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Liver Fibrosis: Difficulties in Diagnostic and Treatment: A Review

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Abstract

Early discovery of liver fibrosis and cirrhosis is becoming more relevant because of enhanced incidence of hepatocellular carcinoma. There a many underlying factors in developing liver fibrosis (i.e. viral hepatitis, steatohepatitis). Diagnosis of liver fibrosis is difficult; chronic liver failure and less distinct fibrosis stages can be underestimated, when laboratory routine parameters and native ultrasound of the liver are unsuspicious. Liver biopsy is a common element of diagnostic workup in hepatic cirrhosis, alongside clinical examination and abdominal ultrasound, and is the accepted diagnostic gold standard. But there is no unitary system of histological classification used to evaluate the degree of fibrosis, and individual systems are often validated only for individual disease entities. On the other hand liver biopsy is of less tolerance for patients. In the last years serological markers for detecting liver fibrosis were developed with different validity. Various imaging modalities have been proposed as methods for assessing liver fibrosis by liver stiffness measurement. They are sufficient to approve the suspicious of liver fibrosis and/or to uncover unknown chronic liver failure. Studies showed the clinical usefulness of acoustic radiation force impulse shear wave elasticity imaging (ARFI-SWEI) is efficient as a preventive screening method to uncover fibrosis. The ARFI-SWEI system is integrated in an ultrasound device has a good accuracy and high reproducibility. Therapy of liver fibrosis depends on underlying disease and degree of liver failure. When liver failure can be cured liver fibrosis can regress. Direct antifibrotic drugs are actually not available but in progress.

Keywords: Liver fibrosis; Liver failure; Liver elastography; Ultrasound; Biomarkers; Antifibrotic therapy

Introduction

The adult human liver typically weighs approximately 1.5kg. It is the largest internal organ and plays many pivotal roles in intermediary metabolism (i.e. metabolism and clearance of xenobiotics, disposal of bile, synthesis for major serum proteins (albumin, clotting factors)); in the normal state, the liver is maintained at a size which provides substantial overcapacity and has a remarkable ability to regenerate in response to functional parenchymal loss even after 70% of the parenchyma is lost [1]. Liver fibrosis (LF) is part of the structural and functional alterations of liver tissue in most chronic liver diseases. It is one of the main prognostic factors as the amount of fibrosis is correlated with the risk of developing liver cirrhosis (LC) [2]. LF resulting from chronic liver injury is a central pathologic healing process in progressive chronic liver disease (CLD). Non-alcoholic or alcoholic fatty liver disease ((N)AFLD) as well as chronic viral hepatitis B (HBV) and C (HCV) are leading CLD in the western world [3] and major cause of morbidity and mortality worldwide [4,5]. Chronic liver injury leads to initiation and perpetuation of inflammatory processes, which, by a cascade of inter-related processes and pathways, leads to deposition of extracellular matrix (ECM) proteins including collagen fibers (fibrous tissue) as a wound healing response. But this response causes tissue scarring. Fibrosis is a dynamic process of hepatic homeostasis mediated by several cellular mediators. In particular, hepatic stellate cells (HSC) have a central role in the pathogenesis of liver fibrosis and comprise 15% of liver cell mass. HSC are activated following liver injury from a relatively quiescent lipid and vitamin A-storing phenotype to a myofibroblastic phenotype, capable of proliferation, contraction and fibrogenesis. Other cell types, such as endogenous portal fibro- and myofibroblasts derived from liver parenchymal cells undergoing epithelial-mesenchymal transition are also suggested to contribute to the myofibroblast pool fibroblasts [6,7]. When liver injury and inflammation are persistent and progressive, liver cannot regenerate normally and causes LF up to LC [8].

Fibrosis has been considered potentially reversible with elimination by removal of causative agents, while the end-stage of the pathological process, cirrhosis, has been considered irreversible and is difficult to treat [6,7].

