

## **REVIEW**

**of dissertation on the topic:**

**"Relationship between erythropoietin resistance and secondary hyperparathyroidism in patients undergoing dialysis "**

**of Dr. Miroslava Stancheva Benkova - Petrova**

**for awarding the scientific and educational degree "Doctor"**

**Supervisor:**

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The dissertation contains 145 standard pages and is illustrated with 12 tables, 59 figures and 1 appendix. The literature includes 390 literary sources, 3 of which are in Cyrillic and 387 in Latin, which are quite sufficient to summarize the topic so far.

The dissertation was discussed and directed to the defense of the Second Department of Internal Medicine at the Medical University "Prof. Dr. Paraskev Stoyanov" - Varna.

Dr. Miroslava Stancheva Benkova - Petrova graduated from high school in 2004 at the Baba Tonka Mathematical High School in Ruse, and in 2010 is a Master of Medicine graduating from Medical University "Prof. Dr. Paraskev Stoyanov", Varna. In 2016 acquires the specialty "Nephrology", and since 2016 was selected as an assistant to the Department of Nephrology, Dialysis and Toxicology. He speaks English, is fluent in computer programs in his professional and scientific activities, has good communication skills, ability to work in a team, a high level of intelligence in medicine and more areas close to the professional. Her professional development is optimal.

The incidence of chronic kidney disease (CKD) has been growing rapidly worldwide in recent years, due more to undiagnosed patients than new ones, and this is a serious health problem worldwide. Anemia in CKD necessarily occurs in the course of its progression by

reducing the quality of life and increasing the risk of cardiovascular disease and mortality in these patients. Erythropoietin therapy can lead to developing of erythropoietin resistance in some of the patients. Erythropoietin resistance is a powerful predictor of cardiovascular accidents and mortality. Frequent monitoring of laboratory parameters, early detection of the causes of erythropoietin resistance and its treatment are important for the prevention of complications.

The dissertation is properly structured and in optimal volume. The goal is clearly defined - to analyze the diagnostic and therapeutic aspects of secondary hyperparathyroidism (HPT) in patients with CKD and their importance for the development of erythropoietin resistance. To achieve it, six tasks are indicated, correctly and consistently meeting the goal: 1. Study of the relationship between secondary HPT and erythropoietin resistance in patients with CKD; 2. Study of other factors responsible for the development of erythropoietin resistance (serum iron, folic acid, vitamin B12, soluble erythropoietin receptor, antibodies to erythropoietin, adequacy and duration of hemodialysis treatment) in patients with CKD ; 3. Correlation between some markers of mineral and bone metabolism (including iPTH, iFGF-23) and more indicators of erythropoietin resistance (serum iron, folic acid, vitamin B12, soluble erythropoietin receptor, antibodies to erythropoietin, CRP) in patients with CKD; 4. Comparison of the results of the treatment of secondary HPT and anemic syndrome and the required doses of drugs; 5. Study in the dynamics of the individual quality of life of patients with secondary HPT and anemia due to CKD; 6. Development of an algorithm for the diagnosis of erythropoietin resistance in patients with CKD. A working hypothesis has been correctly defined - a constellation of diagnostic and therapeutic methods has been adopted, which contribute to elucidating the causes of erythropoietin resistance and their relationship with secondary HPT in patients with CKD, as for optimal results and improvement of the quality of life it is necessary to apply an individual approach.

80 patients with CKD were studied, sufficient to solve the tasks, divided into two groups – pre-dialysis (30 patients) and on hemodialysis treatment (50 patients) from the Clinic of Nephrology and Dialysis of the University Hospital "St. Marina" in Varna, followed clinically and studied by accepted methods. Inclusion and exclusion criteria for patients are correctly defined. The defined survey period and the adopted research methodology are optimal and described in detail.

Some of the research results are of high significance.

An inverse relationship was found between iPTH and the age of the patients ( $r = -0.217$ ;  $p = 0.05$ ), with decreasing iPTH levels with age. These results become even more pronounced against the background of dialysis treatment.

A comparative analysis of the values of ERI (erythropoietin resistance index) compared to those of iPTH in patients in the pre-dialysis and dialysis stages revealed a significant difference ( $p = 0.003$ ).

Significant difference of the results was found with respect to the comparison of the levels of iPTH and phosphorus in the two studied groups ( $p = 0.002$ ).

Another significant difference was found when comparing the levels of iPTH and iFGF-23 (Fibroblast Growth Factor 23) in the two studied groups ( $p < 0.001$ ).

There was a significant difference in albumin levels according to iPTH between the two groups ( $p = 0.003$ ), as in pre-dialysis there was an increase in albumin levels with increasing levels of iPTH, and in the dialysis group feedback was established.

