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Liver Fibrosis: Causes and Methods of Assessment, A Review

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Hepatic fibrogenesis is the final result of injury to the liver. Fibrosis could lead to hepatic dysfunction, important in the pathogenesis of other chronic problems. Therefore, understanding the mechanism, accurate diagnosis and staging of it in early stages accelerates the treatment and reduces the prevalence of chirrosis. Treatment strategies of liver problems and detction methods depend on the amount and progression of liver fibrosis and the rate of cirrhosis development. Traditionally the invasive method, liver biopsy, is reference standard to follow progression and stage of fibrosis. However, during the past decade, progressive development of novel non-invasive methodologies has challenged the invasive method. Non-invasive methods have been initially introduced for chronic hepatitis C with increasing use in other chronic liver diseases. The need for liver biopsy has nowadays decreased significantly as a result of these methodologies. Most of the new non-invasive methods depend on either 'biological' or 'physical' approaches.

In this review, starting from the mechanism of fibrogenesis, the current knowledge about diagnosis, treatment strategies and different methods for its evaluation is discussed. This is followed by a conclusion on what is expected to be known in this field during the future research.

Key words: Liver biopsy, FibroScan®, Fibrosis, Fibrosis mechanism, Fibrotest.

INTRODUCTION

Hepatic fibrogenesis is the final common result of injury to the liver, a critical factor leading to hepatic dysfunction and it may be important in the pathogenesis of other chronic problems such as portal hypertension [1] and biliary cirrhosis [2, 3]. An accurate assessment of fibrosis degree is, therefore, important clinically. Examination of hepatic histopathology has been considered to be the gold standard method for assessment of fibrosis for many years. However, due to its invasive nature, liver biopsy is not favored by patients or physicians on many occasions. Thus, a specific search for alternative approaches to measure liver fibrosis is an attractive area of investigation [4, 5]. Most of the new non-invasive methods depend on either 'biological' or 'physical' approaches. In the biological methods, the level of some biomarkers in serum is indication of liver damage. On the other hand, the basis of physical approach is liver stiffness measured by ultrasonic method, transient elastography (TE).

MECHANISMS OF HEPATIC FIBROGENESIS

A number of liver and other diseases as well as side effects of some drugs lead to liver fibrosis. Significant improvement in diagnosis and treatment of chronic liver disease has resulted in more interest in understanding the mechanism of fibrogenesis in the liver [7]. The occurrence of fibrosis is through integrated signaling networks that regulate the deposition of extracellular matrix. The activation of hepatic stellate cells (HSCs) is due to this cascade of responses. As a result, the HSCs are driven into a myofibroblast-like phenotype that is contractile, proliferative and fibrogenic. Liver fibrogenic cells are a heterogeneous population of cells including α-smooth muscle actin positive myofibroblasts (MFs). They are highly proliferative and contractile with ability to promote fibrogenesis. They possess multiple phenotypic responses to injury including deposition of extracellular matrix (ECM) components and collagen to encapsulate injury. On the other hand, they promot synthesis of growth factor which promotes fibrogenesis. This is followed by chronic inflammatory response and neo-angiogenesis [7].

It is known that sustained fibrogenesis could ultimately lead to cirrhosis. Liver cirrhosis is characterized by a distortion of the liver parenchyma and vascular architecture [8]. The exact mechanism of fibrogenesis is complicated covering a wide range of cellular and molecular events. Therefore, development of targeted therapies to inhibit of reverse fibrogenesis is the aim of many researchs in this area. It has been found that MFs are also differentiated from bone marrow-derived

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stem cells [8]. Using a cross talk mechanism with hepatic progenitor and tumour cells, MFs may modulate the immune responses to hepatocellular carcinomas and metastatic cancers.

As a widely accepted fact, liver fibrosis is a risk factor for hepatoma and activated hepatic stellate cells (HSCs) play a critical role in progression of hepatoma. Although HSCs are important in liver fibrosis formation, their interaction with tumor cells is unclear. It has been hypothesized that HSCs could increase the epithelial-mesenchymal transition (EMT) ability of hepatoma cells. To elucidate the effect of HSCs on hepatoma cells, HSC-T6 has been co-cultured with hepatoma cell line (ML1). They concluded that HSCs can secrete collagen type I to trigger hepatoma cells and subsequently enhance tumor metastasis [9]. The presence of HSCs around tumors and its microenvironment has been reported in a number of researches and case studies [9-12]. It has been reported that the conditioned medium of hepatocellular carcinoma cell can trigger activation of HSCs, proliferation, and cell migration [13]. Therefore, tumors can stimulate HSCs to form stoma inducing the growth of tumor.