In recent years the early discovery of progressive liver failure, LF and LC is becoming more popular because of enhanced incidence of hepatocellular carcinoma (HCC); importantly, the incidence of HCC

will continue to escalate as chronic hepatitis C (HCV) reaches its maturity and as nonalcoholic steatohepatitis (NASH) and obesity become more prevalent in the Western World [9]. HCC is the third leading cause of cancer-related death worldwide [10,11]. Nearly 95% of all HCC are based on LC with an incidence up to 6% per year [12].

Mortality analysis shows that CLD as cause of death range on place 5 in Germany and the risk to develop LC is up to 5% [8]. Data analysis from the U.S. Department of Health and Human Services revealed that CLD range on place 12 of 15 leading causes of death in 2013 [13].

Epidemiologic data from Germany estimates that nearly 4-5 million people suffer because of CLD with or without LF;(N) AFLD and the activated form, (N)ASH, as well as HBV/HCV and hemochromatosis are the main factors in over 90% of the cases. (N)AFLD/ (N)ASH, are growing problems for people of the industrialized countries. Overweight defined as body-mass-index (bmi) of 25.0-29.9kg/m^2 and obese with bmi ≥30.0kg/m^2 are caused by less sporting activity, excess of calories and/or alcohol and are the main reasons for developing fatty liver and/or steatohepatitis with elevated risk of LC and HCC [14,15]. The overweight prevalence is 28.8% and obese ranges from 2.3-12%, mostly affecting females [15]. Nowadays (N)AFLD associated liver cirrhosis is the second leading cause for liver transplant in the USA and will overtake HCV in the next years [16].

Often patients do not know about their possible liver failure because typical symptoms like fatigue or jaundice are missing until the late stage of the disease [17]. The life expectancy and prognosis of patients with LC is significant lower with 1-year mortality of 40% [18]. To prevent LC the aim is to uncover early stages of a LF and corresponding CLD.

Diagnostic of Liver Fibrosis

To estimate the probability of LF comprehensive evaluation of underlying disease and patient history (including drug history) as well as body mass indices are necessary followed by ascertainment of laboratory parameters. These include especially the blood count, liver enzymes (aspartate-aminotransferase (AST), alanine-aminotransferase (ALT), cholinesterase (CHE), gamma-glutamyltransferase (GGT), alkaline phosphatase (AP)) and blood clotting factors. In vague suspicion of CLD additional screening for HBV and HCV, hemochromatosis, autoimmune hepatitis including primary sclerosing (PSC) or primary biliary cholangitis (PBC), M. Wilson and lack of alpha-1-antitrypsin is recommended (Figure 1) [19].

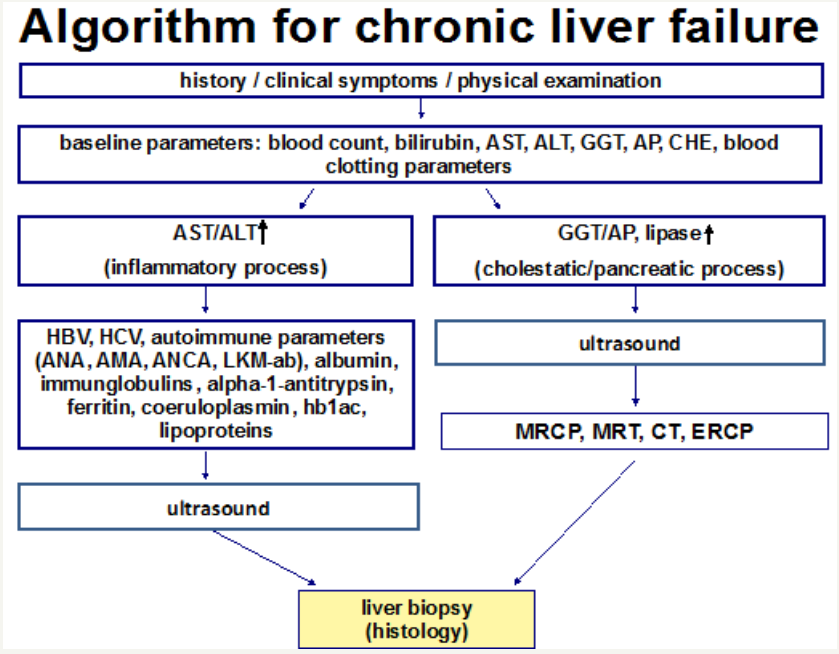

Figure 1: Algorithm for diagnostic chronic liver failure.

