

**REVIEW**  
**by Prof. Dr. Valentina Christova Madjova, Ph.D.**  
**Head of the Department of General Medicine,**  
**Medical University of Varna**

**of the dissertation on the topic**

**"RELATIONSHIP BETWEEN ERYTHROPOTHETIC RESISTANCE AND SECONDARY  
HYPERPARATHYROIDISM IN PATIENTS UNDERGOING DIALYSIS"**

**of Dr. Miroslava Stancheva Benkova**  
full-time PhD student at the Second Department of Internal Medicine  
Faculty of Medicine at the Medical University - Varna  
and  
assistant at the Clinic of Nephrology of University Hospital "St. Marina"

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 №109-580/17.12.2021, Protocol of the Faculty Council № 56/ 07.12.2021 and Protocol № 1 of the meeting of the Scientific Jury I was elected its Chairman and reviewer of the scientific work of Dr. Miroslava Stancheva Benkova.

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 ONS "Doctor".

### **2. Brief biographical data about the PhD student**

Dr. Miroslava Stancheva Benkova graduated from the Mathematical High School in Ruse. After graduating with a master's degree in medicine in 2010 at MU - Varna, she began working as a doctor at University Hospital "St. Marina" - Varna at the Clinic of Nephrology, and in 2016 was elected as an assistant in Department of Nephrology, Dialysis and Toxicology at MU - Varna.

In 2016, Dr. Miroslava Benkova acquired a degree in Nephrology

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

The dissertation of Dr. Miroslava Benkova treats a current and important practical problem in nephrology, which is related to the complications of patients with chronic kidney disease (CKD) undergoing dialysis, namely the relationship between erythropoietin resistance and secondary hyperparathyroidism.

I highly appreciate the chosen topic of the dissertation of Dr. Miroslava Benkova as relevant and important for clinical nephrology practice in our country, due to the growing prevalence of CKD among the elderly population in Bulgaria, 90% of them with advanced kidney

disease and complications, requiring adequate treatment with erythropoietin and correction of secondary hyperparathyroidism.

An important circumstance that directs Dr. Miroslava Benkova to develop her dissertation is the fact that at this time in Bulgaria there is no serious study on the relationship between erythropoietin resistance and secondary hyperparathyroidism dialysis patients.

#### **4. Knowledge of the problem**

Dr. Miroslava Benkova knows very well the material she treats in her dissertation. Proper treatment of anemia not only improves quality of life, but also reduces the risk of cardiovascular disease and mortality, especially in the group of patients with end-stage renal disease (ESRD). In the review section, she examines the various causes of renal anemia: decreased production of endogenous erythropoietin (EPO), resistance to EPO, reduced red blood cell half-life and bone marrow fibrosis, and the fact that secondary hyperparathyroidism is less well known, but a potentially significant cause of anemia in patients with CKD through the action of parathyroid hormone as uremic toxin, which inhibits EPO synthesis, shortens red blood cell survival, and causes myelofibrosis.

Dr. Miroslava Benkova makes an important analysis of scientific data on metabolic changes that occur in patients with CKD and the impact on their mineral and bone metabolism.

#### **5. Research methodology**

The larger section of the dissertation is a study in which Dr. Miroslava Benkova actively participates as a researcher. The complex diagnostic-therapeutic study was conducted for a period of 6 months - April - October 2021 and is carried out under a project funded by the Science Fund at MU-Varna. 80 patients with chronic kidney disease were studied, divided into two groups - pre-dialysis (30 patients) and on hemodialysis treatment (50 patients) from the Clinic of Nephrology and Dialysis at the University Hospital "St. Marina" in Varna, which were monitored clinically and routinely methods.

