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LIVER FIBROSIS AND METHODS OF ASSESSMENT IN LIGHT OF CHRONIC HEPATITIS DELTA

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Summary

Objectives. Liver fibrosis is a wound healing response that causes accumulation of collagen and other extracellular proteins after an insult caused to liver or during a chronic liver disease. When left untreated, it may result in liver cirrhosis and portal hypertension, hepatic encephalopathy, liver failure, and an increased risk of hepatocellular carcinoma, which can ultimately cause organ failure and death.

Material and methods. Research articles from various sources were reviewed and a sum of different methods for non-invasive assessment liver assessment were picked to put forth a constructive composite review.

Results. Only two scores i.e., Baseline-event-anticipation score and Delta Fibrosis Score were found to show applicability in assessing liver fibrosis caused by chronic hepatitis delta virus infection, however, further studies are required.

Conclusion. Although a few non-invasive scoring methods, for assessment of liver fibrosis caused due to chronic hepatitis delta virus infection, have been put forth over the past few years, enough research and data collection is yet to be done for proper validation and use. Even though liver biopsy still remains the gold standard for assessing liver fibrosis, its invasive nature does not make it feasible for all patients.

Keywords: fibrosis, HDV, kupffer cells, non-invasive assessment

Introduction

Liver fibrosis is a wound healing response that causes accumulation of collagen and other extracellular proteins after an insult caused to liver or during a chronic liver disease. When left untreated, it may result in liver cirrhosis and portal hypertension, hepatic encephalopathy, liver failure and an increased risk of hepatocellular carcinoma (HCC) which can, ultimately, cause organ failure and death [1]. The main etiological factors that result in liver fibrosis include hepatitis C virus (HCV) infection, chronic hepatitis B virus (HBV) infection, hepatitis B virus - hepatitis delta virus (HBV-HDV) co-infection and mono-infection, alcohol abuse, autoimmune and cholestatic liver diseases [2, 3]. Thought to be a passive and irreversibly process initially, arguments about the dynamic nature of liver fibrosis have been put forth and is now being considered a reversible process, unless it is progressive and leads to cirrhosis. Elimination of the causative agent of the fibrotic response helps to regress fibrosis as long as the liver is not in the advanced stage of cirrhosis [4, 5]. Liver histopathology has been the gold standard for assessing fibrosis for many years. Due to its invasive nature, patients or physicians, in many cases, may not find liver biopsy feasible. Thus, the search for alternative approaches, to measure liver fibrosis, is an attractive area of research [6].

Material and methods.

Research articles from various sources were reviewed and a sum of different methods for non-invasive assessment liver assessment were picked to put forth a constructive composite review.

Results

The main source of activated myofibroblasts and portal fibroblasts that direct the fibrous process are Hepatic stellate cells (HSCs) [7]. Architectural remodelling is triggered as

Table 1

Factors contributing to HSC activation

Hepatocytes	HSCs line up to engulf the apoptotic bodies, resulting in a profibrogenic response and activation of kupffer cells [13]. Hepatocyte apoptosis mediated hepatic stellate cells (HSC) activation is partially mediated by HSC's Toll like receptor 9 (TLR9) with hepatocyte DNA [14]. Thus HSCs activation can be potentiated by disruption of anti-apoptotic mediator gene like Bcl-xl [15].
Natural Killer Cells (NK cells)	NK cell induced HSC apoptosis occurs due to interferone- γ (IFN-γ). IFN-γ not only inhibits HSC activation, but also upregulates NKG2D and TRIAL receptors on natural killer (NK) cells, thus enhancing NK cell cytotoxicity towards HSC [16, 17]. Activated HSCs are more likely effected by NK cell neutralization, thus exhibiting a direct inhibitory effect on liver fibrosis [18].
Kupffer cells	Kupffer cells and monocyte derived macrophages that accumulate in liver injury express chemokine receptors that control fibrosis progression and resolution. Activation of Kupffer cells → inflammasome assembly and activation in KC and release of IL-1β, IL-18, CCL2 → CCL2 promotes development of Ly-6C+ macrophages from CCR2+/Ly-6Ch monocytes → Ly-6C+ macrophages activate HSCs [19, 20]
Liver sinusoidal endothelial cell	In response to any insult sinusoidal endothelial cells contribute to HSC production by producing cytokines TGF-β1, PDGF and fibronectin [21].