The first response of liver to different chronic insults is, usually, developing fibrosis. Acute and chronic liver injuries are accompanied by prominently increased expression of proinflammatory and profibrogenic mediators and their receptors. It is known that N-glycosylated transmembrane proteins generally form these types of cytokine receptors [14].

The complicated process of cell migration requires a precise regulation and integration of multiple signaling pathways. During the whole process, ECM serves as the molecular scaffold for cell adhesion and migration. On the other hand, the cell surface proteins integrins and ECM are also functionally interconnected developing complex signaling pathways.

Although acute injury will activate the mechanistic pathway of fibrogenesis [15], the sustained signals associated with chronic liver disease caused by infection, co-infection [16], drugs, metabolic disorders, or immune attack are required for significant fibrosis to accumulate.

It has been expressed that any type of liver injury is associated with angiogenesis, sinusoidal remodeling, and expansion of stellate cell [8]. Therefore, mediators known for angiogenesis are also relevant in understanding hepatic fibrosis. These include platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), and their cognate receptors. Besides, vasoactive mediators such as nitric oxide and carbon monoxide are also involved in this mechanism. In heavy smokers suffering from hepatitis C, increased VEGF concentrations could be an important contributer to accelerated progression of fibrosis [17].

PREVENTING AND TREATMENT OF LIVER FIBROSIS

Since N-glycosylation of cell surface proteins cytokine receptors, integrins, and cadherins is affected by GnT-V [14], knockdown of GnT-V could inhibit cell migration. N-acetyl glucosaminyl-transferase V (GnT-V) may provide a feasible and promising therapeutic target in preventing liver fibrosis [18]. By inducing liver fibrosis in mouse, Liu *et al*. [18] observed significant increase of hepatic GnT-V fibrogenesis as well as upregulations of GnT-V in the activated HSCs. They found that knocking down the hepatic GnT-V expression led to reduced expression of GnT-V in fibrotic liver. They concluded that GnT-V is implicated in liver fibrosis, and, therefore, blocking GnT-V could be a feasible and promising approach to treat and prevent liver fibrosis. Although it is known that altered expression of GnT-V could modulate multiple cytokine signaling pathways leading to tumor invasion and metastasis, its role in the development of liver fibrosis is still contravenial.

Myofibroblastic transdifferentiation (MTD) is reported as the key event during liver fibrogenesis, and research in the past few years has identified important mediators and molecular mechanisms responsible for MTD of hepatic stellate cells (HSCs). There is a regulatory mechanism between differentiation of adipocytes and that of HSC, and the shift from adipogenic to myogenic or neuronal phenotype characterizes HSC MTD [19]. The main event of this shift is a loss of expression of the master adipogenic regulator peroxisome proliferator activated receptor γ (PPARγ). Restored expression of PPARγ and/or other adipogenic transcription genes can reverse myofibroblastic HSCs to differentiated cells. The expression of adipogenic transcription factors has been shown to be essential for the maintenance of HSC quiescence *in vitro* [20-22]. Wnt signal pathway in vertebrate is a homologous gene and the translated proteins could participate in the regulation of cell proliferation, cell polarity and cell differentiation. In human fibrosing diseases,

such as pulmonary fibrosis, renal fibrosis, and liver fibrosis Wnt signaling plays a central role. Therefore, it is suggested that blocking the canonical Wnt signal pathway with the co-receptor antagonist Dickkopf-1 (DKK1) could block these epigenetic repressions and restores the gene PPARγ expression and HSC differentiation. This can be regarded as novel therapeutic targets for liver fibrosis and liver regeneration.

Triggers of epithelial-mesenchymal transition (EMT) could induce pathological problems such as organ fibrosis and tumor metastasis [23, 24]. It has been found that collagen I stimulates EMT through increased expression of some transcription factors [25-27]. These factors alter expression of epithelial and mesenchymal markers causing initiation of EMT and stimulation of cell migration.