In her dissertation Dr. Miroslava Benkova uses the following methods:

- 1) Clinical and laboratory tests: complete blood count; intact parathyroid hormone (iPTH); intact fibroblast growth factor -23 (iFGF-23); folic acid; vitamin B12; soluble erythropoietin receptor; antibodies to erythropoietin; serum iron, TIBC, TSAT; CRP; albumin; calcium; phosphorus; Urea reduction ratio (URR) and erythropoietin resistance index (ERI);
- 2) Statistical methods for analysis and interpretation of experimental data: analysis of variance (ANOVA); variation analysis; correlation analysis; regression analysis; comparative analysis (evaluation of hypotheses); analysis for risk assessment (OR - Odd ratio) and assessment of the reliability of the questionnaire used (Cronbach'α).

Data were statistically processed using SPSS v.20 and descriptive indicators for quantitative and qualitative variables were used, presented in tabular and graphical terms.

## **6. Characteristics and evaluation of the dissertation**

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

In the literature review Dr. Miroslava Benkova discusses the problem of CKD, which is growing rapidly every year and is one of the main socially significant health problems affecting society, especially important for nephrological practice are its complications - anemia and secondary hyperparathyroidism.

The main goal of Dr. Benkova's dissertation is "to analyze the diagnostic and therapeutic aspects of secondary hyperparathyroidism in patients with CKD and their importance for the development of erythropoietin resistance."

To achieve it, six main tasks have been identified:

- 1) Study of the relationship between secondary hyperparathyroidism and erythropoietin resistance in patients with chronic kidney disease.
- 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 chronic kidney disease.
- 3) Correlation between some markers of mineral and bone metabolism (including iPTH, iFGF-23) and indicators of erythropoietin resistance (serum iron, folic acid, vitamin B12, soluble erythropoietin receptor, antibodies to erythropoietin, CRP) patients with chronic kidney disease.
- 4) Comparison of the results of the treatment of secondary hyperparathyroidism and anemia and the required doses of drugs.
- 5) Study in the dynamics of the individual quality of life of patients with secondary hyperparathyroidism and anemia due to CKD.
- 6) Development of an algorithm for the diagnosis of erythropoietin resistance in patients with CKD.

Dr. Miroslava Benkova defines the following hypothesis in her dissertation: "The constellation of diagnostic and therapeutic methods developed by us contributes to clarifying the causes of erythropoietin resistance and their relationship with secondary hyperparathyroidism in patients with chronic kidney disease. For optimal results and improvement of the quality of life, it is necessary to apply an individualized approach. "

From her research, the PhD student formulates six main conclusions. All of them correspond to the set goal and the indicated tasks.

## **7. Contributions and significance of development for science and practice**

The data in the study of Dr. Miroslava Benkova summarize and monitor for the first time in our country the level of erythropoietin resistance by direct study of the titer of antibodies to erythropoietin and determine their dependence on other biomarkers. She points out in her dissertation eight scientific contributions, of which five are theoretical and three are practical. I fully accept the conclusions made and the contributions made by the PhD student.

#### **8. Evaluation of the dissertation publications**

The PhD student has attached to the documentation the required number of publications and communications related to the dissertation. The attached list meets the requirements for acquiring an educational and scientific degree "Doctor".

#### **9. Personal participation of the doctoral student**

The conducted dissertation research, the formulated contributions and the obtained results are the merit of Dr. Miroslava Benkova and are supported by her supervisor - Prof. Dr. Svetla Staykova, MD, PSS.

#### **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 do not have critical remarks and recommendations to the conducted research and the materials provided to me.

#### **12. Personal impressions**

I know Dr. Miroslava Benkova from her work as a doctor at the Clinic of Nephrology and I have very good impressions of her as a serious and responsible 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. Miroslava Benkova as relevant and valuable as a scientific work of practical importance for the relationship between erythropoietin resistance and secondary hyperparathyroidism in patients undergoing dialysis.

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 of MU - Varna.

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

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

As a reviewer, I confidently give my positive assessment of the research, dissertation, abstract, results and contributions and offer the esteemed scientific jury to award the educational and scientific degree "Doctor" of Dr. Miroslava Stancheva Benkova in "Nephrology".

21.12.2021  
Varna

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