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“Biomarkers for assessment of non-alcoholic fatty liver disease”

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Non-alcoholic fatty liver disease (NAFLD) is a major public health problem afflicting approximately one billion individuals worldwide. NAFLD is characterized by excessive hepatic fat accumulation, associated with insulin resistance (IR), and defined by the presence of steatosis in >5% of hepatocytes according to histological analysis or by a magnetic resonance imaging (MRI). Exclusion of secondary causes of steatosis, including none or mild daily alcohol consumption is required. NAFLD presents many unsolved questions and problems afflicted pathogenesis and clinical aspect of diagnosis, surveillance, treatment and screening. The prevalence of NAFLD is increasing worldwide parallel to the increasing of prevalence of Metabolic Syndrome and its components including Diabetes Mellitus and Obesity. NAFLD includes two pathologically distinct conditions with different prognoses: non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH); the latter covers a wide spectrum of disease severity, including fibrosis, cirrhosis and hepatocellular carcinoma (HCC). NAFL is a non-progressive form of NAFLD, which confers limited or no risk of progression to cirrhosis and liver-related mortality, and NASH is the progressive form of NAFLD, which confers substantial risk of progression to fibrosis, cirrhosis, hepatocellular carcinoma and liver-related mortality. Predictors of presence of progressive form of the disease are the advanced stages of fibrosis and presence of inflammation. Liver biopsy is considered to be the gold standard for assessment of liver disease severity in patients with NAFLD – fibrosis and inflammation. It is invasive and is associated with adverse effects, and has higher inter-observer variability. Liver biopsy is impractical because of large number of individuals who have NAFLD and is not appropriate for screening. Therefore, non-invasive biomarkers with high specificity and sensitivity to assess disease severity in NAFLD are needed. In addition, these biomarkers can be used not just to identify patients with high risk of unfavorable course of the disease but also to be used to monitor patients and therapeutic response. There is no algorithm for screening the patient with NAFLD. There are current unmet needs in the field how to surveillance patients with NAFLD and how to stratify risk groups. There is no sufficient clinical experience how biomarkers can be used to identify the degree of inflammation, fibrosis and steatosis in clinical practice.

The aim of our study is to investigate the role of non-invasive biomarkers to grade liver fat, inflammation and liver fibrosis, and to assess presence of NAFLD. To implement this aim we address the following questions:

1. To refine the role of the level of the serum cytokeratin 18, as a marker of inflammation for screening, diagnosis and monitoring of patient with NAFLD.

2. To investigate predictive and diagnostic value of non-invasive scores for evaluation of steatosis, inflammation and fibrosis.
3. To estimate combine approach of non-invasive imaging modalities and clinical, biochemical, metabolic and lipid biomarkers to grade liver fat and liver fibrosis, and to assess presence of NASH.

We plan to evaluate the level of serum keratin 18 (K18) in 160 patients, with normal or elevated transaminase activity and with presence of metabolic syndrome or Diabetes mellitus and suspected NAFLD. Methods of our study include – medical history, with exclusion of alcohol consumption, Anthropometric variables (weight, BMI, waist circumference), laboratory exams - liver function tests, full blood count, serum lipids, fasting glucose, serum cytokeratin 18, HOMA – index, and abdominal ultrasonography. We expect to establish combine approach of non-invasive imaging modalities and clinical, biochemical, metabolic and lipid biomarkers to grade liver fat, inflammation and liver fibrosis in patients with NAFLD. Thus, we will stratify group of patients with NAFLD and risk of rapid progression of the disease according to non-invasive biomarkers. We expect the results of our study to increase the knowledge about unsolved problems with screening, diagnosis and clinical assessment of patients with NAFLD and to clarify the role of cytokeratin 18 and non-invasive score systems in estimation of steatosis, inflammation and fibrosis in patients with NAFLD among Bulgarian population. We will study changes of serum level of cytokeratin 18, as a non-invasive marker of inflammation in patients with liver steatosis and will rule in its use in differentiation of simple steatosis from steatohepatitis, as a progressive form of NAFLD. In a long-term plan positive results of our study could be warrant to include this biomarker as a screening or diagnostic tool to detect the progressive form of NAFLD, termed non-alcoholic steatohepatitis. Thus, realization of our study could be a basis for developing of a screening and monitoring program for patients with outspread liver steatosis.