

REVIEW

on

dissertation work of the

Dr. Pavlina Georgieva Boykova-Valcheva

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Second Department of Internal Medicine

Management Board of Gastroenterology, Hepatology and Nutrition

on the topic:

"Screening, diagnosis and clinical evaluation of patients with non-alcoholic fatty liver disease"

to obtain the educational and scientific degree

"Doctor"

Reviewer:

Ass. Prof. Vladimir Andonov, M.D.

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I. Importance and relevance of the problem being developed.

The importance of the problem developed by the dissertant is determined by the fact that gradually and continuously globally the percentage of people with metabolic syndrome increases and, accordingly, the proven definite link with non-alcoholic fatty liver disease increases. As the incidence of overweight people as well as patients with type 2 diabetes mellitus increases, it is considered that the incidence of liver damage as a result of this disease will increase progressively and will take the leading place as the cause of liver transplantation.

From this point of view, this problem is particularly relevant and the study of questions on screening and diagnosis of at-risk patient groups is of particular importance and scientific and practical importance.

II. Technical description of the dissertation work.

The dissertation work of Dr. Pavlina Boykova-Valcheva is written in 157 pages. Structural distribution includes: Content and abbreviations used - 6 p., Introduction - 2 p., Literary overview - 45 p., Purpose and tasks - 1 p., Material and methods - 10 p., Results - 48 p., Discussion - 13 p., Algorithm for screening and diagnosis of the NAFLD - 3 p., Conclusion - 2 p., Conclusions - 1 p., Contributions - 1 p., Applications - 4 p., Bibliography - 15 p.

The proportions between the different sections are kept. A literary Bulgarian language with proper use of medical terminology was used. The dissertation work is illustrated with 58 tables and 50 figures.

III. Consideration of the dissertation.

1. Literary reference.

Represents about 29% of the dissertation work. It is composed of 8 sections.

The first section presents the definition of non-alcoholic fatty liver disease (NAFLD) and the two separate conditions to which it is subdivided - non-alcoholic liver steatosis /NALS/ and non-alcoholic steato-hepatitis /NASH/. The proposal to replace this name with "Metabolic-associated fatty liver disease" has been submitted.

The second section deals with the epidemiology of the NAFLD worldwide.

The third section presents the risk factors for the NAFLD - overweight, type 2 diabetes mellitus, dyslipidemia, age, gender and ethnicity, genetic factors and metabolic syndrome.

The fourth section examines in detail the pathogenesis of the NAFLD and the NASH.

The fifth section is dedicated to the diagnosis of NAFLD, NASH and fibrosis in the NAFLD. Consistently examined invasive methods - liver biopsy with histopathological examination and non-invasive methods - serum markers and imaging studies by ultrasound evaluation, computed tomography and magnetic resonance imaging in THE MSB. The so-called "controlled attenuation parameter" has been detailed. The non-invasive and invasive methods with NASH are then presented. This section ends with the presentation of diagnostic methods of fibrosis in the NAFLD.

The sixth section looks at the natural course, progression and prognosis of the NAFLD.

The seventh section is dedicated to screening in NAFLD, which is carried out by ultrasound examination, laboratory biochemical tests and non-invasive examination of steatosis and fibrosis by elastography.

The last 8th section deals with unresolved problems with the NAFLD in terms of the need for screening, diagnosis, follow-up and treatment of this disease.

In conclusion, as the dignity of the dissertation work, it can be pointed out that the development of the literary reference shows the author's personal opinion and critical attitude to the problems at issue, and that it contains the necessary arguments for the choice of purpose and the tasks of the dissertation work.

2. Purpose and tasks.

The goal is presented clearly and accurately - "To study screening, diagnosis and clinical evaluation in patients with NAFLD".

In order to fulfill this goal, Dr. Pavlina Boykova-Valcheva sets seven tasks.

This is also supported by the logical correlation between the literary review, the purpose and the tasks of the work.

3. Material and methods.

The dissertation included 148 patients examined in the Clinic of Gastroenterology at UMHAT St. Marina" - Varna. The study period is within 6 years - 2016-2022. All patients had NAFLD, 38 of them with NASH, 100 patients with steatosis and 10 patients with liver cirrhosis.

The inclusive and exclusionary criteria are described in detail. The methods used for examining patients are presented - anamnesis and physical examination, standard laboratory tests, examination of cytokeratin 18, abdominal ultrasound and transient elastic ography. Several recent systems have been used to assess steatosis, fibrosis and the presence of NASH.

