REVIEW
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Member of the scientific jury appointed by Order of the Rector of MU-Varnaa
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Dr. Miroslava Stancheva Benkova Petrova was born on December 31, 1985. She graduated from the Baba Tonka Mathematical High School in Ruse in 2004. In 2010 she graduated from the Medical University of Varna.

Professional Development:
- Acquired a degree in nephrology in 2016.

Academic development:
- Elected Assistant to the Board of Nephrology, Dialysis and Toxicology in 2016.

Publications: 3 issues
Reports: 4 issues
She is a member of professional organizations: BMA, BCN
Fluent in: Bulgarian and English

The presented dissertation "Relationship between erythropoietin resistance and secondary hyperparathyroidism in patients undergoing dialysis" examines one of the most important and current issues in the field of nephrology and in particular chronic kidney disease and one of its complications - anemia. CKD is a serious health problem worldwide.

The dissertation contains 145 pages and is illustrated with 12 tables, 59 figures and 1 appendix. The literature reference includes 390 literary sources, 3 of which in Cyrillic and 387 in Latin.

Anemia is a common complication of chronic kidney disease (CKD), which reduces quality of life and increases the risk of cardiovascular disease and mortality, especially in patients with end-stage CKD. Causes of renal anemia are decreased production of endogenous erythropoietin, resistance to erythropoietin, reduced red blood cell half-life and bone marrow fibrosis. Secondary hyperparathyroidism is a lesser known but significant cause of anemia in patients with CKD. Parathyroid hormone is considered a uremic toxin that inhibits the synthesis of endogenous erythropoietin, shortens the survival of red blood cells and causes myelofibrosis. Erythropoietin resistance is directly related to the incidence of comorbidity in dialysis patients and is one of the most potent predictors of the risk of cardiovascular events and mortality.

The aim of the dissertation is clear and accurate and analyzes the diagnostic and therapeutic aspects of secondary hyperparathyroidism in patients with CKD and its importance for the development of erythropoietin resistance.

The tasks are properly structured:
- To investigate the relationship between secondary hyperparathyroidism and erythropoietin resistance in patients with CKD.
- To study the other factors that may be responsible for erythropoietin resistance, such as serum iron, folic acid, vitamin B12, soluble erythropoietin receptor, antibodies to erythropoietin, and the adequacy and duration of hemodialysis treatment in patients with CKD.
- To make a correlation between some markers for mineral and bone metabolism and indicators determining erythropoietin resistance (level of serum iron, folic acid, vitamin B12, soluble erythropoietin receptor, antibodies to erythropoietin and CRP.
- To compare the results of the treatment of secondary hyperparathyroidism and anemia and the required doses of medication.
- To study in the dynamics the individual quality of life of patients with secondary hyperparathyroidism due to CKD.

- To develop an algorithm for the diagnosis of erythropoietin resistance in patients with CKD.

The hypothesis is well thought out and corresponds to the set goal and tasks.

Materials and methods

The study included 80 patients with CKD divided into two groups: pre-dialysis patients with CKD stage III and IV (30) and patients undergoing dialysis (50) from the Clinic of Nephrology and Dialysis at the University Hospital "St. Marina" in Varna, followed clinically and examined by routine methods. The current complex, diagnostic and therapeutic study was conducted for a period of 6 months (April-October 2021), carried out under a project funded by the Science Fund at MU-Varna.

Laboratory methods:: CBC, intact parathyroid hormone, intact fibroblast growth factor-23, folic acid, vitamin B12, soluble erythropoietin receptor, antibodies to erythropoietin, serum iron, total iron binding capacity, CRP, albumin, calcium, phosphorus, erythropoietin resistance index, urea reduction ratio.

Statistical methods: analysis and interpretation of experimental data in order to reveal the nature of the observed phenomena. Used:

- Dispersion analysis
- Variation analysis
- Correlation analysis
- Comparative analysis
- Risk assessment analysis
- Assessment of the reliability of the questionnaire used

Results and discussion:

The obtained results are presented extremely well graphically, which makes it possible to discuss in detail the causes that lead to erythropoietin resistance. The discussion is clear, accurate, specific and contributes to the analysis of the problem of anemia in CKD, as well as to determine the therapeutic behavior.

Based on the results obtained and the analysis made, 6 conclusions were drawn:

- A significant association was found between iPTH and ERI (erythropoietin resistance index) in dialysis patients (rather negative).
- ERI correlates with iFGF-23 and hemoglobin levels, and the risk of developing EPO resistance is significantly higher in patients in the dialysis group
- The markers for mineral and bone metabolism (iPTH and iFGF-23) have a negative color with BMI and a positive color with folic acid.
- There is a significant difference in treatment regimens in patients in pre-dialysis and dialysis stage in terms of hyperparathyroidism and anemia.
- Treatment with drugs, containing iron strongly correlates with dialysis treatment, and a clear relationship between ERI and ESA (erythropoiesis - stimulating agents) is established.
- Individual quality of life correlates with the duration of dialysis, pain and a sense of calm.
- **Contributions:**
- **Theoretical contributions - 5:**
- A detailed review of the literature on erythropoietin resistance and the factors that determine it has been made.

- Non-invasive biomarkers have been studied and monitored in patients at risk of CKD (pre-dialysis and dialysis stages). They can be introduced into clinical practice for diagnosis and follow-up of treatment.

- For the first time a study was conducted in the country, which determines the level of erythropoietin resistance, with a direct study of the titer of antibodies to erythropoietin, as well as determining their dependence on other biomarkers.

- The association between secondary hyperparathyroidism and erythropoietin resistance in patients with CKD has been demonstrated.

- The individual quality of life of patients with erythropoietin resistance and secondary hyperparathyroidism was assessed.

Applied contributions used in practice - 3:

- Biochemical parameters that are not routinely used in practice have been studied: iFGF-23, vitamin W12, folic acid, soluble erythropoietin receptor, antibodies to erythropoietin.

- Developed and proposed algorithm for diagnosis of erythropoietin resistance in patients with CKD.

- The adequacy of the therapy in relation to anemia, secondary hyperparathyroidism and individual quality of life among patients in pre-dialysis and dialysis stages of CKD was assessed.

Conclusion: The dissertation of Dr. Miroslava Stancheva Benkova - Petrova "Relationship between erythropoietin resistance and secondary hyperparathyroidism in patients undergoing dialysis" considers one of the current problems in patients with CKD - anemia and erythropoietin resistance. Given that anemia is one of the most common complications of CKD, it reduces the quality of life and increases the risk of cardiovascular disease in the group of patients with ESRD. Erythropoietin resistance is one of the powerful predictors of cardiovascular events and mortality. This requires, through the control of laboratory parameters, properly identification of the reasons for its development and properly treatment with one main goal - potential complications. Attention is also drawn to a lesser-known cause of anemia in patients with CKD.

The dissertation of Dr. Miroslava Stancheva Benkova - Petrova reminds us of Fullar's words: "Theory is a treasure, the key to which is good clinical practice."When a clear goal is developed and the tasks are defined, the realization of the dissertation topic meets the modern requirements."

An extremely difficult and risky contingent of patients (pre-dialysis and dialysis) is covered. The main goal is to shed light on the future of these patients to improve their quality of life, which requires an individual approach to treatment, provision of hemodialysis centers with highly qualified medical staff, good collaboration between patients and medical staff.

I propose to the esteemed scientific jury to award the educational and scientific degree "Doctor" in the scientific specialty "Nephrology" to Dr. Miroslava Stancheva Benkova - Petrova.

30.12.2021

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Prof. D. Bliznakova, MD, PhD