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EDITORIAL

Metabolomics in liver diseases: A novel alternative for liver biopsy?

Yasuo Tanaka

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Abstract

Hepatitis C virus (HCV) remains a significant public health problem as it can cause acute and chronic hepatitis. Chronic HCV infection is a major cause of liver fibrosis, and evaluation of liver fibrosis is essential because the prognosis of patients with chronic HCV infection is closely related to the stage of fibrosis. Liver fibrosis is traditionally evaluated based on pathological analysis of biopsy specimens, which is considered the gold standard. Nevertheless, liver biopsy is invasive and susceptible to sampling error and inter- and intraobserver variation in pathological interpretation; it is also costly. Therefore, noninvasive diagnostic investigations have been developed, including the use of fibrotic markers, scoring systems based on routine blood tests, and transient elastography with magnetic resonance imaging or ultrasonography. Recently, metabolomics, an emerging technology, has been used to detect the fibrosis stage. In this editorial, I comment on the article titled "Metabolomics in chronic hepatitis C: Decoding fibrosis grading and underlying pathways" by Ferrasi *et al* published in the recent issue of the *World Journal of Hepatology*. I discuss previous studies on the use of metabolome analysis for the diagnosis of HCV-related liver fibrosis and the potential development of biopsy-free diagnostic techniques.

Key Words: Metabolomics; Hepatitis C virus; Liver fibrosis; Liver cirrhosis; Serum biomarker

Core Tip: Metabolomics, a rapidly emerging technology, offers a non-invasive alternative to conventional blood tests and transient elastography with magnetic resonance imaging or ultrasonography for fibrosis staging. I consider the article titled "Metabolomics in chronic hepatitis C: Decoding fibrosis grading and underlying pathways" by Ferrasi *et al,* published in the latest issue of the *World J Hepatol*. I review prior studies concerning the role of metabolomics in diagnosing hepatitis C virus-related liver fibrosis and establishing a foundation for non-invasive diagnostic techniques.

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INTRODUCTION

Hepatitis C virus (HCV) remains a significant public health concern as it can lead to acute and chronic hepatitis. The development of direct-acting antiviral therapy has substantially improved the rate of sustained virologic response and has generated interest in the goal of HCV elimination. In 2016, the World Health Organization called for the elimination of HCV infection by the year 2030[1].

Chronic HCV infection is a major cause of liver fibrosis, which is characterized by the formation of fibrous scar tissue resulting from the accumulation of extracellular matrix proteins, primarily cross-linked collagens. This tissue replaces injured liver tissue[2] and can lead to liver cirrhosis, defined as the histological development of regenerative nodules surrounded by fibrous bands. In turn, liver cirrhosis can lead to portal hypertension and end-stage liver disease[3].

Assessing the stage of liver fibrosis is essential because the prognosis of patients with liver fibrosis is closely linked to the stage of fibrosis, with those having advanced fibrosis being at higher risk for experiencing liver disease-related clinical events, such as hepatic failure and hepatocellular carcinoma[4]. Physicians require accurate methods to evaluate the progression of liver fibrosis to guide patient management and predict long-term outcomes.

Liver biopsy has traditionally been considered the gold-standard investigation for evaluating such disease. Nevertheless, it has several limitations. It is an invasive procedure that is associated with potential sampling error, inter- and intraobserver variability in pathological interpretation, and high cost[5]. To address these limitations, noninvasive diagnostic investigations have been developed.

Direct fibrotic markers, such as hyaluronic acid[6] and tissue inhibitor of metalloproteinase-1[7], and scoring systems based on routine blood tests, such as the Fibrosis-4 Index based on four factors[8] and the Aspartate Transaminase to Platelet Ratio Index[9], are cost-effective and easily accessible alternatives to liver biopsy.

Transient elastography using magnetic resonance imaging[10] or ultrasonography[11] is another option. However, their availability is limited due to the high cost of equipment.