inflammatory mediators promote activation of HSC, which are a major source of hepatic collagen, extracellular matrix (ECM) proteins secretion, tissue inhibitors of metalloproteinases, and matrix metalloproteinases [8, 9]. HSCs also promote synthesis of growth factor that, in turn, promote fibrogenesis, which is followed by chronic inflammatory response and neo-angiogenesis [10]. Apart from collagen, other matrix proteins include elastin, hyaluronan, proteoglycans and fibronectin. Accumulation of these proteins can activate the quiescent HSCs, leading to loss of hepatocyte microvilli and disappearance of endothelial microvilli [11, 12]. Various factors, contributing to activation of HSCs, are given in Table 1.

Fibrosis in HDV infection

HDV is the cause of the most severe form of viral hepatitis due to its higher propensity to cause liver cirrhosis. Widely regarded as a non-cytopathic virus, HDV viremia does not determine the extent of liver disease and HDV replication or hepatitis delta antigen (HDAg) expression. Like HBV and HCV, HDV also presents an altered phenotype of natural killer (NK) cells with regressed cytolytic function and cytokine production [22, 23]. Comparatively level of CD4+ T cells and NK cells in peripheral blood is increased in HDV-positive patients than in patients with HBV or HCV, however the level of mucosal-associated invariant T (MAIT) cells is decreased [24, 25]. Usai, et al, in their study, showed that majority of the inflammatory infiltrate included activated T-lymphocytes, NK cells and pro-inflammatory microphages. However, the damage induced by HDV infection was caused by the activation of Tumor Necrosis Factor alpha (TNF-alpha) pathways and HDV antigens [26].

Various studies from around the world have shown consistence with the fact that HDV-infections increases and accelerates chances of cirrhosis/fibrosis. In a study conducted in Gambia HBV-HDV coinfected Gambians had a highly increased risk of HCC or cirrhosis (without HCC) compared to uninfected or HBV-monoinfection people [27]. Among 69 cases from Kure, Japan, where antibodies to hepatitis delta antigen (anti-HD) was detected, eight (12%) developed liver cirrhosis (LC) and six (9%) developed hepatocellular carcinoma (HCC). However, among 1058 cases without anti-HD, there were 43 patients (4%) who developed LC and 29 (3%) who developed HCC. The prevalence of LC and HCC was significantly higher among the cases with anti-HD than those without anti-HD [28]. Similarly, the clinical profile from a study in Amazon (Brazil) suggested greater severity of liver disease among the patients super-infected with HDV [29].

Non-invasive methods for evaluation of fibrosis in HDV patients

Non-invasive estimation of fibrosis is essential in patients with chronic viral hepatitis, especially chronic delta viral hepatopathy, given the poor efficacy of interferon-based therapy, the many and burdensome side effects it entails and contraindications for patients with Child-Pugh B and C cirrhosis [30]. In addition to this drawbacks of liver biopsy, such as high risk of complications, invasiveness, high cost and patient's reluctance to accept render it to be of limited use [31]. Methods for non-invasive estimation of liver fibrosis are given in Table 2. However, none of the methods mentioned in Table 2 are validated for hepatitis D.