Invasive Diagnostic of Liver Fibrosis

In the past the diagnosis and follow-up of progressive LF by CLD based on histological examination using liver biopsy (LB) [20]. For patients with hepatitis of various etiologies, liver biopsy is used not only to establish the cause of the disorder, but also to assess the degree of inflammatory activity (grading) and the extent of fibrosis (staging). LB is an important aid to treatment planning and prognostication [21]. But recently its value as a method to assess the severity of liver disease (or to follow-up disease progression) has been questioned. The success of LB depends not only on the selection of the puncture method (i.e. percutaneous, ultrasound-guided liver biopsy (the Menghini method), trans jugular liver biopsy etc.) and on due attention to the relative and absolute contraindications, but also on the experience of the person carrying out the procedure. Although LB is still considered the "gold standard" for histological evaluation it is well known that this procedure has except poor tolerance as a stressful medical procedure for many

patients several limitations [20,22]. Liver biopsy is expensive, it needs hospitalization for at least 6-18 hours, is invasive and carries a risk of complications with an associated morbidity rate between 0.3% and 0.6%, and with a mortality rate of 0.05% [23].

Liver biopsies only sample an extremely small portion of the liver (1/50,000) and therefore, sampling errors can occur, especially when smaller sized biopsies are analyzed [20,24,25]. Sampling mistakes and inter- and intra observer variations may result in under staging of cirrhosis or high graded fibrosis, which may occur even when widely validated systems are used to score liver damage (Table 1) [5]. The single histologic liver scores are established in context with special liver diseases and partially have different definitions for fibrosis stages.

Table 1: Different histopathologic staging systems.

Staging System	Stage	Histologic Description	Features
Scheuer [26]	0	No fibrosis	Preferred for HBV/HCV
	1	Enlarged portal tracts	
	2	Periportal fibrosis±periportal septa	
	3	Architectural distortion, no obvious cirrhosis	
	4	Cirrhosis (probable or definite)	
Batts-Ludwig [27]	0	No fibrosis	Preferred for HBV/HCV
	1	Portal/periportal fibrosis Septal fibrosis	
	2	Bridging fibrosis with architectural distortion	
	3	Cirrhosis	
	4		
METAVIR [29]	0	No fibrosis	Simple, reproducible, validated in clinical practice; extensively used for HCV
	1	Portal fibrosis without septa	
	2	Few septa	
	3	Numerous septa without cirrhosis	
	4	Cirrhosis	
Ishak et al. [30]	0	No fibrosis	Preferred for research purposes still reproducible and validated in clinical practice
	1	Expansion of some portal areas with/without septa	
	2	Expansion of most portal areas with/without septa	
	3	Expansion of most portal areas with portal-portal bridging	
	4	Expansion of most portal areas with portal-portal and portal-central bridging	
	5	Bridging with occasional nodules	
	6	Cirrhosis	
Laennec [31]	0	No fibrosis	Histologic substages of cirrhosis are related to clinical cirrhosis stages
	1	Minimal fibrosis	
	2	Mild fibrosis	
	3	Moderate fibrosis	
	4A	Cirrhosis, mild or probable	
	4B	Cirrhosis, moderate	
	4C	Cirrhosis, severe	
Brunt et al. [32]	0	No fibrosis	Preferred for NASH
	1	Zone 3 (perisinusoidal, focal or extensive)	
	2	Zone 3 as above and focal/extensive portal-based fibrosis	
	3	Same as 1 or 2 with bridging fibrosis	
	4	Cirrhosis	
Kleiner et al. [33]	0	As per Brunt et al. [13] but stage 1 is further subdivided in	Preferred for NAFLD

	1	1a: delicate zone 3 sinusoidal/pericellular fibrosis (z3s/pf)	
	2	1b: dense z3s/pf	
	3	1c: portal fibrosis only	
	4	/	

HBV: Chronic Hepatitis B; HCV: Chronic Hepatitis C; NAFLD: Nonalcoholic Fatty Liver Disease; NASH: Nonalcoholic Steatohepatitis [5].