Recently, novel diagnostic investigations based on emerging technologies, such as metabolomics, have been developed. Metabolomics involves comprehensive profiling and comparison of metabolites in biological samples, including plasma, serum, urine, and cell and tissue extracts[12]. The collected samples undergo pretreatment, and metabolites are measured using nuclear magnetic resonance or mass spectrometry (MS) combined with liquid chromatography (LC-MS), gas chromatography (GC-MS), or electrospray ionization (ESI-MS). Metabolomics offers a unique advantage because it represents the current physiological "state" of an individual, allowing exploration of factors that influence the human phenotype. The data obtained from these analyses are analyzed to determine the signatures of cellular biochemical activity. This approach is relatively novel; therefore, few studies have evaluated the associations between the metabolome and HCV-related liver disease and even fewer related to HCV-related liver fibrosis (Table 1).

Fitian *et al*[13] performed a comprehensive analysis of the global serum metabolomes of 30 patients with hepatocellular carcinoma, 27 patients with HCV-related cirrhosis, and 30 healthy controls using GC-MS and ultrahigh-performance LC-MS-MS. They found a strong association between elevated levels of bile acids (such as taurochenodeoxycholate and taurocholate) and dicarboxylic acids (such as azelate, undecanedioate, and sebacate) and cirrhosis.

Sarfaraz *et al*[14] evaluated noninvasive biomarkers for liver fibrosis, steatosis, and inflammation in patients with chronic HCV, and found that the upregulated metabolites in severe fibrosis included 1,7 dimethylxanthine, caffeine, methylsuccinate tyrosine, histidine, 2-hydroxyisovalerate, propionate, methionine, methylguanidine, 2-oxoisocaproate, and formate. Conversely, the downregulated metabolites included N-acetylaspartate, creatinine, urea, threonine, glycine, methylhistidine, adenosine, N-acetylglycine, glutamine, and asparagine.

Cano *et al*[15] examined serum metabolomics and fibrosis progression in HCV patients 1 year after transplantation. Patients at fibrosis stages F0–F1 were categorized as slow "fibrosers," whereas those at stages F2–F4 were categorized as rapid fibrosers. The investigators found that the levels of glycocholic acid, taurochenodeoxycholic acid, and sphingomyelins (SMs) (d18:0/18:0) were increased in rapid fibrosers. Conversely, the ratio of branched-chain amino acids to aromatic amino acids was reduced in rapid fibrosers. Furthermore, they developed a model to discriminate between rapid and slow fibrosers using an algorithm consisting of four lipid metabolites: two SMs [SM (d18:2/16:0) and SM (38:1)] and two phosphatidylcholines (PCs) [PC (16:0/16:0) and PC (16:0/18:0)]. This model accurately classifies rapid and slow fibrosers after transplantation.

Gaggini *et al*[16] analyzed the sera collected at baseline from 75 HCV patients using GC-MS and LC-MS, and revealed that low ceramide (18:1/22:0), ceramide (18:1/24:0), and diacylglycerol (42:6) levels and a high phosphocholine (40:6)

Table 1 Metabolites as the fibrotic biomarkers of hepatitis C

Ref.	Analyzed cases	Analytical method	Increased metabolites in fibrosis progression	Decreased metabolites in fibrosis progression
Fitian *et al*[13], 2014	Cirrhosis *vs* healthy non-diabetic controls	GC/MS, UPLC/MS-MS	Bile acids (taurochenodeoxycholate, taurocholate, *etc.*), dicarboxylic acids (azelate, undecanedioate, sebacate, *etc.*)	
Sarfaraz *et al*[14], 2016	F3- 4 *vs* F0- 2 (Metavir)	^{1}H-NMR	1,7 dimethylxanthine, caffeine, methylsuccinate, tyrosine, histidine, 2-hydroxyisovalerate, propionate, methionine, methylguanidine, 2-oxoisocaproate, formate	N-acetylaspartate, creatinine, urea, threonine, glycine, methylhistidine, adenosine, N-acetylglycine, glutamine, asparagine
Cano *et al*[15], 2017	F2- 4 *vs* F0- 1 (Metavir)	UPLC/MS	Glycocholic acid, taurochenodeoxycholic acid, sphingomyelins (d18:0/18:0)	BCAA/ArAA
Gaggini *et al*[16], 2019	F5- 6 *vs* F3- 4 *vs* F1- 2 (Ishak score)	UPLC/QTOF-MS	Phosphocholine (40:6)	Ceramides (18:1/22:0), (18:1/24:0), diacylglycerol (42:6)
Shanmuganathan *et al*[17], 2021	F2- 4 *vs* F0- 1 (Metavir)	MSI-CE-MS, ^{1}H-NMR	Choline, histidine	
Khalil *et al*[18], 2022	Cirrhosis *vs* non-cirrhosis *vs* healthy controls	UPLC/MS	Taurocholic acid, glycholic acid, glycoursodeoxy-cholic acid, taurochenodeoxycholic acid, glycochen-odeoxycholic acid	
Ferrasi *et al*[19], 2023	F1 *vs* F2 *vs* F3 *vs* F4 (Metavir)	ESI/MS		

