

## OPINION

by Prof. Raina Robeva, Ph.D

regarding the dissertation work of Dr. STANISLAVA LYUBOMIROVA  
ILIEVA

for the acquisition of the educational and scientific degree "Doctor", scientific  
feld: Medicine 7.1. Doctoral program: "Internal Medicine",  
on the topic: "ROLE OF SOME PATHOGENETIC AND GENETIC  
FACTORS IN THE DEVELOPMENT OF DIABETIC NEPHROPATHY IN  
PATIENTS WITH TYPE 2 DIABETES

Dr. Ilieva completed her secondary education at "St. Sedmochiselnitsi" -  
the city of Sofia in 1991 and medicine at the Medical University of Sofia in  
1997. After graduation, he started working as a resident doctor at the First  
Nephrology Clinic SBALENG"Acad. Ivan Penchev", subsequently UMBAL  
"Tsaritsa Yoanna - ISUL", Sofia. Since 2007, he has been a doctor in the  
Nephrology Department of the Internal Medicine Clinic of Acibadem City  
Clinic UMBAL "Tokuda" EAD, Sofia. In 2004, he acquired a specialty in  
internal medicine, and in 2013 - in nephrology. He has recognized  
qualifications for conventional abdominal ultrasound (2015) and biopsy  
methods in nephrology (2017). She trained in 8 qualification courses in the  
period 2000-2010. She is fluent in written and spoken English and Russian.

The presented dissertation contains 103 pages and is illustrated with 33  
tables and 15 figures. The bibliography includes 148 sources, of which 15 are  
in Cyrillic and 133 are in Latin

The literature review is based on up-to-date information - most  
bibliographic sources are from recent years and provide an opportunity to  
assess the topicality of the topic and, after a thorough analysis, to formulate  
the purpose of the development - to establish a connection between specific  
clinical and laboratory biomarkers and the appearance of diabetic  
nephropathy in patients with type 2 diabetes mellitus, with a view to  
establishing predictors of its development and optimizing the diagnosis of  
diabetic kidney damage.

The topic defined in this way is modern, with theoretical and practical significance. To realize the goal, 6 specific, well-formulated tasks are specified.

The dissertation analyzed data concerning 91 patients with biopsy-proven glomerulopathies in the period January 2018 - February 2024 in UMBAL "Tokuda" aged between 22 and 76 years. Of these, 55 were men and 36 were women, 55 had type 2 diabetes and 36 were not diabetic. The type of renal damage was determined by histological and immunofluorescence examination of material from a puncture renal biopsy. Complex laboratory and instrumental studies and consultations were carried out, necessary to clarify the state of kidney function and that of the thyroid gland, proteinuria, early and late complications of diabetes. All patients were tested for the following MTHFR gene variants: A1289C and C677T. The carrier of the pathological alleles is considered to be clinically significant, respectively, 1289C and 677T in heterozygous or homozygous form.

Established modern statistical methods were used to assess the significance of the established facts.

The results are presented in three main chapters (histological findings; demographic and clinical indicators; laboratory biomarkers related to the manifestation of diabetic nephropathy) and are illustrated very well through tables and figures.

The discussion of the obtained results and their comparison with those of the world medical literature is very comprehensive, thorough and detailed. It once again shows the good knowledge of the problem.

Dr. Ilieva formulated 9 detailed conclusions, from which it is clear that in 64% of diabetics without diabetic nephropathy, tubulointerstitial and vascular-hypertensive changes are present, alone or in combination between them, and in 26.7% of diabetics with diabetic nephropathy have the same changes, which gives the doctoral student reasons to assume a connection between the mentioned changes and diabetes mellitus. The author considers male gender as a risk factor for diabetic nephropathy. Although formally, the appearance of diabetic nephropathy is not directly related to age and diabetes mellitus, age over 60 years and prescription over 10 years are associated with a higher incidence of some forms of chronic kidney disease. It is interesting

to conclude that arterial hypertension, poor glycemic control, obesity, hyperuricemia and dyslipidemia are not pathogenetic factors for diabetic nephropathy, but play a role in the progression of chronic kidney disease in diabetics. Observation that increased inflammatory and coagulation markers do not lead to a direct manifestation of diabetic nephropathy, but could be considered as possible predictors of chronic kidney disease in diabetics. Dr. Ilieva evaluated some genetic and biomarkers and found that the carrier of the pathological alleles of MTHFR-gene: 1289C and 677T, as well as increased levels of homocysteine and decreased serum folates have no predictive value for diabetic nephropathy. It is noteworthy that 16% of patients with type 2 diabetes have abnormalities in thyroid function and/or concomitant autoimmune thyroid disease.

Along with valuable theoretical conclusions, based on her research and her long experience, Dr. Ilieva formulated three significant recommendations for clinical practice.

Dr. Ilieva's dissertation has serious scientific and practical contributions. For the first time in Bulgaria, a generalized study and analysis of a complex of pathogenetic and genetic factors leading to the appearance of diabetic nephropathy has been carried out. Of great importance is the study of the relationship between diabetic nephropathy and the methylenetetrahydrofolate reductase gene (MTHFR-gene), variant A1289C, the established widespread carrier of mutant alleles of MTHFR-gene (1289C and 677T), mainly in heterozygous form among the studied subjects, which, in contrast to previous studies, did not show an association with the appearance of diabetic nephropathy. The role of puncture kidney biopsy as the only reliable diagnostic criterion for diabetic nephropathy, as well as for other, non-diabetic kidney damage in diabetics and for their differentiation. A predominance of tubulo-interstitial and vascular damage was established in diabetics, compared to non-diabetics. For the first time in Bulgaria, the relationship between diabetic nephropathy and thyroid dysfunction and a high frequency of thyroid disorders and autoimmune thyroid diseases was found in diabetics. The role of male gender as a risk factor for diabetic nephropathy was established.

Dr. Ilieva has the required number of publications in scientific journals and reports at scientific forums, related to the dissertation work.

In conclusion: All these data give me reasons to believe that the dissertation work is up-to-date and valuable, meeting all the requirements of the law on the development of the academic staff and the rules for its application, that is why Dr. Stanislava Lubomirova Ilieva can be awarded the scientific degree "doctor".



30.12.2024

Prof. Rayna Robeva