Noninvasive Diagnostic of Liver Fibrosis

Thus, in recent years interest increased in identifying and describing liver fibrosis by using non invasive technical methods [20]. Noninvasive methods can be divided in two categories: serological and imaging-based technologies.

Serum Biomarkers

Serum biomarkers have been studied in detail to detect early fibrotic changes as blood tests are quick and acceptable to patients [6]. Today there is wide range of serum biomarkers used to identify liver damage. These biomarkers can be divided into two broad categories -direct and indirect. Indirect markers reflect liver function, which may decline with the onset of higher graded liver fibrosis or cirrhosis (i.e. blood clotting parameters, platelet count, cholinesterase). Direct markers reflect extracellular matrix (ECM) turnover, and include many molecules involved in hepatic fibrogenesis (i.e. hyaluronic acid, amino terminal of serum procollagen III peptide (PIIINP), tissue inhibitor of metalloproteinase (TIMP-1) [33]. In total there are a lot of indirect and direct test methods used in various contexts (i.e. HBV/HCV, NAFLD). The advantage of indirect test is using serological routine parameters. Direct tests are more expensive and often they are available to a limited extent in hospitals. Because of its quantity only few established tests are listed here (Table 2).

Table 2: Indirect and direct tests for liver fibrosis.

Test (Indirect/Direct)	Use	Validity
AST/ALT-Ratio (indirect)	various liver diseases	Low validity in identifying liver fibrosis
AST-to-Platelet-Ratio-Index (APRI) (indirect)	chronic hepatitis c or b	HCV: good accuracy for fibrosis ^{3}f2
HBV: limited in indentifying fibrosis/cirrhosis		
NAFLD fibrosis score (indirect)	NAFLD	In context with NAFLD/NASH good predictor
Forns´index (indirect)	various liver diseases	Good accuracy for fibrosis ^{3}f2
FIB-4 index (indirect)	chronic hepatitis C (various liver diseases)	Good accuracy for fibrosis f3/4
Fibrotest/Fibrosure (indirect)	various liver diseases	Good accuracy for fibrosis ^{3}f2; limited by acute inflammation, hemolysis, hyerpbilirubinemia
Hyaluronic acid (direct)	chronic hepatitis c (NAFLD)	Good accuracy for fibrosis ^{3}f2
Matrix metalloproteinases (MMPs) and inhibitor (direct)	various liver diseases	unclear expensive; dependence of specilized laboratory
Procollagen type III amino-terminal peptide (PIIINP) (direct)	various liver diseases	Unclear expensive; dependence of specilized laboratory
Enhanced liver fibrosis score(direct)	chronic hepatitis c (N)AFLD	Unclear, accuracy for fibrosis f3/4 Expensive, dependence of specilized laboratory

Indirect Tests

AST/ALT-ratio

The AST/ALT-ratio (AAR) or De-Ritis-Quotient used more than 30 years describes the relation of AST and ALT. It finds use in estimation of various liver diseases. The range of the dimensionless ratio is between 0.6-0.8. The area under the receiver operating characteristic curve (AUROC) for LF≥F3 varies between 0.68-0.78. In daily routine AST/ALT-ratio <1 reflects slightly and ratio >1 severe liver failure (i.e. cirrhosis) [34].

