

STATEMENT

From Prof. Diana Vasileva Stefanova - Petrova, MD, PhD,

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Concerning: Dissertation on the topic: "Hepatic steatosis and non-alcoholic steatohepatitis - clinical evaluation and application of transient elastography (Fibroscan)" for obtaining the educational and scientific degree "Doctor" in higher education 7. Health and sports, professional field 7.1. Medicine, doctoral program "Internal Medicine"

Candidate: Dr. Rosalina Ivanova Balabanska, doctorant of independent training at the Clinic of Gastroenterology of Acibadem City Clinic UMBAL Tokuda EAD.

Scientific adviser: Prof. Simeon Stoynov, MD, PhD, Doctor of Medical Science

Based on Order № 269 of 09. 06. 2021 of the Executive Director of Acibadem City Clinic University Hospital Tokuda EAD, Sofia, pursuant to Article № 4 of the Law on the Development of Academic Staff, Article 31 of PPZRASRB, Article 29 of the Rules for the Development of the Academic Staff of Acibadem City Clinic UMBAL Tokuda EAD, Sofia and the decision of the Scientific Council (Protocol №37 of 20. 05. 2021)

Brief biographical data

Dr. Rosalina Ivanova Balabanska was born on November 6, 1963 in the city of Plovdiv. She graduated from the 35th language school in Sofia in 1981 with a gold medal. In 1987 she graduated medicine at the Medical University - Sofia with honors. She has worked and specialized successively in the District Hospital, Pernik, in the 5th City Hospital, Sofia and in the Military Medical Academy in the team of Prof. Grigor Mechkov, MD, PhD, Doctor of Medical Science, who built her as a polyvalent specialist - internist and gastroenterologist. Since 1996 she has been a specialist in internal medicine, and since 1999 she has been a specialist in gastroenterology and dietetics. From 2007 she works as gastroenterologist at Tokuda Hospital EAD, under the guidance of another leading gastroenterologist in the country: Prof. Simeon Stoynov, MD, PhD, Doctor of Medical Science. She has specialized in the Netherlands, Spain and Italy. She studied transient elastography in Barcelona and Paris. She is a member of the Bulgarian Medical Union, the Society of Gastroenterology, the European Association for the Study of the Liver, the American Association for the Study of the Liver, the International Gastro-Surgical Club, the European Federation of Ultrasound in Medicine, the World Federation of Ultrasound in Medicine, the Bulgarian Association of Ultrasound in Medicine. Fluent in Russian, Italian and English languages.

Data on the topic of the dissertation

Scientific significance of the chosen topic and innovations.

Non-alcoholic steatosis liver disease (NAFLD) is a socially significant disease affecting 25% -30% of the world's population. Represents the hepatic manifestation of the metabolic syndrome, including central obesity, insulin resistance, hyperlipidemia, hyperglycemia and hypertension. NAFLD is found in 70% of overweight or obese people, in 90% of those with morbid obesity, in 70% of diabetics. Twenty percent of patients with nonalcoholic steatohepatitis (NASH) develop liver cirrhosis. Advanced fibrosis is crucial for the prognosis of liver disease. Over time, 14% of patients with cirrhosis develop hepatocellular carcinoma (HCC).

Criteria for assessing the severity of steatosis and fibrosis in NAFLD still include histological analysis of liver tissue. Invasiveness, complications of liver biopsy and variations in the interpretation of the histological result by various experts motivate the introduction of non-invasive methods for the assessment of steatosis and fibrosis in patients with NAFLD.

The transient elastography of the French company Echosens (VCTE™, FibroScan®; Echosens, Paris), known as FibroScan, is a non-invasive method for quantifying liver density corresponding to fibrosis and allowing simultaneous measurement of steatosis using a controlled Attenuated parameter). In 2009, Echosens received approval in Canada and the United States and was approved by the FDA in April 2013 as a non-invasive method for assessing liver fibrosis.

The ability to rapidly assess the extent of liver fibrosis and the good reproducibility of the study are important for initiating treatment, monitoring, prognosis and risk of complications in patients with NAFLD.

Structure and characteristics of the dissertation

The dissertation is presented on 145 pages, in a form and volume in accordance with the generally accepted requirements and corresponding to the specific requirements of the hospital and contains: title page (1 page), content (2 pages), abbreviations used in the text (2 pages), introduction (3 pages), literature review (44 pages), research methodology (goal and tasks; material and methods - 11 pages), own results (53 pages), discussion of the results (15 pages), conclusions and recommendations (2 pages), contributions to the dissertation (2 pages), bibliography (8 pages), publications related to the dissertation (1 page), dedication to the team that assisted in the preparation of the dissertation (1p.). The structure of the dissertation is well balanced. The text is perfectly illustrated with 59 figures and 29 tables. The bibliography includes 133 literary sources, 11 of which are in Bulgarian; 73 of the literature sources were published after 2015.

The literature review reflects current understandings of nonalcoholic steatosis of the liver, including the shift of histological evaluation from new non-invasive diagnostic methods to assess liver status. It is stated that the term MAFLD - [metabolic (dysfunction) associated fatty liver disease] more accurately reflects the pathogenesis of liver damage, and the criteria for diagnosis are based on the presence of hepatic steatosis and one of the three indicators - overweight or obesity, diabetes. type 2 and metabolic dysregulation.