The statistical analysis is done with a wide range of parametric methods, well selected and informative for assessing the diversity of the results obtained.

4. Own results.

They represent about 30% of the dissertation work. They are divided into several sections, respectively, of the assigned tasks.

The first section presents the demographic characteristic of the surveyed contingent. Of the 148 patients studied, 65 (44%) were male and 83 (56%) were women. Their average age is 55.68 /23-82 years/.

The second section examines the clinical characteristics of the study group. Consistently, the studied components of metabolic syndrome are presented. Proven type 2 DM was established in 70 patients /47.29%, 23 patients /15.55% had prediabetes and 55 patients /37.16% had no deviations in blood sugar values. Presence of hypertensive disease was found in 120 patients /81.08%. The body mass index results were then presented in 131 patients, with an average of 33.47 ± 6.74 , with values similar between male and female sex. Patients are stratified according to BMI values. The values of the abdominal circumference are presented as one of the most important anthropometric indicators for the presence of visceral obesity. In 126 patients, it averaged 113.21 ± 13.41 cm. /85-150 cm./ In all 52 men it is over 94 cm. and in all 74 women it is over 80cm, which are limit values. Metabolic syndrome was established in 131 patients /88.5%. In 61 patients, the homa index was calculated, with an average of 6.15 ± 8.43 . The results of the studies of AST, ALT, GTTP, AF and bilirubin were presented in the study group. The results of the study of triglycerides, HDL cholesterol and total cholesterol are presented. Increased triglycerides were found in 66 patients (47.48%),

decreased HDL cholesterol values in 40 patients (59.7) and elevated total cholesterol values in 66 patients (66.0%).

In all 148 patients, abdominal ultrasound was performed. In three patients /2.0%/ steatosis was not established, 28 patients /19.0%/ had mild steatosis, 51 patients /34.4%/ had moderate steatosis and 66 patients /44.6%/ had pronounced steatosis.

The third section presents the results of the determination of the controlled attenuation parameter. It was measured in 84 patients. The average value obtained is 304.39 ± 47.50 dB/m /211-400 dB/m/. Cut-off values for steatosis: S0 - ≤ 215 dB/m, S1 - up to 253 dB/m, S2 - up to 300 dB/m and S3 - over 300 dB/m.

The following section presents the results of the recently examined scales for the presence of steatosis - HIS, LAP, FLI and NAFLD liver fat score.

A statistical analysis of cap results and the relationship with the clinical characteristics of patients, the specified steatosis indices and comparison with the results for fibroscan fibrosis is presented. Correlation analysis shows a strong degree of association between CAP and BMI, as well as with waist circumference and weak association between CAP and hypertriglyceridemia. The regression pattern indicates the greatest pre-onset value and degree of severity of steatosis determined by CAP has the increase in abdominal circumference. A moderately strong statistical correlation between CAP and the two recent FLI and HSI indexes has been established.

The following section presents the results of determining the stage of fibrosis by measuring liver density with fibroscan. It was carried out in 91 patients. The average established value is 7.45 ± 5.03 kA /2.50-29.9 kA/. In this group of patients, missing or mild fibrosis was found in 66%, significant fibrosis in 16.4% and advanced fibrosis or cirrhosis at 17.6%.

FiB-4 results in 146 patients showed an average of 1.20 ± 0.73 /0.31-5.37/, of the NFS mean of 1.19 ± 1.41 /-4.49-2.58/, at APRI the mean was 0.34 ± 0.32 /0.07-2.29/, BARD score in 130 patients showed a lack of advanced fibrosis in 14.61% of them, FAST score was studied in 81 patients with an average value of 0.26 ± 0.23 /0-0.91/.

Correlation analysis shows a moderately strong relationship between liver density and BMI and abdominal circumference, as well as between the fibrosis stage and the presence of type 2 DM. Statistically significant differences were found between fibrous liver density and the increase in used scores, as well as between CAP values and fibrosis rate.

Cytokeratine 18 /SC 18/ has been studied in 61 patients with hepatic steatosis. Among them, normal SC18 values were established in 55 patients /90.17%/ and elevated in 6 patients /9.83%/ who received the diagnosis of steatohepatitis. A strong correlation relationship has been established between the values of SC 18 and those of triglycerides. The values of AST, ALT and GGT were higher in patients with steatohepatitis.