Integrin-linked kinase (ILK) is an ubiquitously expressed serine/threonine protein kinase implicated in development, progression and metastasis of cancer [28]. The role of ILK in glioma cell invasion and migration has been characterized with concluding remark that ILK could be regarded as a potential for therapeutic interference.

Regulation of EMT and ILK signaling pathways plays an important role in tumor progression [29]. Xiong *et al*. found evidences to demonstrate that EMT was implicated in metastasis of bladder cancer. They have suggested that ribonuclease inhibitor (RI) could suppress development of cancer and prevent metastasis of bladder through regulating EMT and ILK signaling pathway.

The central and determinant role of ILK in EMT and metastasis has been demonstrated in the case of colorectal cancer, CRC [30]. ILK and EMT signaling pathways could open ways for novel therapeutic opportunities to treat cancers including CRC.

CAUSES OF LIVER FIBROSIS

Liver problems are among the most causes of death due to alcohol abuse in many countries. On the other hand, nonalcoholic fatty liver disease (NAFLD) is a common hepatic abnormality in the Western world, and progresses to cirrhosis and hepatocellular carcinoma in a significant portion of cases [31].

It has been estimated that in about 20-30% of patients suffering from chronic hepatitis C cirrhosis develops in almost 20 years. The virus causing the disease (HCV) possesses some certain proteins, including core and NS5A that induce derangement of lipid metabolism or alter signal transduction of infected hepatocytes which leads to the production of reactive oxygen radicals and profibrogenic mediators, in particular TGF-beta1 [33]. The effect of telaprevir-based antiviral regimens on improving liver health in patients infected HCV has been studied [33]. In that retrospective study, 1208 patients treated with a telaprevir-based regimen were included. The base of grouping patients was their baseline Metavir score (F0-F1, F2 and F3-F4). The results obtained from non-invasive biomarker tests, FibroTest, APRI, FIB-4 and Forns' Score, were then monitored before and after HCV treatment. It was concluded that attaining treatment with telaprevir-based regimen led to significant improvements in liver health as determined by four biomarker examinations [34, 35].

Liver fibrosis also occurs in other liver diseases including autoimmune and cholestatic liver diseases [36]. It is known that the mechanism of pathogenesis primary biliary cirrhosis, a cholestatic liver disease, is different from other chronic liver diseases. Portal fibroblasts located in the connective tissue surrounding bile ducts are somehow different from hepatic stellate cells regarding an appropriate response to the profibrogenic and mitogenic stimuli and expression of marker proteins.

On the other hand, many liver diseases originated from various causes in children and younger patients could become complicated by development of liver fibrosis and progression to cirrhosis [37]. In the case of paediatric liver disease, too, liver fibrosis has different histopathological patterns and their management depends on the stage of liver fibrosis.

In addition to modification of many liver functions, among the most important consequences of fibrosis in liver is portal hypertension. This abnormal condition results from an increased intrahepatic resistance and increased hepatic and portal arterial blood flow. The various changes in fibrotic and angio-architecture of liver tissue cause increased intrahepatic resistance [38]. On the other hand, the progressive failure of one of the detoxification mechanisms of liver together with toxic substances from the splanchnic circulation and end-products of bacterial functions lead to a systemic pro-inflammatory state with further accelerating disease progression.

ASSESSMENT OF LIVER FIBROSIS

Despite its invasive character, liver biopsy is the most common and highly recommended 'reference standard' for diagnosis and staging of hepatic fibrosis. However, the progressive development of new methods and the need for a non-invasive method for accurate assessment of fibrosis has purposed the use of two alternative strategies to biopsy, i.e. 'biological' or 'physical' approaches. Biochemical markers of fibrosis in the serum could be tested and compared with the results of biopsy. On the other hand, transient elastography (TE, FibroScan®) is a new physical method which non-invasively could assess and represent the state of hepatic fibrosis.

TE is a rapid and non-invasive technique that can easily be performed at the bedside resulting in immediate outcomes with highly reasonable reproducibility. This novel non-invasive method has been designed for assessment of hepatic fibrosis in patients with chronic liver diseases [39]. However, its validity could highly be increased if combined with other no-invasive devices including serum markers. This technique has considerably minimized the need for the invasive liver biopsy in today's diagnostic strategies. It has been found that TE is a reliable method for early detection of cirrhosis having a prognostic value as well. It is also a fast method that is highly accepted both by specialist and the patients. The accuracy of transient elastography for diagnosis and staging of fibrosis in those suffering from alcoholic liver disease has been compared to liver biopsy. In this study with 330 participants it has been found that sensitivity and specificity of transient elastography were 0.95 and 0.71 with LR+ 3.3 and LR- 0.07. The study has concluded that transient elastography could be a reliable and useful physical method to be used as an alternative liver biopsy [39].

