REVIEW
From Prof. Dr. Boryana Deliyska, PhD, DSc
of dissertation for awarding the scientific and educational degree "Doctor" in the field of higher education 7.0 Health and sports, professional field 7.1 Medicine and specialty "Nephrology"

To Dr. Diana Dimcheva Nenova
Topic Adequacy of dialysis treatment and the relationship with achieved quality of life and survival in patients with stage V chronic kidney disease
Scientific adviser: Assoc. Prof. Dr. Alexandar Stoyanov, PhD

I was elected a member of the scientific jury, voted by Faculty Council of the Faculty of Medicine at MU – Varna Protocol No. 61 / 01.03.2022 and appointed by order of the Rector № R-109-105 / 09.03.2022 for the acquisition of the educational and scientific degree "Doctor" in higher education 7.0 Health and Sports, professional field 7.1 Medicine and specialty " Nephrology". The dissertation was discussed and scheduled for defense at the Department Council of the Second Department of Internal Medicine at the Medical University "Prof. Dr. Paraskev Stoyanov" - Varna.

Brief biographical data

Dr. Diana Dimcheva Nenova graduated with honors in medicine at the Medical University "Prof. Dr. Paraskev Stoyanov" - Varna. In 2013 she was hired as a resident at the Dialysis Clinic of the University Hospital "St Marina", Varna. She has been majoring in nephrology since 2018. Since March 2018 she has been an assistant professor of nephrology at the Second Department of Internal Medicine, MU-Varna. She has completed a course in work with „Fresenius Medical Care 5008S V4.5 ONLINE Plus", as well as vascular access and renal biopsy courses.

Analysis of the dissertation

The dissertation submitted to me for review contains 200 standard pages and is perfectly illustrated with 24 tables, 43 figures and 1 appendix.

The literature review is based on a significant bibliographic reference from 379 literature sources, 10 of which are in Cyrillic, and the main part of the articles are from the last 5 years, which determines its relevance. The literature reviews in detail the urea-kinetics modeling with its various variants, uremic toxins, markers of dialysis adequacy and protein balance, connection of dialysis dose with survival, nutritional status, and anemic syndrome, as well as methods for direct measurement of dialysis dose in real time. The current recommendations of KDOQI for the adequacy of dialysis are analyzed, as well as the peculiarities of vascular access and quality of life of dialysis patients. The literature review ends with a separate chapter, which critically summarizes some debatable issues and prospects.

Based on the literature, the dissertation student determines the purpose of her development, namely, to study the effect of non-standardized high dialysis dose spKt / V≥1.5, obtained by various dialysis techniques - conventional and convective, on clinical outcome and determining its importance for survival and quality of life in patients with CKD-5D. The working hypothesis is that high non-standardized dialysis dose (through conventional or convective

therapies) improves clinical outcome, survival and quality of life, and that ionic dialysis allows for dialysis dose assessment.

From the formulated goal and working hypotheses, the dissertation student specifies to develop 9 tasks that cover different aspects of dialysis treatment, namely: quality of life in patients with CKD-5D at different dosage regimens by assessing the dialysis dose and its impact on indicators for nutritional status, reporting serum hemoglobin levels and the average weekly dose of the drug for a period of five years, considering the importance of vascular access, respectively blood flow for dialysis dose and clinical outcome, the effect of different dialysis membranes and techniques on dialysis dose, the importance of convective volume as an indicator of the effectiveness of convective therapy, the effect of convective volume and OL-HDF on intradialysis hypotension and recovery time, the importance of dialysis dose and dialysis techniques on survival, mortality and quality of life, comparison of UKM and ionic dialysis methods for dialysis dose through online monitoring and blood urea clearance in order to develop new therapeutic strategies and develop a treatment algorithm to increase survival and quality of life.

The dissertation includes 100 dialysis patients. The importance of vascular access on the indicators of adequacy, nutritional status and anemic syndrome was studied in 87 patients, and the effect of convective therapies on dialysis dose, nutritional status and anemic syndrome was analyzed in 41 patients. In 32 the relationship between the adequacy indicators calculated by UKM and the results of online monitoring was studied, and in 50 patients the quality of life was reported.

Patients were selected according to inclusion and exclusion criteria. The laboratory and treatment methods used in the dissertation are described in detail. The obtained data are processed with 8 statistical methods, which determines the reliability of the obtained results and conclusions. Each of the developed chapters ends with a discussion and summary.

The dissertation ends with 12 conclusions. The most significant of them are that ionic dialysis is a new non-invasive tool with high predictive value for adequate dialysis and allows cheap assessment of dialysis, high dialysis dose significantly improves nutritional status, anemic syndrome and quality of life, and its lasting effect shows by the third year, that high dialysis dose has a positive effect on nutritional status in young and middle-aged patients, but is unsatisfactory for adults, where age-related weight loss and malnutrition is observed, that high-dose dialysis is associated with better survival, that non-standardized high dialysis dose is associated with poor nutritional index scores. Of interest is the conclusion, which is of significant practical value, that AVF significantly surpasses other types of vascular access in terms of dialysis dose, control of anemic syndrome by determining 4 times better survival compared to PC with fewer complications and hospitalizations. Some of the conclusions are related to the generalization of the advantages of OL-HDF, considering that it also determines better survival, that at lower volumes, the clinical effect is comparable to conventional dialysis, and at old age high convective volumes are associated with hemodynamic instability, prolonged recovery time and deteriorating nutritional status.

The contributions from the dissertation are formed by Dr. Nenova as such with theoretical and practical-applied character. In my opinion, all contributions are of significant practical value, as they consider the adequacy of dialysis from different angles and provide full information on the importance and benefits of different dialysis techniques for survival, nutritional status, hospitalizations, and the benefits of different vascular access as a factor associated with the clinical result. For the first time in our country the effect of convective therapies, which are not

routinely applied in clinical practice, on the dialysis dose, the parameters of the nutritional status and the control of the anemic syndrome has been studied and evaluated. For the first time in the country the convective volume was studied as an indicator for OL-HDF dosing and the threshold value for efficiency was established, as well as the connection of high-volume OL-HDF with the improved survival compared to the conventional HD was proved. For the first time in our country, ionic dialysis has been studied as a method for estimating the dialysis dose. The risk groups for OL-HDF have been assessed, and high-dose HD and OL-HDF have been shown to improve quality of life. Dr. Nenova suggests that ionic dialysis routine be implemented in practice and develops an algorithm for therapeutic behavior and choice of dialysis regimen, associated with a complex and individualized approach to achieving adequate dialysis, improved quality of life and survival. I highly appreciate the original diagnostic-therapeutic algorithm for dialysis treatment proposed by Dr. Nenova, which has significant practical value, as it is based on both the literature data and the analyzed results of the dissertation.

The abstract is written clearly, with good scientific style and illustration and accurately reflects the integrity of the dissertation. It has a slightly larger volume - over 80 pages, but this in no way reduces its qualities.

I do not know any evidence of plagiarism

Dr. Nenova provides 4 publications in connection with the dissertation.

Conclusion

Based on the above, I accept that the dissertation of Dr. Diana Dimcheva Nenova fully meets the requirements for the award of educational and scientific degree "Doctor" in higher education 7.0 Health and Sports., Professional 7.1 Medicine and specialty "Nephrology" and offer to the distinguished members of the Scientific Jury to vote in favor.

12.03.2022 **Prof. Dr. Boryana Deliyska, PhD, DSc**