AST-to-platelet-ratio-index (APRI)

This index was developed by Wai et al. [35]. APRI was proposed as an alternative to biopsy in patients with chronic HCV infection and it is calculated as (AST/upper limit of normal range)/platelet count (109/L)×100. A large meta-analysis by Lin et al. suggest that APRI can identify HCV-related fibrosis with a moderate degree of accuracy and AUROC scores for the diagnosis of significant fibrosis (≥F2) between 0.77-0.83 respectively [36]. But APRI seems to be limited in identifying hepatitis B-related significant fibrosis and cirrhosis [37].

NAFLD Fibrosis score

Angulo et al. established a score including age, hyperglycemia, bmi, platelet count, albumin and AST/ALT-ratio as a good predictor (AUROC 0.88) for progressive liver fibrosis (F3-4) [38].

Forns index

Forns et al. developed a multivariate analysis-based model in a cohort of 476 subjects. The score includes four variables: age, GGT, cholesterol, platelet count. The usefulness of this index is restricted to patients with early-stage fibrosis (negative predictive value to exclude fibrosis≥F2 96% for scores below 4.2) [6,39].

FIB-4 index

This index combines the liver enzymes AST/ALT, the platelet count and age into the formula: age (years)×AST (U/L)/(platelets (109/L)×ALT (U/L)). The FIB-4 index was specifically developed as an alternative to biopsy in patients with chronic HCV infection, but has shown use in other causes of liver disease. In a study of 529 HCV-infected patients, the FIB-4 index enabled the correct identification of patients with severe fibrosis (F3-F4) and cirrhosis AUROC of 0.85 and 0.91, respectively [40].

Fibrotest®/Fibrosure®

Fibrotest® (Bio Predictive, Paris, France) and Fibrosure® (Lab Corp, Burlington, NC, USA) use five different serum markers: α2-macroglobulin, haptoglobin, apolipoprotein A1, GGT and total bilirubin. In contrast to the other indirect fibrosis tests, calculation of the Fibrotest/Fibrosure by a patented algorithm is subject to payment of a fee to the manufacturer. It has been validated in meta-analysis in multiple etiologies including NAFLD (AUROC 0.84), alcohol-related liver disease (AUROC 0.86) as well as chronic viral infection (HBV: AUROC 0.80; HCV: AUROC 0.85) [6,41]. Test accuracy is limited by acute inflammation, hemolysis or hyperbilirubinemia [42,43].

Direct fibrosis tests

Serum levels of ECM protein reflect the balance between hepatic fibrogenesis and fibrolysis and have been proposed as direct (bio) markers of hepatic fibrosis. Several fibrosis panels, combinations of such biomarkers, have been developed for commercial use. Their diagnostic performance in hepatic fibrosis may be limited by extrahepatic confounding factors such as systemic inflammation or renal failure [43].

Hyaluronic acid (HA)

HA is a polysaccharide present in ECM and elevated in serum in patients with hepatic fibrosis. The diagnostic accuracy was confirmed for fibrosis≥F2 in a large study of 486 HCV Patients (AUROC 93-99%) and in context with NAFLD [44,45].

Matrix metalloproteinases (MMPs) and inhibitor

Excess ECM proteins are degraded by MMPs which are in turn inhibited by tissue inhibitors of metallo proteinases (TIMPs). Both MMPs and TIMps are related to matrix protein turnover. But their usefulness is unclear because of conflicting results in context with LF in various studies [43].

Procollagen type III amino-terminal peptide (PIIINP)

In the healthy human liver the most abundant collagens are the fibril-forming types I and III. In its mature form, the collagen is integrated into the ECM, and its relative concentration in the basement membrane is higher in hepatic fibrogenesis followed by an increase in serum levels. In CLD, serum PIIINP reflects the stage of LF, but it is not specific for LF (i.e. also elevated in lung fibrosis, rheumatologic disease) [46].

Enhanced liver fibrosis score

The enhanced liver fibrosis score (ELF®) score (Siemens, Munich, Germany) is a combination of three direct markers of LF: hyaluronic acid, TIMP-1 and PIIINP. A higher score will indicate a higher rate of fibrogenesis. The test has good performance for detection significant fibrosis in chronic HCV (93% sensitivity and 83% specificity), in NAFLD (sensitivity 89% and specificity 96%) and ALD (100% sensitivity and 16.7% specificity). Test-results can be influenced by gender, age, and sex [6,47-49].