A review in 2011 has discussed the advantages as well as inconveniences of both biological and physical non-invasive methods in comparison with liver biopsy for the management of patients with chronic liver diseases [4]. During a 5 years research project, 1457 patients with chronic hepatitis C, liver stiffness and fibrosis were assessed by non-invasive methods including FibroTest, the aspartate aminotransferase to platelet ratio index (FIB-4) and compared to liver biopsy samples. They reported that 77 patients had died and 16 patients had undergone liver transplantation during 5 years. It was also found that 91.7% had survived. It was concluded that noninvasive tests for liver fibrosis, FibroTest can predict 5-year survival of patients with chronic hepatitis C. These tools might help physicians determine prognosis at earlier stages and discuss specific treatments, such as liver transplantation [40].

Non-invasive methods of investigating fibrosis have also been used in the case of hepatitis C patients by other groups of investigators [41]. The accuracy of aspartate aminotransferase-to-platelet ratio index (APRI) in predicting fibrosis has been examined in a group of HCV infected patients and HCV/human immunodeficiency virus (HIV) coinfected individuals. The study was performed to find out significant fibrosis, severe fibrosis, and cirrhosis stages in patients [42]. They found that for severe fibrosis, a threshold of 1.0 was 61% sensitive and 64% specific, while for cirrhosis, a threshold of 1.0 was 76% sensitive and 72% specific. It was concluded that APRI can identify hepatitis C-related fibrosis with a moderate degree of accuracy. A more recent study has also evaluated significant fibrosis (SF) and cirrhosis in patients with chronic HCV [43]. In this 2014 study, platelet count, ALT, AST, AST to ALT Ratio, AST to Platelet Ratio Index (APRI), Forns index, FIB-4 and Age Platelet Index were investigated from the history of 202 HCV patients who had undergone liver biopsy. The study concluded that SF and cirrhosis could be predicted with accuracy using fibrosis index which potentially decrease the need for liver biopsy in 76% and 83% of patients.

The validity of APRI to-platelet ratio index and FIB-4, an index from serum fibrosis markers (ALT, AST, and platelets plus patient age) for staging liver disease has been studied [44]. In that study, 2372 liver biopsies were identified from HCV-infected patients together with laboratory values for inputing APRI and FIB-4. They reported that FIB-4 was sufficient at differentiating 5 stages of chronic HCV infection. They, therefore, announced it useful in screening patients who need biopsy and therapy, for monitoring patients with less advanced disease, and for longitudinal studies.

Developing an appropriate treatment plan for patients with various liver related problems, such as patients infected with HCV and those on chronic hemodialysis (HD), is highly determined by extent of fibrosis. Therefore, assessment of liver fibrosis in such cases could be one of the primary important steps. In such cases, the use of non-invasive methods for measuring fibrosis is always preferred by most specialists. In this regard, alternations in

standard laboratory tests (AST, ALT, yGT, cholesterol and platelet count) and indirect serum fibrosis markers: AST-to-platelet ratio index (APRI), FIB-4 and Forns index, have been reported in chronically HCV-infected patients with and without antiviral treatment [45]. The study concluded that simple indices including APRI and FIB-4 were useful in monitoring for liver fibrosis rate after antiviral treatment in patients on maintenance HD infected by HCV and can be used as non-invasive methods for staging liver fibrosis progression.

In a systematic review by Shaheen and Myers [46], the performance of the APRI in hepatitis C virus (HCV)-infected patients was investigated. Based on a random meta-analysis, it was concluded that APRI accuracy was not affected by the prevalence of advanced fibrosis, or study and biopsy quality. On the other hand, in the cases of cirrhosis, the accuracy was greater in studies including HCV and HIV/HCV-co-infected patients.