There was a significant difference in the ERI values according to the studied group ( $p = 0.003$ ), and patients in the dialysis stage have a higher risk of developing erythropoietin resistance. There was no significant difference in the mean ERI values according to the patient's diagnosis.

Comparative analysis between iFGF-23 levels and ERI revealed significantly higher values in dialysis patients ( $p < 0.001$ ) except for the highest ERI  $> 22.29$  where in both groups iFGF-23 are high.

ERI correlates strongly negatively with hemoglobin levels ( $r = -0.588$ ;  $p < 0.001$ ). No significant difference was found between hemoglobin levels according to ERI in the two studied groups.

ERI correlates moderately inversely with URR ( $r = -0.305$ ;  $p = 0.031$ ), suggesting that inadequate dialysis treatment is associated with an increased risk of developing erythropoietin resistance.

Iron deficiency was also associated with an increased erythropoietin resistance index ( $r = -0.398$ ;  $p = 0.004$ ), with serum iron levels significantly lower at ERI  $> 15.0$  ( $p < 0.05$ ).

The duration of hemodialysis treatment is moderately proportional to the ERI ( $r = 0.373$ ;  $p = 0.008$ ).

No dependence or significant difference in folic acid and ERI levels was observed, with higher levels of folic acid in dialysis patients due to oral substitution.

Similar results were found for vitamin B12 concentrations and ERI in the two studied groups, where compensatory effects of Vitamin B12 treatment were observed in dialysis patients.

No correlation between iPTH levels and CRP was found.

Examination of the relationship between ERI values and ESA doses revealed a proportionally strong dependence ( $r = 0.551$ ;  $p < 0.001$ ), which showed that increasing ESA doses also increased ERI.

The studies did not show a relationship between the duration of treatment and antiEPOab, nor in terms of ESA doses.

The development of an algorithm for the diagnosis of erythropoietin resistance in patients with CKD is of particular importance in the dissertation.

The conclusions are logically made and correspond to the set tasks and the purpose of the dissertation, respectively:

1. A significant association between iPTH and ERI has been established in patients in the dialysis group, which is more negative.
2. ERI correlates with iFGF-23 and hemoglobin levels and the risk of developing EPO resistance is significantly higher in dialysis patients.
3. Markers for mineral-bone metabolism (iPTH and iFGF-23) correlate negatively with BMI, but positively with folic acid.
4. There is a significant difference in the treatment regimens of patients in the pre-dialysis and dialysis stages with regard to secondary HPT and anemia.
5. Treatment with iron supplements correlates significantly with dialysis treatment, and a significant relationship is found between ERI and ESA dose.
6. An individual quality of life correlates negatively with the duration of dialysis, pain and a sense of calm.

By solving the tasks, the goal of the dissertation is completely achieved.

The developed constellation of diagnostic methods contributes to the elucidation of the causes of erythropoietin resistance and their relationship with secondary HPT in patients with CKD. For optimal results and improving the quality of life in this group of patients it is necessary to apply an individualized approach to treatment, provision of dialysis structures with highly qualified medical staff, good collaboration between patients and medical staff, proper care for vascular access.

The dissertation has significant contributions.

They are of a theoretical nature:

- 1) Non-invasive biomarkers in patients in the risk groups of CKD - pre-dialysis and dialysis stages, which can be implemented in practice in the diagnostic and treatment process, have been studied and followed.
- 2) A detailed review of the literature data on the nature of erythropoietin resistance and the factors that determine it.
- 3) For the first time, a follow-up was conducted in the country to determine the level of erythropoietin resistance with a direct study of the titer of antibodies to erythropoietin and determine their dependence on other biomarkers.
- 4) The relationship between secondary HPT and erythropoietin resistance in patients with CKD has been established.
- 5) An assessment of the individual quality of life of patients with erythropoietin resistance and SHPT was made.

Practical contributions:

- 1) Biochemical parameters that are not routinely analyzed among patients were studied - iFGF-23, level of folic acid and vitamin B12 and not studied so far in the country (antibodies to erythropoietin, soluble erythropoietin receptor) .
- 2) An algorithm for the diagnosis of erythropoietin resistance in patients with CKD has been developed.
- 3) The conducted therapy was evaluated in terms of the adequacy of the anemia, the secondary HPT and the individual quality of life of the patients in the pre-dialysis and dialysis stages of CKD.

The presented publications on the topic of the dissertation are three in number, including in a foreign language with an impact factor, sufficient for according to current requirements.

## CONCLUSION

The dissertation is properly structured with a topic that has not been studied in our country. The goal and tasks are precisely defined and solved with significant results. Contributions with significant practical orientation have been formed - an algorithm for the diagnosis of erythropoietin resistance in patients with CKD. The dissertation has the necessary publications. This gives me a reason to evaluate and vote positively for the dissertation.

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Sofia

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