

To the Chairman of the Scientific Jury  
according to Protocol from Faculty Council № 56 / 07.12.2021  
and Order № R-109-580 / 17.12.2021.  
of the Rector of the Medical University - Varna

## **REVIEW**

for dissertation for the award of educational and scientific degree "Doctor"  
in the scientific specialty "Nephrology" of Dr. Miroslava Stancheva  
Benkova-Petrova Medical University "Prof. Dr. Paraskev Stoyanov "-  
Varna, Faculty of Medicine, Second Department of Internal Medicine  
on the topic: "Relationship between erythropoietin resistance and secondary  
hyperparathyroidism in patients undergoing dialysis"  
by Assoc. Prof. Dr. Alexander Ivanov Osichenko, MD,  
Scientific specialty - nephrology, Head of Dialysis Clinic, Acibadem City  
Clinic Tokuda University Hospital, Sofia

There are about 3800 patients undergoing dialysis in Bulgaria. There are more than 2.5 million of them worldwide. Anemia and secondary hyperparathyroidism are among the main factors contributing to deteriorating quality of life and high mortality among this patient population. More than 90% of dialysis patients are on erythropoietin replacement therapy; about 50% - have secondary hyperparathyroidism /SHPT/. The definition of the relationship between erythropoietin resistance and SHPT as an important component of the factors determining the treatment of these patients and is of particular importance.

This determines the relevance of the presented dissertation of Dr. Miroslava Stancheva Benkova-Petrova, who aims to investigate and define the diagnostic and therapeutic aspects of secondary hyperparathyroidism in patients with CKD and their importance for the development of erythropoietin resistance.

In order to achieve the set goal, 6 main tasks are clearly and precisely formulated.

It is hypothesized that the developed constellation of diagnostic and therapeutic methods contributes to the elucidation of the causes of erythropoietin resistance and their relationship with secondary hyperparathyroidism in patients with CKD. For optimal results and improvement of the quality of life it is necessary to apply an individualized approach.

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

Dr. Miroslava Stancheva Benkova-Petrova is well aware of the state of the problem and has presented a creative assessment of the analyzed literature.

The dissertation covers 80 patients with chronic kidney disease, divided into two groups – pre-dialysis patients (30) and 50 patients undergoing dialysis from the Clinic of Nephrology and Dialysis at the University Hospital "St. Marina" Varna, followed clinically and examined by routine methods. The inclusion and exclusion criteria are formulated clearly and precisely. The study was conducted for a period of 6 months (April - October 2021) and is carried out in connection with a project funded by the Science Fund at MU-Varna.

The following laboratory parameters were studied: complete blood count (including hemoglobin), intact parathyroid hormone (iPTH), intact fibroblast growth factor -23 (iFGF-23), folic acid level, vitamin B12 level, soluble erythropoietin receptor level, antibodies to erythropoietin, serum iron, TIBC, TSAT, CRP, albumin, calcium, phosphorus, urea reduction ratio (URR), erythropoietin resistance index (ERI). The individual quality of life was studied through a specialized guide to quality of life in patients with kidney disease with 36 questions (Kidney Disease Quality of Life - Short Form - 36, KDQOL-36) after modification by S. Staykova. The statistics were processed using SPSS v.20. The various modern methods used correspond to the objectives of the study.

The obtained results are interpreted in depth and in comparison with the data from studies published in the literature, in cases where such are available. The results show that an individualized approach is needed to improve the quality of life of patients undergoing dialysis. The developed constellation of diagnostic and therapeutic methods contributes to the elucidation of the causes of erythropoietin resistance and their relationship with secondary hyperparathyroidism in patients with CKD.

The contributions of the dissertation work have a certain scientific-theoretical and applied-practical character.

Theoretical contributions 1) Non-invasive biomarkers in patients in the risk groups of CKD - pre-dialysis and dialysis stages, which can be implemented in practice in terms of 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 in Bulgaria a follow-up was conducted, which determines the level of erythropoietin resistance by direct examination of the titer of antibodies to erythropoietin, as well as determination of their dependence with other biomarkers. 4) The association between secondary hyperparathyroidism and erythropoietin resistance in patients with CKD has been demonstrated. 5) The individual quality of life of patients with erythropoietin resistance and secondary hyperparathyroidism was assessed.

Practical contributions: 1) Biochemical indicators that are not routinely analyzed - iFGF-23, folic acid and vitamin B12 levels, as well as those not studied in Bulgaria so far (soluble erythropoietin receptor and antibodies to erythropoietin), have been studied. 2) An algorithm for the diagnosis of erythropoietin resistance in patients with CKD has been developed and proposed.

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

In association with the topic of the dissertation Dr. Miroslava Stancheva Benkova-Petrova has 3 publications in scientific journals.

The presented materials on the procedure meet the requirements of the Law for the development of the academic staff of the Republic of Bulgaria and the Regulations for the development of the academic staff of MU - Varna for awarding the scientific degree "Doctor".

**In conclusion,** I believe that the dissertation of Dr. Miroslava Stancheva Benkova-Petrova is complete, modern, thorough, well structured and shaped, with clear and accurately formulated and completed tasks, with certain conclusions and contributions to modern science and for practice in an interesting socially significant field, such as renal replacement therapy. All this gives me reason to recommend to the members of the esteemed scientific jury to award Dr. Miroslava Stancheva Benkova-Petrova the educational and scientific degree "Doctor" in the scientific specialty of nephrology in the professional field 7.1. Medicine in the field of higher education 7. Health and sports.

28.12.2021.

Sofia

Assoc. Prof. Dr. Alexander Ivanov Osichenko, MD