A more recent work has systematically reviewed practical performance of APRI and Fibrosis 4 index (FIB-4) in hepatitis B virus (HBV) infection of adults. The diagnostic accuracy of APRI and FIB-4 for significant fibrosis, advanced fibrosis, and cirrhosis was investigated in a systematic review [47]. They included 16 articles of APRI only, 21 articles of APRI and FIB-4 and two articles of FIB-4 for detecting different levels of liver fibrosis. The results of a meta-analysis indicated that APRI and FIB-4 can identify hepatitis B-related fibrosis with a moderate sensitivity and accuracy.

The frequency, amplitude, disease activities, and associated factors of ALT and/or AST flares were assessed in 47 Asian patients with CHB [48]. The results from their study showed that ALT flare was not associated with baseline ALT level, fibrosis stage, inflammation grade, hepatitis B virus (HBV) DNA load, HBeAg status, HBV genotype, HBV precore and basal core promoter mutations. This was an attempt towards using non-invasive methods for diagnosis and following the progress of liver fibrosis.

Many disadvantages of significant limitations of liver biopsy have been partly overcome using noninvasive biomarkers for prediction of fibrogenesis in HBV infected patients with hepatitis B virus [49]. The systematic review was based on the assessment of the effectiveness and accuracy of these biomarkers for predicting HBV-related fibrosis. They reported that the heterogeneity of FIB-4 and FibroTest were not statistically significant. The heterogeneity of APRI for detecting significant fibrosis was affected by median age, while for cirrhosis it was affected by etiology. It was, therefore, concluded that FibroTest had excellent diagnostic accuracy for identification of HBV-related significant fibrosis and cirrhosis.

Assuming that liver biopsy is not only an invasive and expensive method, but it is also an imperfect gold standard, the relative accuracy of two widely used non-invasive techniques, Fibro Test®, and liver stiffness measurement (LSM) using FibroScan® have been validated and compared to biopsy [50,51]. The study was performed on 1289 CHC patients and a 604 healthy volunteer control group. The stage of fibrosis was examined by the three techniques and measurement of ALT was taken as a control test. Based on the results obtained from their analysis, the accuracy of FibroTest and FibroScan® for the diagnosis of advanced fibrosis and cirrhosis in patients with chronic hepatitis C was confirmed.

Many advantages known for FibroScan® necessitated its modification for overweight patients. It has been reported that XL probe could facilitates liver stiffness measurement (LSM) by transient elastography (TE) in obese patients [51]. They examined the prevalence, risk factors, and causes of discordance between fibrosis estimated by biopsy and the FibroScan® XL probe in 102 patients (BMI) ≥ 28 kg/m^2) with chronic liver disease. Their results showed that discordance was 4- to 5-fold more frequent in highly obese patients (BMI ≥ 40 kg/m^2: 32% *vs*. 8%) and liver stiffness above the median of 7.0 kPa (20% *vs*. 4%; both $p < 0.0005$).

The use of TE for the staging of liver fibrosis has been established in a meta-analysis. The technique was employed for the diagnosis of liver fibrosis due to various factors and to analyze factors influencing the diagnostic accuracy [52-54]. It was reported that age, body mass index, and biopsy quality did not have a significant effect on the area under the receiver operating characteristic curve, AUROC [55]. They reported an excellent diagnostic accuracy of TE for the diagnosis of cirrhosis and progress of fibrosis and that its performance did not depend on underlying liver disease [56, 57].

The diagnostic accuracy of transient elastography for diagnosis and staging hepatic fibrosis has been compared to liver biopsy in people with alcoholic liver disease [39]. A number of 834 studies were reviewed to provide data for analyses. In conclusion remarks they have reported that

summary sensitivity and specificity of transient elastography (seven studies with 330 participants) were 0.95 and 0.71 with LR+ 3.3 and LR-0.07. These results suggested that transient elastography is considered as a useful technique to predict and show the presence of cirrhosis and could open the way to avoid invasive biopsy.

However, increasing prevalence of nonalcoholic fatty liver disease and the importance of viral hepatitis also demand a reliable non-invasive method for screening of liver damage. The benefits and pitfalls of vibration-controlled transient elastography have been reviewed aiming to introduce a framework to interpret its results [58]. The results of their review have revealed that transient elastography can be a reliable technique to show the fibrosis and its progress with about 60-70% accuracy.

