

STANDPOINT

by Assoc. Prof. Diana Todorova Gancheva-Tomova, MD, PhD

Clinic of Gastroenterology, St. Marina University Hospital of Varna

Department of Physiology and Pathophysiology, Medical University 'Prof. Paraskev Stoyanov'
of Varna

Concerning: the dissertation work for the acquisition of the educational and scientific degree of "doctor of philosophy" by **Pavlina Georgieva Boykova-Valcheva, MD**, within the doctoral programme of "Internal medicine", professional trend No 7.1 Medicine, field of higher education No 7 Public health and sports, and scientific speciality of "Gastroenterology"

Theme the dissertation work: „Screening, diagnosis and clinical evaluation of the patients with non-alcoholic fatty liver disease”

Adviser: Prof. Iskren Andreev Kotsev, MD, PhD, DSc

1. General presentation of the procedure

The standpoint is prepared in concordance with the requirements of the Statute-book for structure and activity and the Statute-book for development of the academic staff of the Medical University "Prof. Paraskev Stoyanov" of Varna and the Law for development of the academic staff in the Republic of Bulgaria.

The set of materials submitted on paper and electronic carrier is in concordance with the procedure for the acquisition of the educational and scientific degree of 'doctor of philosophy' in the Medical University "Prof. Paraskev Stoyanov" of Varna.

2. Brief biographical data

Pavlina Boykova-Valcheva, MD, was born in Varna in 1972. She graduates in the speciality of medicine from the Medical University of Varna in 1997. She starts her professional development as physician in 1998 in the Clinic of Gastroenterology at St. Marina University Hospital of Varna. In 2004, she acquires the speciality of "Internal medicine", and in 2001 - the speciality of "Gastroenterology". She starts her lecturer's activity as part-time assistant in internal medicine and since 2015, she is full-time assistant in gastroenterology in the Clinic of Gastroenterology. Pavlina Boykova-Valcheva, MD, builds-up further her knowledge and clinical skills. Consecutively, she acquires qualification for the performance of abdominal echography at level I, II, and III as well as competence for the performance of upper and lower endoscopy at level I and II. She participates in clinical trials for the treatment of viral hepatitis, inflammatory bowel diseases, and non-alcoholic fatty liver disease. She participates in research projects, too, related to hepatocellular carcinoma, colorectal cancer and biomarkers in non-alcoholic fatty liver disease. She is member of the Bulgarian Society of Gastroenterology, Gastrointestinal

Endoscopy and Abdominal Echography, EASL, and ECCO. She has command of English language.

3. Actuality, significance and practical directedness of the theme

The non-alcoholic fatty liver disease (NAFLD) is an essential health problem of global importance affecting approximately one million individuals worldwide. NAFLD is defined as the presence of hepatic steatosis in more than 5% of the hepatocytes established by means of imaging methods or histological examination among individuals making use of a small amount of alcohol or even no alcohol at all and in whom, a secondary reason for steatosis is excluded. It is subdivided into non-alcoholic steatosis and non-alcoholic steatohepatitis (NASH).

On a world scale, an increasing incidence rate of the metabolic syndrome is observed along with epidemic of obesity that supposes a tendency towards an increasing incidence rate of the NAFLD, too, which is a progressive disease related to a higher lethality rate. Liver biopsy is the gold standard for the diagnosis of NAFLD. Because of the known risks and difficulties, liver biopsy is not suitable for the evaluation of NAFLD incidence and prevalence rates among the general population. The necessity of development and application of the non-invasive methods for the assessment of disease activity and the degree of fibrosis which is a basic predictor for the aggressive course with a view to the evaluation of disease progression increases more and more. NAFLD poses a lot of unsolved questions in terms of the pathogenesis, diagnosis, and treatment. The approved scoring systems and serum biomarkers could contribute to the distinguishing of the steatosis from the inflammation and could be a comfortable tool in the screening and early diagnosis of this socially significant disease. These key issues are profoundly studied in the present dissertation.

4. Structure and contents of the dissertation work

The dissertation work is elaborated in 157 pages and illustrated by 50 figures and 58 tables. The reference list includes 172 sources, of which nine are in Cyrillic and 163 in Latin. The work is correctly structured and contains the following parts: literature survey, purpose, tasks, material and methods, results, discussion, conclusions, contributions, and bibliography.

The literature survey is comprehensive and complete. It is entirely focused on the theme. It covers all the aspects of the problem and logically deduces the grounds for the performance of this clinical elaboration. A profound analysis of a series of investigations on the theme has been performed. It demonstrates doctoral student's extraordinarily good scientific preparation and excellent awareness of the scientific problem as well as her skill to analyze and generalize literature data.

The purpose of the dissertation work is clearly formulated - investigation of the screening, diagnosis and clinical evaluation of NAFLD patients. The seven tasks are logically deduced and correspond to the achievement of the purpose.