Table 2

Methods for non-invasive estimation of liver fibrosis

Indirect serological markers	Patented serum panel	Imaging methods
FIB-4 INDEX Initially developed for chronic HCV/HIV coinfection. Now validated for other liver diseases such as HBV and NAFLD [32-35].	**FIBROTEST** Combination of basic serum biomarkers like alpha2 macroglobulin, alpha2 globulin (or haptoglobin), gamma globulin, apolipoprotein A1, gamma glutamyltranspeptidase, and total bilirubin are used to predict cirrhosis [46]. Now validated for both hepaptitis B and C.	**TRANSIENT ELASTOGRAPHY (FIBROSCAN, ECHOSENS)** It uses the principle of VCTE, a probe generates pressure wave that is detected by a transducer on the same probe after passing through the liver tissue. The stiffer the liver, the higher is the velocity, indicated by a numeric value between 4.0 to 75 kPa. Validated for fibrosis assessment in several liver diseases including HBV [51].
APRI Proposed by Wae, et al, to predict fibrosis and cirrhosis in HCV [36]. APRI = [(AST/ULN)/Platelet count] ×100	**FIBRO INDEX** Platelet count, AST, and gamma globulin are used in estimation of fibro index. Used for predicting significant fibrosis and as a surrogate marker during anti-fibrotic treatment [47].	**ARFI ELASTOGRAPHY** Measures liver stiffness by using radiation forced impulses, while using B-mode ultrasonography. Used for both HCV and HBV [52, 53].
ALT/AST Mean AST/ALT ratio of 0.59 is found in patients without liver cirrhosis and 1.02 in patients with cirrhosis [37]. However, it has been found to be inferior to other blood based non-invasive algorithms [38].	**FIBROSPECT** Three-marker panel (Hyaluronic acid, TIMP-1 and alpha2-macroglobulin) helpful in differentiating moderate/severe fibrosis from no/mild fibrosis [48].	**REAL-TIME SHEAR WAVE ELASTOGRAPHY (SWE)** It allows the visualization of stiffness quantitatively in kilopaascals (kPa) [54].
FORNS INDEX Scoring system based on combining age, GGT, cholesterol and platelet count. Used for ruling out significant hepatic fibrosis in HCV infected patients. Forns index = 7.811 –3.131 × ln platelet + 0.781 × ln GGT + 3.647 × ln age – 0.014 × cholesterol [39].	**HEPASCORE** Automated panel test that requires a single analyzer and serum sample. This test takes into account age, gender, HA, bilirubin, GGT, and α2-marcoglobulin [49].	**FIBRO-CT** It is a simple and readily available method that uses CT images to determine the stage and distribution of liver fibrosis [55].
The Göteborg University Cirrhosis Index (GUCI) Helps to determine liver fibrosis in HCV patients. GUCI = normalized AST × prothrombin-INR × 100 / Platelet count (× 10^9/L) [40]	**FIBROMETER** This test combines: age, platelets, HA, AST, prothrombin index, urea, and α2-macroglobulin. Validated for hepatitis B and C [50].	**MR ELASTOGRAPHY** It is a non-invasive, reproducible modified contrast technique that helps in staging of liver fibrosis [56].

ZENG INDEX Alpha2-macroglobulin, age, gamma-glutamyl-transpeptidase and hyaluronic acid are used in scoring. Cutoff score < 3.0 rules out fibrosis and a score of > 8.7 predicts significant fibrosis [41].		
HUI SCORE BMI, platelet count, serum albumin, and total bilirubin levels were used as independent predictors of fibrosis/cirrhosis [42].		
FPI Fibrosis probability index is measured with routinely assessed markers along with insulin resistance in the patients suffering from hepatitis C [43].		
LOK INDEX This index uses platelet count, AST/ALT ratio, and INR to predict the development of cirrhosis in patients infected with hepatitis C [44].		
AFP/APTT - AA INDEX The AA index is calculated as log index = −9.164 + 0.114 × AFP + 0.236 × APTT. It is used to predict significant cirrhosis in patients infected with HBV [45].		