A number of other non-invasive techniques were also introduced during the last few decades and their effectiveness and performances examined and compared to each other and to the liver biopsy. A recent study has compared the diagnostic performances FibroScan® with that of Supersonic Shear Imaging (SSI) for the diagnosis of liver fibrosis in chronic liver disease [59]. In the mentioned study, liver stiffness of 349 consecutive patients with chronic liver diseases who had liver biopsy was assessed by supersonic shear imaging (SSI), Acoustic Radiation Force Impulse (ARFI) imaging and compared to FibroScan® within two weeks of liver biopsy. Their results showed that SSI, Fibro Scan®, and ARFI significantly correlated with histological fibrosis score. It was also found that SSI had a higher accuracy than FibroScan® for the diagnosis of severe fibrosis, and a higher accuracy than ARFI for the diagnosis of significant fibrosis. However, they reported that no significant difference was observed for the diagnosis of mild fibrosis and cirrhosis. It was concluded that SSI is an efficient method for the assessment of liver fibrosis in chronic liver diseases, as compared to FibroScan® and ARFI [59].

The accuracy of FibroScan® has also been compared with King's score using liver histology as the reference standard [60]. In this London King's College and the Royal Free Hospital study, liver fibrosis was scored in 187 patients who had undergone a biopsy and diagnosed with chronic hepatitis C virus (HCV) mono-infection (HCV RNA-positive by RT-PCR) using the Ishak method. It was reported that the non-invasive markers and, particularly, FibroScan® were effective tests for the prediction of cirrhosis in chronic hepatitis C [60]. It is worth reminding that the King's score (KS) is a simple non-invasive test that has been introduced and widely used to predict the prevalence of significant fibrosis or cirrhosis at the bedside or in the clinic.

The accuracy of transient elastography (TE) for the diagnosis of liver fibrosis in patients suffering from Chronic Hepatitis C (CHC) has been examined in a cohort of consecutive patients with Genotype 1 (G1) CHC [61]. The patients have been assessed by clinical, ultrasonographic and histological (Scheuer score) features. It was found that patients with G1 CHC, the presence of moderate-severe steatosis, detected by histology or by US, should always be taken into account in order to avoid overestimations of liver fibrosis assessed by TE.

Early detection of liver cirrhosis could prevent liver failure and lead the clinician to find the cause and reduce its progress. In order to detect cirrhosis, in early stages by a non-invasive method, the use of transient elastography (TE) for the detection of cirrhosis and oesophageal varices (OV) in chronic hepatitis C (CHC) has been reported [62,63]. The accuracy of CE is compared with other non-invasive methods including AST/ALT ratio (AAR), APRI, prothrombin index (PI), platelet count (PC) and FibroTest™ (FT). The gld standard, liver biopsy (LB), has been used as reference, in 298 consecutive CHC patients. According to the report from that study, TE had the best diagnostic accuracy for detection of cirrhosis (AUROCs: TE 0.96 *vs*. FT 0.82, Lok and APRT 0.80, PC 0.79, PI 0.73, AAR 0.61. On the other hand, the percentage of saved LB was found to be: TE (cut-off: 12.5 kPa) 90%, PC 82%, FT 79%, PI 77%, AAR 76%, APRI 70%, and Lok 45%, respectively.

Steatosis, the most common consequence of fibrosis, should also be controlled and assessed with care. Controlled attenuation parameter (CAP) evaluated with transient elastography (FibroScan®) is a recent method for non-invasive assessment of steatosis. As the usefulness of the method in clinical practice has been unknown, a prospective based study investigated the determinants of CAP failure and the relationships between CAP and clinical or biological parameters. The study was performed in a large cohort of consecutive adult patients with suspected chronic liver disease [55, 64]. In these research works, the possible influence of some variants including age, gender, body mass index, waist circumference, hypertension, diabetes, metabolic syndrome and alcohol use, liver stiffness measurements have been analyzed for their influence

on CAP value. The results of multivariate analysis indicated that factors independently associated with CAP measurement failure were female gender, BMI, and metabolic syndrome. However, the same type of analysis showed that factors significantly associated with elevated CAP were BMI (25-30) kg/m^2, BMI >30 kg/m^2, metabolic syndrome, alcohol >14 drink/week and liver stiffness > 6 kPa. They concluded that CAP could provide an immediate assessment of steatosis simultaneously with liver stiffness measurement. It has been suggested that the strong association of CAP with the metabolic syndrome and alcohol use could be of interest for the follow-up of NAFLD or alcoholic patients [65].

