patients in the clinic
- Anthropometric methods.
- Laboratory tests: PTH, calcium, phosphorus, alkaline phosphatase, vit. D, sclerostin.
- Statistical methods: non-parametric Kolmogorov-Smirnoff test to check the type of frequency distribution, parametric and non-parametric methods, analysis of variance, graphical analysis.

Statistical processing of the obtained data was performed using SPSS v.25 and Jamovi v.2.1.1. using quantitative and qualitative variables and presented in tabular and graphical form.

The individual quality of life of 86 hemodialysis patients was investigated using the specialised questionnaire (36 questions) on quality of life in patients with kidney disease.

Results and Discussion:

CKD is a global health problem affecting 5 to 10% of the world's population, with the majority of patients at risk of developing a bone mineral metabolism disorder. The clinical presentation of these disorders is bone pain, muscle tendon rupture, pruritus and a high incidence of fractures. Patients have been shown to be predisposed to cardiovascular calcification with high morbidity and mortality. Patients who suffer with end-stage CKD have reduced renal function which alters the metabolism of calcium, phosphorus and vit.D. Leading changes are those expressed with secondary hyperparathyroidism, which can lead to pathological bone and vascular damage and to bone fractures and cardiovascular events. High levels of PTH, calcium, and phosphorus are associated with increased mortality rates in patients with secondary hyperparathyroidism on hemodialysis. A major revision of the problem of hyperphosphatemia, its evaluation and dynamic follow-up is fixed on genetic phosphorus restriction, use of phosphate-lowering agents and dialysis for patients with stage five CKD. The role of diet, dialysis and treatment with medications (phosphorus-binding agents, vitamin D analogues and/or calcimimetics) is indicated. They are referred to as the "3D" of the correction of hyperphosphatemia, diet, dialysis and medications. Of critical importance is knowledge of phosphorus-binding medications that are administered with nutrition to limit phosphate absorption from the gut by forming a non-absorbable complex with phosphate. The three main classes of phosphorus-binding medications are aluminium-based: calcium-based phosphates and non-calcium-based phosphate binders. The choice between the use of calcium-binding or calcium-non-binding phosphates (Sevelamer) should be guided by serum calcium levels and PTH. Specificity and dynamic changes in serum concentrations of the included modern and traditional bone mineral metabolism parameters in patients with advanced CKD were found in an original constellation. When comparing the two groups of pre-dialysis and dialysis patients in terms of calcium, phosphorus and PTH values, the hemodialysis groups had higher phosphorus and PTH values and lower calcium values compared to the control group.

Etelcalcetide directly interferes with the pathophysiology of secondary hyperparathyroidism by increasing the sensitivity of the calcium-sensitive receptor of the parathyroid glands to extracellular calcium. Etelcalcetide is an intravenous calcimimetic, and treated patients can achieve clinically

significant and sustained reductions in PTH, calcium, and phosphorus. When administered intravenously, Etelcalcetide contributes to improved treatment adherence. Studies have been performed on Etelcalcetide for the treatment of secondary hyperparathyroidism in adult patients with CKD on hemodialysis.

Elevated serum sclerostin levels have been reported in recent years, which are closely related to serum phosphate and FGF-23 levels and treatment with Vit. D in dialysis patients with low serum PTH levels. The role of Sclerostin in CKD, bone mineral disorders is an area of active research, still with conflicting results evaluating the association between Sclerostin serum levels vascular calcification, cardiovascular and other cause of mortality.

The causes of the increased cardiovascular risk associated with kidney disease are in three strands hyperphosphatemia, vascular calcification and increased fibroblast growth factor-23. Sclerostin presents as a novel biomarker for bone and vascular disease. Patients with CKD have been reported to have higher levels of sclerostin that decrease during dialysis.

Over the past few decades, hemodialysis has been the main renal replacement therapy for patients with end-stage renal disease. Hemodiafiltration is a dialysis modality using a type of "high flux" hemodialysis water filter combined with high number plasma technology to increase convective transport for removal of uremic toxins. Online hemodiafiltration is a novel haemodialysis technique combining convection and diffusion and enabling the purification of large molecules. Modern dialysis machines are equipped with specific balanced control systems for fluid reinfusion and ultrafiltration simultaneously. The PhD student found that there was an improvement in phosphate elimination in patients on online hemodiafiltration.

Of importance in this dissertation is the questionnaire used for the research and evaluation of the Kidney Diseases Quality of Life-Short form-36 after modification. This instrument has a number of advantages: validated in Bulgarian, with easy interpretation, possibility to calculate two summary indicators of physical and mental health, comparison of the obtained data with other populations. The questionnaire has 8 scales that assess different aspects of health: physical activity, physical endurance, emotional stability, social activity, mental health, bodily pain, vitality (energy, fatigue), perception of general health. The widespread use of this questionnaire is related not only to its universal applicability to different diseases, but also to the general perception of particular aspects of health in general.

In conclusion, this dissertation is a crucially important and socially relevant problem: hyperphosphatemia as a predictor of bone-mineral disorders in dialysis patients. Abnormal calcium and phosphorus values are common and metabolic bone disease develops frequently in patients with CKD. Prevention of hyperphosphatemia, maintenance of serum calcium concentrations regulate PTH secretion by using vit. D analogues. Phosphate-containing agents that do not contain calcium and new vit. D and calcimimetics offer new therapeutic alternatives for the management of bone mineral disorders in CKD. In the integrated "3D" approach - diet dialysis, drugs are used simultaneously to manage not only phosphorus but also all key laboratory values (calcium, phosphorus, PTH). Etelcalcetide is a new calcimimetic drug for intravenous administration that shows good control of biochemical parameters. Online hemodiafiltration is the better choice in

patients in whom we need to increase replacement therapy. Online hemodialysis is safe and better tolerated than convection hemodialysis.

The two types of contributions of theoretical and practical-applied nature are extremely valuable for clinical practice. Theoretical discussion and interpretation of the serum biomarker sclerostin in patients with CKD on dialysis and pre-dialysis stage, which has diagnostic and prognostic significance. The high effectiveness of Sevelamer and Cinacalcet in controlling hypercalcemia in patients with CKD is also discussed. The use and advantages of intravenous Etelcalcetide and its effect on serum sclerostin and PTH levels in hemodialysis patients are evaluated.

CKD carries its own risks of damage to a number of organs and systems and leads to severe complications. The physical and mental health of these patients is crucial. The dissertation work of Dr. Snezhana Atanasova Atanasova is a contribution to the care, comfort and lifestyle of these patients. And perhaps we return to a Latin phrase "Primum non nocere", which reminds us that in our knowledge and our practice we should not harm the patient, but help him in his suffering to cope by being in comfort with his mental thought.

I propose to the esteemed scientific jury to award the educational and scientific degree "Doctor" in the scientific specialty "Nephrology" to Dr. Snezhana Atanasova Atanasova.

15.03.2022

Prof. Dr. D. Bliznakova

