Hepatobiliary & Pancreatic Diseases International 18 (2019) 1–3

Contents lists available at ScienceDirect

Hepatobiliary & Pancreatic Diseases International

journal homepage: www.elsevier.com/locate/hbpd

Editorial

Noninvasive diagnosis of nonalcoholic steatohepatitis: Emerging approaches

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Nonalcoholic steatohepatitis (NASH), a severe type of nonalcoholic fatty liver disease (NAFLD), progresses toward liver fibrosis/cirrhosis, liver failure, and furthermore, hepatocellular carcinoma (HCC) [1]. The pathological manifestations are hepatocyte steatosis (>5%), lobular inflammation, and ballooning degeneration, with or without fibrogenesis [2]. NAFLD/NASH results from sedentary life style, western diet, and obesity. We have witnessed the conversion of spectrum of chronic liver diseases from viral hepatitis as the leading cause to NAFLD/NASH worldwide [3]. Diagnosis of NASH is therefore of great importance for the clinical management, evaluation, and follow-up.

Currently, it is well recognized that liver biopsy is the "gold" standard for NASH diagnosis [4–8]. Its clinical application, however, remains limited for the sake of cost-effectiveness, sampling error, and procedure-related complications [9]. Therefore, there has recently been growing interest in the development of noninvasive diagnostic methods to identify NAFLD in patients, especially those with NASH. Given the complicated pathophysiological mechanisms and dynamic activities underlying NASH, both serological and physical biomarkers are employed for the assessment of metabolic abnormality, inflammation, apoptosis, and fibrogenesis.

Hepatocyte death with significant increase in cytokeratin 18 (CK-18) release reflects the critical hallmark of NASH. Thus serum/plasma CK-18 and its fragments, M30 and M65 associated with apoptosis and total cell death respectively, have been extensively investigated for NASH diagnosis. A meta-analysis of 11 relevant studies convinces the value of CK-18 in predicting NASH and monitoring post-treatment histological response [10,11]. But its moderate accuracy (pooled sensitivity: 66%; specificity: 82%) and failure in differentiating NASH from simple steatosis disqualify CK-18 as an independent predictor of NASH. Combinations of CK-18 and apoptosis-mediating surface antigen FAS (sFAS), fibroblast growth factor 21 (FGF21), cathepsin D (CTSD), and controlled attenuation parameter (CAP) respectively [12], is suggested to promote the diagnostic utility.

A number of inflammatory cytokines and mediators, such as C-reactive protein (CRP), high-sensitivity CRP (hsCRP), CC-chemokine ligand-2 (CCL2)/monocyte chemoattractant protein-1 (MCP-1), CXC-chemokine 10 (CXCL10), interleukin-1 receptor antagonist protein (IL-1RA), soluble IL-1R type 1 (IL-1R1), IL-6, IL-8, tumor necrosis factor-α (TNF-α), plasminogen activator inhibitor 1 (PAI1), activated PAI1 (aPAI1), and pentraxin-3, have also been tested as serum biomarkers of NASH. In spite of their association with hepatic inflammation, concomitant systemic inflammatory state in NASH patients downgrades the diagnostic performance. In results, stand-alone measurement of these biomarkers is probably of little value in the clinical practice.

Study on omics highlights another kind of NASH-related diagnostic markers. The abnormal products [e.g., soluble receptor for advanced glycation endproducts (sRAGE), fucosylated haptoglobin (Fuc-Hpt)] and index [homeostasis model assessment of insulin resistance (HOMA-IR)] of glycometabolism demonstrate the risk of ballooning, fibrosis, and NASH. Moreover, circulating products of arachidonic acid metabolism [11-hydroxyeicosatetraenoic acid (11-HETE)] and oxidative stress [9-hydroxyoctadecadienoic acid (9-HODE), 13-HODE, 9-oxo-octadecadienoic acids (9-oxo-ODE), and 13-oxo-ODE] are recognized to be biomarkers of NASH. oxNASH score with the combination of 13-HODE/linoleic acid ratio, age, body mass index (BMI), and aspartate aminotransferase (AST) improves the diagnostic accuracy to a reasonable level. Furthermore, serum prolidase enzyme activity (SPEA) and plasma CTSD level reflect the potential predictors of steatohepatitis and/or liver fibrosis.