It is a well-known fact that one of the most common results of injury to the liver is hepatic fibrogenesis, a critical factor leading to hepatic dysfunction and it may be important in the pathogenesis of portal hypertension.

A new bidimensional elastography technique, supersonic shear imaging (SSI), has been used to evaluate liver fibrosis in 113 patients with HCV infection and compared with FibroScan® [66]. According to the results SSI appears as a fast, simple and reliable method for non-invasive liver fibrosis evaluation.

A review in 2012 has reported recent findings on non-invasive alternatives for the diagnosis of fibrosis and cirrhosis in patients who are coinfected with HIV and HCV [67]. By analyzing data obtained from literature, they have summarized that serum biomarkers as well as transient elastography can accurately diagnose fibrosis and cirrhosis and are better at excluding than at predicting liver disease in HIV/HCV-coinfected patients.

Using a combination of various non-invasive tests for staging liver fibrosis could improve diagnostic accuracy. This was examined in the case of 116 HIV/HCV coinfected patients [68]. In this study, the validity of transient elastography (TE), Fibrotest (FT), the aspartate aminotransferase-to-platelet ratio index (APRI) were compared. It was found that in HIV/HCV-coinfected patients, TE and FT had a similar diagnostic accuracy for significant fibrosis, whereas TE had the best accuracy for cirrhosis.

In a similar study the effectiveness of the novel FibroScan® was compared to measurement of serum indices as alternatives to liver biopsy in HIV/hepatitis C virus (HCV)-coinfected patients [69]. Their results concluded that transient elastography accurately predicted liver fibrosis as compared to other simple non-invasive indexes in HIV/HCV-coinfected patients. It was, therefore, suggested that TE could be a rapid, accurate and helpful tool for guiding therapeutic decisions in clinical practice.

CONCLUSIONS

Liver fibrosis, characterized by excessive deposition of extracellular matrix, occurs in various conditions including chronic alcohol consumption, hepatitis virus, nonalcoholic steatohepatitis and genetic disorders.

It is initiated when chronic liver injury stimulates production of mediators by hepatocytes, bile duct epithelial cells, platelets, kupffer cells, and other inflammatory cells. They, therefore, cause cells in the liver to differentiate into myofibroblasts. Myofibroblasts originate from hepatic stellate cells (HSCs), peribiliary fibroblasts, hepatocytes, bile duct epithelial cells, and bone marrow-derived cells. Growth factors are produced during the genesis of this disease that stimulates myofibroblast proliferation, and chemokines are produced that stimulate these cells to migrate to injured regions of the liver. Once the myofibroblasts accumulate in these regions, they are stimulated to produce collagen and other components of extracellular matrix causing fibrosis.

While the mechanism of fibrosis has been identified, there are almost no therapies currently available that directly prevent or reverse fibrosis. Therefore, further studies are needed to identify new and effective therapeutic targets to treat this disease.

Explaining the underlying mechanism of fibrogenesis, in this review article, the advantages and pitfalls of various non-invasive methods for diagnosis and staging liver fibrosis, including vibration-controlled transient elastography, were studied.

Early detection and staging of fibrosis could help reduce the danger and prevent its development to cirrhosis. Liver biopsy is known as the gold standard for diagnosis and detection of fibrosis as well as staging its progress. However, the method is invasive, expensive and hardly accepted by patients. Most of the new non-invasive methods depend on either ‘biological’ or ‘physical’ approaches.

Vibration-controlled transient elastography, commonly delivered by the FibroScan device, is a new and novel technique recently approved by the Food and Drug Administration for the noninvasive assessment of liver disease. Transient elastography

(TE) is currently the most accurate non-invasive method for early detection of cirrhosis in CHC as compared with other available methods, but it cannot replace endoscopy for OV screening.

TE is a simple, reliable, painless, rapid and useful method for assessing liver fibrosis in primary biliary cirrhosis. It has excellent patient acceptance and is useful for monitoring fibrosis progression and regression in the individual case.

It is also concluded that SSI is an efficient method for the assessment of liver fibrosis in chronic liver diseases, comparing favourably to FibroScan® and ARFI.

On the other hand, the combined use of FibroScan® and FibroTest to evaluate liver fibrosis could avoid a biopsy procedure in most patients.

Conflict of interest: The author confirms that he had no conflict of interest.