5. Discussion

The discussion of the results is thorough and competent. It shall consistently analyse and summarize the results obtained in terms of the clinical characteristics of the patients examined, the laboratory test data and the imaging methodologies used, the cytokeratin 18 study, the scales applied and, accordingly, the results obtained from the statistical methods used to determine the relevant correlation. The discussion of the results ends with a proposed algorithm for screening and diagnosis of NAFLD. This is one of the strongest strengths of the dissertation work - an algorithm of

behavior in patients with risk factors - metabolic syndrome, type 2 diabetes mellitus and excess weight, in which there is a high probability of the presence of NAFLD. In a very accessible way, the necessary steps for behavior in these patients are presented.

6. Conclusions.

The dissertation ends with the formulation of nine conclusions. Each of them is properly formulated and contains adequate information. These conclusions fully accurately and summarised reflect the data obtained and correspond to the objectives and tasks assigned.

7. Bibliography.

The bibliography of the dissertation work contains 172 titles. Of these, 9 are in Cyrillic and 163 in Latin. A significant part of the citations are from the last 5 years. All the authors cited have an immediate attitude to the problem studies. They are quoted correctly where necessary, according to the purpose and tasks of the dissertation.

IV. Scientific value of the dissertation.

The dissertation work of Dr. Pavlina Boykova-Valcheva is a prospective study dedicated to patients with NAFLD and NASH. Risk factors are defined and diagnostic methods are thoroughly examined - invasive and non-invasive, which are applied to them. With particular scientific and practical importance for the country is the created algorithm for screening and diagnosis in patients with NAFLD.

I fully accept the dissertation's contributions, which can be set out as follows:

1. Contributions of an original nature.

1.1. An algorithm for screening and diagnosis of patients with NAFLD has been proposed.

1.2. For the first time, a study of cytokeratin 18 was carried out as a marker of inflammation in a wide population of patients with NAFLD in Bulgaria.

2. Contributions of a scientifically applied and confirmatory nature.

2.1. A full clinical assessment of patients with NAFLD has been carried out, confirming the importance of metabolic risk factors for disease progression.

2.2. The role of anthropometric indicators in the clinical evaluation of patients with NAFLD has been confirmed.

2.3. The role of the echographic examination for diagnosis and screening of NAFLD in daily practice has been confirmed.

2.4. The importance of determining the degree of steatosis by CAP as a routine imaging method in the clinical evaluation of patients with NAFLD has been demonstrated.

2.5. The importance of measuring liver fibrosis by transient elastography has been confirmed and its use in routine practice for the staging of liver fibrosis in NAFLD and the identification of patients at high risk of progressive disease has been confirmed.

2.6. A comparative analysis has been carried out between non-invasive serum and imaging methods for staging of steatosis and fibrosis and their role in daily clinical practice has been clarified.

V. Publications:

In connection with the dissertation work, Dr. Pavlina Boykova-Valcheva has published a total of five scientific publications, all of which are first authors. She also has three participations in Bulgarian scientific conferences. This is quite enough to meet the requirements.

A summary of the dissertation's analysis shows that it is a large-scale long-standing work of a built gastroenterologist with deep clinical thinking, who has the ability to skillfully realize his ideas and perfectly connect his own results with the many diverse and often opposing data in literature.

Conclusion:

The presented work is the result of many years of studies by Dr. Pavlina Boykova-Valcheva. It contains original and scientifically applied contributions to the screening and diagnosis of patients with NAFLD. For this purpose, a large set of different methodologies is used. In importance, actuality and originality, the work possesses all the qualities of a dissertation for the acquisition of the educational and scientific degree "Doctor" and meets the conditions for this described in the Law on Development of Academic Staff, "Rules of Procedure for acquisition of scientific degrees and academic positions" at the Medical University "Prof. Dr. Paraskev Stoyanov" Varna.

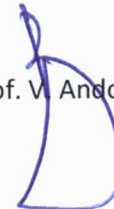
All these merits of the dissertation work give me the right to give a positive review to Dr. Pavlina Boykova-Valcheva for obtaining the educational and scientific degree "Doctor" and to call on the members of the esteemed scientific jury to also give a positive assessment.

19 September 2022

Plovdiv

Reviewer:

/Ass. Prof. V. Andonov, M.D./

A handwritten signature in blue ink, consisting of a stylized, cursive letter 'V' followed by a loop and a horizontal stroke at the bottom.