Imaging Based Methods

Standard ultrasound

Native ultrasound in b-mode for estimation liver tissue is important for screening liver damage or lesions. But its sensitivity for detection LF is low and higher graded LF can be underestimated.

Liver elastography, liver stiffness measurement

In the recent years various imaging modalities have been proposed as methods for assessing LF by liver stiffness measurement. Transient elastography (TE; FibroScan®, Echosens, Paris) was first developed. Briefly, this system is equipped with a probe consisting of an ultrasonic transducer mounted on the axis of a vibrator. A vibration of mild amplitude and low frequency is transmitted from the vibrator to the tissue by the transducer itself. This vibration induces an elastic shear wave which propagates through the tissue. In the meantime, pulse-echo ultrasonic acquisitions are performed to follow the propagation of the shear wave and measure its velocity, which is directly related to tissue stiffness (or elastic modulus). The harder the tissue, the faster the shear wave propagates (AUROC:≥F3 0.93) [50].

Several studies substantiated good accuracy of Magnetic Resonance Elastography (MRE) for estimation LF. A prospective, cross-sectional study of more than 100 patients, demonstrated MRE to be more accurate than TE in identification of LF (≥F1) [51]. Studies utilize visual morphometry (MRI T1 sequence) to quantify the amount of fibrosis in liver biopsy and showed AUROCs for advanced fibrosis and cirrhosis of 0.931 and 1.000 respectively for pathologists versus 0.763 and 0.972 for T1 MRI sequence [52]. The advantage of this method is the evaluation of great volume of hepatic tissue and shows the often heterogeneous lesion distribution as well as it quantifies fibrosis, fat content, and iron content in the same 25min examination.

Acoustic Radiation Force Impulse Shear Wave Elasticity Imaging (ARFI-SWEI) is a novel ultrasound method for LF assessment [53-55]. This dynamic method is a real time dual display-imaging mode and allows a quantitative assessment of tissue stiffness by using acoustic radiation force to produce an acoustic “push” pulse that generates shear waves, which propagate into the tissue; their speed (meter/second, m/s) reflects the underlying tissue stiffness and severity of LF. This method is comfortable for the patient and examiner and takes only few minutes. It can be used for assessing

different degrees of liver stiffness (fibrosis stages) and correlated to the b-mode aspect of the liver in the same session [54,56].

In the last years studies verified ARFI-SWEI as a powerful noninvasive method in predicting fibrosis ≥F2 with high diagnostic accuracy and validity. The accuracy of ARFI-SWEI is well tested and it is reliable in prediction of fibrosis in early stages (≥F2). The sensitivity and specificity of the ARFI-SWEI method is ascertained of 83-88% and 89-90% and its accuracy, expressed as area under the curve receiver-operating characteristic (AUROC), is near 1 [56].

Many studies proofed the impact of possible influencing factors of ARFI measurements or SWV values, for example obese, small intercostal space, food intake, ultrasound transducer, operators expertise, cholestasis, breathing maneuvers or body position [57,58].

Recently a study on 382 patients with aim to investigate the clinical usefulness of ARFI-SWEI- screening for uncovering possible LF during routine ultrasound of the abdomen showed that in cases of normal native ultrasound scan liver damage can be underestimated. By using ARFI-SWEI as an additional method tissue damage of the liver was uncovered for further diagnostic evaluation [60].

Therapeutic options in liver fibrosis

If cirrhosis is not completed regression of fibrosis is possible, when underlying disease is treated. Recent clinical studies comprising patients successfully treated for viral hepatitis showed that liver fibrogenesis and even cirrhosis may be reverted [54]. Today successful therapeutic options for HBV and HCV minimize the risk of progressive LF up to LC and/or HCC. HCV treatment with direct acting antivirals is successful with sustained viral response over 92-98% and therapy of HBV with nucleotide-/nucleoside-analog-inhibitors are able to suppress viral load and initiate regression of fibrosis [60].