The aim of the dissertation is to analyze non-invasive methods for assessment of hepatic steatosis and non-alcoholic steatohepatitis and to develop a clinical algorithm for liver examination in patients with metabolic syndrome, obesity, diabetes mellitus or elevated liver enzymes. Nine tasks have been formed that meet the goal of the study.

The study included 170 patients with metabolic syndrome and non-alcoholic fatty liver disease at various stages - from simple steatosis to non-alcoholic steatohepatitis with varying degrees of fibrosis to the stage of initial cirrhosis. A comprehensive assessment of the condition of the liver was performed, which includes: anamnestic data with subjective symptoms, concomitant diseases, anthropometric indicators (height, weight, BMI, waist circumference), laboratory and imaging studies. Blood counts were analyzed with platelet count analysis; liver enzymes - AST, ALT, GGT, AF; lipid profile; uric acid; blood sugar; HbA1c; serum iron; ferritin; transferrin; highly sensitive C-reactive protein. FAST score (Fibroscan-AST); NAFLD Fibrosis score; FIB-4; and HOMA-IR were calculated

All patients underwent a standard ultrasound examination of the abdominal organs with an ultrasound machine General electric Pro 7 and Logic 5. US-FLI (Ultrasound fatty liver index) and MFS (Modified fatty score) were used, as well as an assessment of inhomogeneous spotted structure with of focal fatty changes (focal fatty changes) and areas devoid of steatosis (focal sparing). A Zardi score (including ultrasound attenuation, focal sparing, and increased longitudinal spleen size) was determined to differentiate simple steatosis from NASH.

All patients were examined with Fibroscan 502 Touch, from Ehosens, France, device number F 60271, with two probes - M and XL - probe M or XL for transient elastography with simultaneous measurement of density and hepatic steatosis.

135 patients underwent liver biopsy for histological evaluation of steatosis, inflammatory activity and fibrosis using the SAF scoring system, Metavir and Kleiner fibrosis evaluation. The evaluation was carried out including by leading external international experts

Liver Multiscan was performed in 20 patients - magnetic resonance spectroscopy with determination of the amount of fat in the liver, iron content, LIF score was determined for the degree of progression of liver damage.

The assessment of steatosis and fibrosis; the progression of liver damage and the development of diagnostic models for non-invasive assessment of hepatic steatosis and fibrosis was performed using statistical programs: STATISTICA (version 13.0, StatSoft Inc., Copyright 1991-2015) and STATA (version 16.1, StataCorp LLC, Copyright 1985-2019). Descriptive statistics, nonparametric analysis, correlation analyzes, LASSO method were used.

The results of the study show a direct correlation between body weight, BMI and waist circumference with the degree of fat accumulation in the liver. A statistically significant correlation was found between Fibroscan and histological examination of hepatic steatosis and fibrosis. Own cut offs (limit values) have been developed to stage hepatic steatosis based on Fibroscan measurements with CAP. With non-invasive methods - Fibroscan, ultrasound examination, serum markers, the cases of simple steatosis are distinguished from those with non-alcoholic steatohepatitis. An easily performed FAST score was applied in clinical practice (based on the results of Fibroscan and AST), which successfully distinguished patients at increased risk of progression and complications from NASH. FIB-4

and transient elastography have been found to be sufficient markers for non-invasive determination of the severity of liver fibrosis

The 9 conclusions made correspond to the obtained results. Six contributions with confirmatory character and 3 with original character have been formed.

Dr. Balabanska's research shows that transient elastography should be established as a standard in everyday practice for non-invasive detection and quantification of hepatic steatosis and fibrosis.

Transient elastography should displace the liver biopsy in a large percentage of cases and is suitable as a non-invasive method for periodic monitoring of the condition of the liver during the therapeutic response.

Based on the results of the study, the following original contributions were made: algorithms were developed for non-invasive assessment of the liver condition in patients with metabolic syndrome, diabetes mellitus and obesity; A model for testing and non-invasive assessment of the condition of the liver in patients with impaired liver enzymes has been developed. An important original contribution of the study is the creation of own cut off (limit values) for staging of hepatic steatosis based on Fibroscan measurement with CAP.

The dissertation of Dr. Rosalina Balabanska is her original development, the result of her extensive clinical experience, her many years of work with high-class ultrasound machines, significant experience in conducting invasive liver examinations, unique experience in the assessment of steatosis and fibrosis with Fibroscan, and excellent knowledge of modern aspects of the problem. Six publications and participations in scientific forums related to the topic of the dissertation are presented.

Conclusions.

The dissertation of Dr. Balabanska is original, with great scientific significance and important scientific and practical contributions to clinical practice, associated with a radical change in diagnostic behavior in patients with metabolic-associated fatty liver disease. The study meets all the requirements of the Law for the development of the academic staff in the Republic of Bulgaria (ZRASRB) and corresponds to the specific requirements of the Regulations for the development of the academic staff of Acibadem City Clinic UMBAL Tokuda EAD, Sofia.

I confidently give my positive assessment and propose the honorable scientific jury to award the educational and scientific degree 'Doctor' in the field of higher education 7. Health and sports, professional field 7.1. Medicine, doctoral program "Internal Medicine" to Dr. Rosalina Balabanska.

29 June 2021


(Prof. Diana Vasileva Stefanova-Petrova)