^{1}H-NMR: Proton nuclear magnetic resonance. GC: Gas chromatography; MS: Mass spectrometry; UPLC: Ultrahigh-performance liquid chromatography; QTOF: Quadrupole time-of-flight; MSI-CE: Multisegment injection-capillary electrophoresis; ESI: Electrospray ionization; BCAA/ArAA: The ratio of branched-chain amino acids (BCAA) to aromatic amino acids (ArAA).

level were associated with greater fibrosis.

Shanmuganathan *et al*[17] demonstrated that serum levels of choline and histidine were consistently higher in HCV patients with late-stage (F2–F4) liver fibrosis compared to early-stage (F0–F1) fibrosis.

Khalil *et al*[18] found that changes in serum levels of several bile acids exhibit a linear trend across hepatocellular carcinoma, cirrhosis, non-cirrhosis, and healthy controls, potentially reflecting disease progression. Furthermore, receiver operating characteristic (ROC) curve analysis identified five conjugated acids (taurocholic acid, glycocholic acid, glycoursodeoxycholic acid, taurochenodeoxycholic acid, and glycochenodeoxycholic acid) that effectively distinguished hepatocellular carcinoma (HCC) from patients with non-cirrhotic livers.

Ferrasi *et al*[19] provided new insights into the pathogenesis and progression of liver fibrosis in HCV infection through metabolite analyses. They analyzed sera from 46 HCV patients and 50 healthy controls using ESI-MS. ESI is a soft-ionization technique that limits ion excitation, resulting in minimal or no analyte fragmentation[20]. This ionization technique has revolutionized the analysis of large biomolecules, such as the detection of coenzyme A in the present study. Statistical analysis was performed using partial least squares discriminant analysis and the variable importance score. The six most important ions were selected for each group, encompassing various metabolites categorized as sterols, lipids (glycerolipids, eicosanoids, sphingolipids, prenol lipid, and glycerophospholipids), coenzyme A, polypeptide, methyl-adenosine, amino acid derivatives, and acylcarnitines. The investigators performed ROC curve analysis to determine the diagnostic accuracy of metabolites associated with each grade of fibrosis. The metabolites demonstrated high sensitivity and specificity for each fibrosis grade except for F2. Consistent with the findings by Cano *et al*[15], detection of sterols, such as 18:0 and 20:5 cholesteryl esters, among patients with F1 fibrosis revealed downregulation of cholesteryl esters in rapid "fibrosers." Furthermore, the detection of diacylglycerols among patients with F1 fibrosis supported previous results that diacylglycerols were downregulated in patients with severe fibrosis[16]. Conversely, the significant upregulation of acylcarnitines among patients with F4 fibrosis mirrored the hyper-carcinogenic state observed in HCC patients [13]. These studies have provided useful information regarding detection of the fibrosis grade and underlying pathways in HCV infection.

However, the aforementioned results raise concerns about whether these metabolites are specific to HCV-related liver fibrosis or if they may also be caused by other etiologies, such as hepatitis B virus infection, alcohol consumption, and nonalcoholic steatohepatitis.

Given the absence of overlap between each fibrosis stage, the changes in metabolites with fibrosis progression remain unclear. In particular, it remains to be explored whether the metabolite levels exhibit a linear relationship with fibrosis stage. Furthermore, the biological significance of each metabolite is not yet known. Further studies with larger sample sizes are needed to verify these results.

CONCLUSION

Metabolomics is a newly developed technology that has several limitations due to the influence of several factors, including sampling time, collection protocol, and measurement methods. Furthermore, it is more time-consuming and expensive compared to other methods. However, this novel approach offers valuable information for diagnosis, prognosis, and treatment of liver disease. The role of metabolomics in HCV requires further investigation. In the future, metabolomics may enable the diagnosis of liver diseases without the need for biopsy.

FOOTNOTES

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