Until today there exists no direct anti-fibrotic drug for treating fibrosis. The hepatic capacity to remodel scar tissue and to revert into a normal liver follows specific mechanistic principles that include the termination of chronic tissue damage, shifting the cellular bias from inflammation to resolution, initiation of myofibroblast apoptosis or senescence and, finally, fibrinolysis of excess scar tissue. The plurality of molecular and cellular triggers involved in initiation, progression and resolution of hepatic fibrogenesis offers an infinite number of therapeutic possibilities [61]. For instance, inflammatory macrophages can be targeted via inhibition of chemokine or its receptor (i.e. by Cenicriviroc) as well as by transfer of restorative macrophage subsets [62]. Another target is galectin-3 that acts at various stages along the continuum from acute to chronic inflammation. Profibrogenic cytokines like transforming growth factor-β, matrix cellular proteins or signaling pathways involved in fibrogenesis offer further possible targets. Other options are the application of therapeutic antibodies directed against components involved in biogenesis or remodeling of connective tissue such as lysyl-oxidase-like-2 or synthetic bile acids like obeticholic acid that activate the farnesoid X receptor and was antifibrotic in a phase 2 study (FLINT trial) [63,64]. Obeticholic acid has already been proven to have efficacy when combined with ursodeoxycholic acid in the treatment of PBC [65]. Factors affecting the gut barrier function or the intestinal microbiome further expanded the repertoire of drug targets.

Animal studies showed positive side effects of the dipeptidyl peptidase-4 inhibitor (DPP4-I), Sitagliptin, attenuating LF via suppression of activated hepatic stellate cell and collagen synthesis in rats. Since DPP4-I is widely used in clinical practice, this drug may represent a potential new therapeutic strategy against LF in the future, and also in combination with angiotensin-II type 1 receptor blocker, Lorsatan [66,67].

Recently, Sorafenib, an FDA approved molecular targeted drug for the treatment of advanced hepatocellular and renal cell carcinomas, has been reported to exert anti-fibrotic effects in LF. Animal models showed that Sorafenib ameliorated intrahepatic vascular resistance, reduced portal hypertension, and reduced intrahepatic fibrosis, inflammation and angiogenesis. Further studies are required to clarify its anti-fibrotic role, effective dose, and side effects [68,69].

Conclusion

LF is part of the structural and functional alterations of liver tissue in most chronic liver diseases with the risk to develop LC. To avoid LB several non-invasive methods have been suggested for the diagnosis of LF, including serum markers, liver stiffness measurements and ultrasound parameters. Serum parameters are useful but complex scores including direct biomarkers are expensive or unavailable in daily use. Research results have shown their high diagnostic accuracy for advanced LF/LC. Native ultrasound gives hint for LF but can underestimate high graded liver fibrosis. TE and ARFI-SWEI may play a pivotal role in the study of LF. Studies have shown that elastography can detect both the progression and regression of fibrosis in individual course. To that fact the best validity seems to have ARFI-SWEI, because with this method LF≥F2 and liver failure can be uncovered. This easy handling method together with indirect fibrosis tests the accuracy in detecting liver fibrosis is higher. LF stops when underlying cause for liver failure is eliminated. The liver is capable to regenerate itself. Until today no drug for treating LF directly is available. However, it is still unknown if either non-invasive biomarkers of LF or elastography may contribute to a more accurate staging of LC, in terms of prognosis and fibrosis regression after effective therapy. In fact, not enough studies have shown both the fibrosis regression in different cirrhosis stages and the point beyond which the prognosis does not change - even in the event of fibrosis regression. Therefore, future studies are needed to validate non-invasive methods in predicting the different phases of liver LF.

Competing Interest

The author declare that he has no competing interests.

Financial Disclosure

The author has no financial disclosure to report and no conflict of interest.

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