Material and methods. In the observation, a total of 148 subjects are included who have been examined in the Clinic of Gastroenterology, St. Marina University Hospital of Varna, during the

period between October 2016 and May 2022, as well as patients from the Clinic of Endocrinology. The patients selected meet the correctly defined including and excluding criteria. A clinical examination of the patients has been performed. Standard laboratory examinations, abdominal echography, transient elastography for measurement of the degree of fibrosis and steatosis have been realized; scoring models for the non-invasive assessment of the steatosis and fibrosis have been calculated. In 61 persons, cytokeratin 18 (CK18) as serum marker for the hepatocytic apoptosis and indicator of a liver inflammation has been examined. Adequate and trustworthy statistical methods ensuring the reliability of the results and conclusions obtained have been made use of.

Results and discussion. The demographic distribution, the presence of metabolic syndrome with its manifestations such as arterial hypertension, type 2 diabetes mellitus, body weight, insulin resistance as well as the laboratory parameters related to NAFLD clinical characteristics have been analyzed in detail. Several correlations between the parameters examined such as demographic, laboratory, scores and instrumental have been analytically and critically presented. The author establishes that the increasing abdominal circumference being the main factor indicating the extent of visceral obesity possesses the greatest predictive value for the occurrence and the degree of severity of the steatosis as estimated by Controlled Attenuation Parameter (CAP). The performance of the elastography with CAP determination has been recommended for the more precise determination of the echographically established steatosis and the differentiation between the moderate and severe steatosis. The examination of liver stiffness is of extraordinary importance for patients' clinical evaluation and risk stratification as well as for the determination of the further behaviour. The results from the analysis indicate that F values of fibroscan increase in parallel with the rising fibrosis scores such as FIB-4 score, NAFLD fibrosis score and APRI. The juxtaposition between CAP and fibrosis stage establishes statistically significant differences, i.e. a concordance of a higher CAP value towards a higher F value. The results from the correlation analysis demonstrate the presence of a moderately strongly positive relation between the levels of triglycerides and CK18. This testifies to the increase of triglyceride value in parallel with CK18 values. This dependence proves the importance of the triglycerides in the inflammatory process of NAFLD patients and their role in the progressive course of the disease. A statistically significant relation between the increased CK18 values and the increased ASAT and ALAT ones has been established. The analysis carried out demonstrates that there exists a statistically significant relation between type 2 diabetes mellitus presence and liver steatosis. Dr. Boykova-Valcheva establishes a moderately strong relation between the degree of fibrosis and type 2 diabetes mellitus presence. In the work, it has been convincingly indicated that steatosis indexes represent an easy and exact method for steatosis prediction and they are comfortable for the selection of the patients for the ultrasound examination and necessity of consultation about life style change. They can be used for the prognostication of liver morbidity. In the group of patients examined, statistically significant differences between absent fibrosis and its mild forms towards F3 and F4 have been established. This proves that, similarly to literature data, fibrosis scores can with confidence be used as first-line risk stratification for the

exclusion of an advanced disease. The author presents an original algorithm for NAFLD screening and diagnosis.

The results obtained from the observation are richly illustrated by figures and tables. The doctoral student analyzes her own data within the juxtaposition with data available in the medical literature. Dr. Boykova-Valcheva handles freely and skillfully the scientific facts which demonstrates her excellent awareness of and competence in the problem elaborated.

The dissertation work terminates with **nine conclusions** which are in concordance with the results obtained and logically respond to the defined purpose and tasks.

I accept the eight contributions deduced six of which are of scientifically applicable and of confirmatory nature and two are of original nature. For the first time in Bulgaria, cytokeratin 18 as a marker of inflammation in patients with NAFLD has been examined.

5. Author's dissertation summary

The contents and quality of the author's dissertation summary completely conforms on the work elaborated.

6. Assessment of doctoral student's publications and personal contribution

In relation to the dissertation work, four full-text publications in Bulgarian language have been realized. There are several participations in scientific forums, too. Dr. Boykova-Valcheva is the first author of all the elaborations which indicates her leading role in the investigations performed and results obtained which is her own deed.

7. Critical remarks

I have no critical remarks concerning the scientific investigation performed and the materials submitted. I recommend an enlargement of the investigations within a future research work.

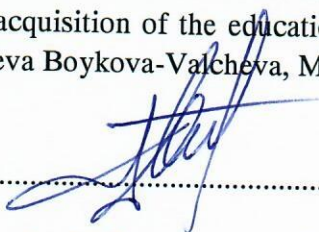
Conclusion

Dr. Pavlina Boykova-Valcheva's dissertation work is devoted to a topical and socially significant theme. It reflects profound knowledge, professional skills and opportunities for the investigation and analytical presentation of own results and adequate argumentation of the corresponding conclusions. A profound and value work with a precise statistical processing is presented. The dissertation work meets the requirements of the Law for development of the academic staff in the Republic of Bulgaria, the Statute-book for its application and the Statute-book for development of the academic staff of the Medical University "Prof. Paraskev Stoyanov" of Varna for the acquisition of the educational and scientific degree of "doctor of philosophy".

I convincingly give my positive evaluation and recommend to the honoured members of the Scientific jury to vote positively for the acquisition of the educational and scientific degree of “doctor of philosophy” by Pavlina Georgieva Boykova-Valcheva, MD.

September 12, 2022

City of Varna



.....

(Assoc. Prof. Diana Todorova Gancheva-Tomova, MD, PhD)