With the exception of CK-18, measurement of individual biomarker is hardly able to provide solid and consistent results in the NASH diagnosis. Biomarker panels are then subjected to establishment and validation as an alternative. Diagnostic utility has resultantly been proposed in small groups by panels comprising clinical features (e.g., age, sex, height, weight, and BMI), serological indexes [e.g., Gamma-glutamyl transferase (GGT), alanine aminotransferase (ALT), AST, total bilirubin, triglyceride, cholesterol, apolipoprotein AI, CK-18, adiponectin, ferritin, Fuc-Hpt, macroglobulin-2 binding protein, resistin, soluble Fas, and Fas ligand], and components of metabolic syndrome (e.g., type 2 diabetes mellitus, hypertension, and insulin resistance), including NASH test [13], NASH diagnostics [14], apoptosis panel [15], Gholam

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https://doi.org/10.1016/j.hbpd.2018.12.010

model [16], hypertension, ALT, and insulin resistance (HAIR) [17], Nice model [18], and Palekar score [19]. In spite of their difference in panel, NASH test [formula using α2 macroglobulin (α2-MG), haptoglobin, apolipoprotein AI, total bilirubin, GGT, ALT, AST, triglycerides, cholesterol, age, sex, height, and weight), NASH diagnostics (formula using CK-18 M30, CK-18 M65, adiponectin, and resistin), and apoptosis panel (formula using CK-18 fragments, soluble Fas, and Fas ligand) among these ones obtain external validation.

Liver fibrosis acts as the key histopathological characteristics of NASH with an outcome of cirrhosis [1]. In contrast to the undetermined noninvasive methodology of NASH diagnosis, there are relative substantial proofs for the recognition of NASH-related fibrosis. Noninvasive scores [NAFLD fibrosis score (NFS), fibrosis-4 (FIB-4), fatty liver index (FLI), index of NASH (ION), BMI, AST/ALT ratio, diabetes (BARD), AST/ALT ratio (AAR), AST to platelet ratio index (APRI), and BMI, age, ALT, and triglyceride (BAAT)] have now been feasible for fibrosis screening on the basis of clinical data (e.g., age, BMI, waist circumference, waist-to-hip ratio, fasting glucose, AST, ALT, AST/ALT ratio, platelet, albumin, and triglyceride) [20]. Some other tools [FibroTest, enhanced liver fibrosis (ELF) panel, Hepascore, Fibrometer, and Hepascore] combining clinical data and serum biomarkers [e.g., α2-MG, hyaluronic acid (HA), tissue inhibitor matrix metalloproteinase 1 (TIMP-1), aminoterminal peptide of pro-collagen 3 (P3NP), and ferritin] bring about better sensitivity and specificity [20]. Most of these methods show well performance in the exclusion of advanced liver fibrosis/cirrhosis. But innovations are still valuable for the better accuracy of fibrosis diagnosing.

Apart from the algorithms with indirect correlation to fibrotic property, liver stiffness measurement (LSM) by imaging techniques offers an opportunity to highlight the fibrosis-related physical characteristics of liver parenchyma [21]. Transient elastography (TE), magnetic resonance elastography (MRE), and shear wave elastography among these ones represent the major kinds of validated modalities in clinical application [20–23]. They demonstrate moderate to high accuracy in the detection of liver fibrosis or cirrhosis [20–24]. Combining LSM and FibroMeter (FibroMeter vibration-controlled transient elastography algorithm) may facilitate the differentiation of F3–F4 fibrosis from F0–F2 fibrosis. Nevertheless, problems of cost and availability still preclude LSM from widespread application.

To conclude, liver biopsy is the gold standard in diagnosing NASH at present. Noninvasive diagnostic approaches relying on both serum and imaging biomarkers of NASH are now undergoing fruitful development, yet their reliability remains to be validated by large-group, multi-center studies. In NASH patients with advanced fibrosis, the American Association for the Study of Liver Diseases (AASLD) guideline recommends FIB-4, NFS, TE and MRE as the first-lines of noninvasive diagnosis. Combined use of serological tests and imaging tools has also been suggested by the Asia Pacific Association for the Study of the Liver (APASL) guideline for an aim of gathering comprehensive information of disease progress without invasive procedure.

Contributors

FJG proposed the study. PQ wrote the paper under the supervision of FJG. Both authors contributed to the design and interpretation of the study and to further drafts. FJG is the guarantor.

Funding

This work was supported by grants from the National Key Research and Development Plan "Precision Medicine Research" (2017YFC0908903); National Natural Science Foundation of China (81070346, 81270492, 81470859, 81270491, and 81470840); State Key Development Program for Basic Research of China (2012CB517501); and Shanghai Leading Talents (019).

Ethical approval

Not needed.

Competing interest

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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Received 14 September 2018
Accepted 20 December 2018
Available online 28 December 2018