Fibrogeneza hepatică este rezultatul final al leziunii hepatice. Fibroza duce la disfuncție hepatică ce determină alte comorbidități. Înțelegerea aşadar a mecanismelor fibrogenetice, realizarea unui diagnostic corect încă din stadiile timpurii duce la scăderea prevalenței cirozei hepatice. Strategiile terapeutice şi metodele de detecție depind de progresia fibrozei hepatice şi de rata dezvoltării cirozei. Tradițional, standardul de aur pentru evaluarea cirozei hepatice este puncția, biopsia hepatică, o manvera invazivă. În ultimul timp însă au fost dezvoltate mai multe metode non-invazive pentru a putea evalua mai uşor fibroza hepatică. Inițial aceste metode au fost dezvoltate pentru pacienții cu hepatită cronică cu virus hepatitic C. Astfel că necesitatea biopsiei a scăzut foarte mult în ultima vreme.

În acest articol tip review sunt trecute în revistă principalele mecanisme fibrogenetice, diagnosticul fibrozei hepatice, strategiile pentru evaluarea şi tratamentul fibrozei hepatice.

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ABBREVIATIONS

AE2	Anion exchanger 2
AIP	Autoimmune pancreatitis
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase;
AMAs	Antimitochondrial antibodies
ANIT	Alpha-naphthylisothiocyanate
APRI	Aspartate-to-Platelet Ratio Index
ARFI	Acoustic Radiation Force Impulse
AST	Aspartate AminoTransferase
AST/ALT	Aspartate aminotransferase/alanine aminotransferase ratio index
AUROC	Area under the receiver operating charac-teristic curve
BMI	Body mass index
CAP	Controlled attenuation parameter
CFTR	Cystic fibrosis transmembrane conductance regulator
CHB	Chronic hepatitis B
CHC	Chronic hepatitis C
CI	Confidence interval
CLDs	Chronic liver diseases
CRBP	Cellular retinol-binding proteins
CRC	Colorectal cancer
CTGF	Connective tissue growth factor
DCC	3.5-diethoxycarbonyl-1.4-dihydrocollidine
ECM	Extracellular matrix
EMT	Epithelial-mesenchymal transition
ERCP	Endoscopic retrograde cholangio-pancreaticography
ETM	Epithelial-mesenchymal transition
FGF-2	Fibroblast growth factor-2
FLI	Fatty liver index
FT	FibroTest®
G1	Genotype 1
GFAP	Glial fibrillary acidic protein
GGT	Gamma-Glutamyl Transpeptidase
Gnt-V	N-acetyl glucosaminyltransferase V
HBV	Hepatitis B virus
HCC	Hepatocellular carcinomas
HCV	Hepatitis C virus
HD	Hemodialysis
HGF	Hepatocyte growth factor
HSC	Hepatic stellate cells
IGF1	Insulin-like growth factor 1
ILK	Integrin-linked kinase
IQR	Interquartile range
KO	Knockout
kPa	Kilopascal
KS	King's score
LB	Liver biopsy
LRAT	Lecithin-retinol acyltransferase

LSM	Liver Stiffness Measurement
LXR	Liver X receptor
MCP-1	Monocyte chemoattractant protein-1
MFs	Myofibroblasts
MRCP	Magnetic resonance cholangio-pancreaticography
NAFLD	Nonalcoholic fatty liver disease
NASH	Nonalcoholic steatohepatitis
NGF	Nerve growth factor
NPV	Negative predictive value
OR	Odds ratio
pANCA	Perinuclear antineutrophil cytoplasmatic antibody
PBC	Primary biliary cirrhosis
PDC-E2	E2 subunit of pyruvate dehydrogenase complex
PDGF	Platelet-derived growth factor
PPARγ	Peroxisome proliferator activated receptor γ
PPV	Positive predictive value;
PSC	Primary sclerosing cholangitis
PT	Prothrombin time
RI	Ribonuclease inhibitor
ROI	Region of interest
SF	Significant fibrosis
SSI	Supersonic shear imaging
STAP	Stellate cell activation-associated protein
TE	Transient elastography
TGFβ	Transforming growth factor β
UDCA	Ursodeoxycholic acid
US	Ultrasonography
VCTE	Vibration-controlled transient elastography
VDR	Farnesoid X receptor (FXR), vitamin D receptor
VEGF	Vascular endothelial growth factor

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