Legend: *HCV – hepatitis C virus; HIV – human immunodeficiency virus; HBV – hepatitis B virus; NAFLD – non-alcoholic fatty liver disease; VCTE – vibration controlled tissue elastography; AST – aspartate aminotransferase; ALT – alanine aminotransferase; APRI – AST to platelet ratio index; ULN – upper limit of normal; ARFI – acoustic radiation force impulse; TIMP-1 – tissue inhibitor of matrix metalloproteinase-1; GGT – gamma-glutamyl-transpeptidase; HA – hyaluronic acid; CT – computed tomography; INR – international normalized ratio; MR – magnetic resonance; BMI – body mass index; FPI – fibrosis probability index; AFP – α-fetal protein; APTT – activated partial thromboplastin time.*

Studies conducted by Lutterkort, et al. and Kalkan, et al. reveal the poor performance accuracy of existing non-invasive scores in patients with chronic hepatitis delta [57, 58]. These studies highlight the need for development of new scoring methods with high specificity to HDV.

Over the past 7-8 years a few scores have been developed and validated for chronic-HDV infection. One such scoring method is the baseline-event-anticipation score (BEA score). BEA score includes variables such as age, sex, region of origin, bilirubin, platelets and INR. BAE score characterizes patients in three groups BEA-A, BEA-B, BEA-C, in order of A<B<C of hazard ratio [59].

Table 3

BEA score in patients with chronic hepatitis delta.

PARAMETERS	SCORE	STAGE	RISK GROUP
INR > 1.2	+1	CLASS-A (0-1 Points)	Mild risk
Thrombocytes < 100 X 10^3 / ml			
Thrombocytes < 50 x 10^3 /ml		CLASS-B (2-4 Points)	Moderate risk
Sex-MALE			
Origin-Eastern Mediterranean		CLASS-C (>5 points)	Severe risk
Age > 40			
Billirubin > ULN			

Legend: *INR – international normalized ratio; ULN - upper limit of normal*

BEA score was shown to be resourceful in distinguishing risk groups and predicting disease progression with high accuracy [59].

Another score proposed for non-invasive assessment of fibrosis caused due to chronic delta hepatitis is Delta Fibrosis Score (DFS). Variables for this score include cholinesterase level, GGT, albumin level and age. According to this score, patients at high risk progression of liver fibrosis are older people with low chilonesterase levels, low albumin and increased GGT levels. DFS consists of points from 0-4 calculated as:

1 (if Alb<1.19[*LLN]) + 1 (if GGT>0.5[*ULN]) + 1 (if CHE <1.46[*LLN]) + 1 (if age >42)

where: Alb – albumin; LLN – lower limit of normal; GGT – gamma-glutamyl-transpeptidase; ULN – upper limit of normal; CHE – cholinesterase.

Each variable contributes 1 point if the criteria for inclusion of variable is met [57].

Invasive methods for assessment of fibrosis (biopsy)

Although advances have been made in assessing liver fibrosis, via non-invasive methods, liver biopsy still remains gold standard for grading and staging of liver fibrosis. In addition to this it can also confirm HCC and other associated diseases, however, due to its invasive nature, patient remains at risk of serious bleeding, pain, perforation and even death. It also has a limited feasibility in obese patients and in those with bleeding tendencies or ascites [60, 61]. METAVIR, Ishaq and Kondell are the most widely used histological scoring systems for assessment of fibrosis and treatment response. In histological scoring subjective visual analysis of the architectural changes of fibrosis is done without quantifying fibrosis as a variable but rather as a semi-quantitative numerical stage [62]. Increased use of digital image analysis with collagen quantification using collagen proportionate area (CPA) has provided an objective method for fibrosis assessment as the number of hepatocytes decreases with increasing number of collagen deposition, the functional reserve gets diminished accordingly. However, this quantitative assessment of collagen cannot be seen as a substitute to descriptive analysis of architectural changes in liver but should rather be seen as an additional way of evaluation [62-64].

Conclusion

Although a few non-invasive scoring methods for assessment of liver fibrosis caused due to chronic HDV infection have been put forth over the past few years, enough research and data collection is yet to be done for proper validation and use.

Liver biopsy still remains the gold standard for assessing liver fibrosis, but its invasive nature causes reluctance among the patients and doctors who do not find it feasible. Therefore, further studies are required to formulate new non-invasive methods of assessment of liver fibrosis that are specific for chronic HDV.

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