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An Overview of Hepatic Fibrogenesis

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Hepatic fibrosis is a dynamic process that results from chronic liver injury. It kills over one million people a year worldwide and has many etiologies. While the common mechanism involves hepatocyte injury, inflammation and eventual distortion of hepatic architecture, each etiology has a unique pathway. In this review we discuss major causes such as alcoholic liver disease, non-alcoholic fatty liver disease, chronic viral hepatitis and cholestatic liver disease. In addition we review current diagnostic modalities and provide general management principles.

Hepatic fibrosis is a major public health problem that carries with it a high morbidity and mortality. It results from the wound-healing response to chronic liver injury and can result in cirrhosis and hepatocellular carcinoma (HCC).[1,2] Common causes include alcoholic liver disease, non-alcoholic liver disease (NAFLD), chronic viral hepatitis, and cholestatic liver disease. Other less common etiologies include autoimmune hepatitis, Wilson's disease, hemochromatosis, and schistosomiasis (See Table 1).[2-7] Regardless of etiology, the end result of chronic hepatic injury is a fibrotic liver with hepatic stellate cells playing a pivotal role in the formation of hepatic fibrosis.[8-10]

Fibrogenesis begins with hepatocyte injury and inflammation that activates hepatic stellate cells (HSC). These activated HSCs then transdifferentiate into myofibroblasts, which results in an increased extracellular matrix (ECM) deposition in the liver leading to fibrosis.[2,11-13] This is shown pictorially in Figure 1. Bone marrow derived fibrocytes and epithelial-mesenchymal transition (EMT) from hepatocytes and cholangiocytes also contribute to fibrosis. Several fibrogenic mediators get recruited in the inflammatory cascade including transforming growth factor (TGF-beta), platelet derived growth factor (PDGF), insulin-like growth factor I (IGF-I), endothelin-I (ET-I), and reactive oxygen species (ROS).[13,14] Repeated hepatic injury results in this proinflammatory microenvironment and leads to liver fibrosis, cirrhosis, and the development of HCC. Early intervention can lead to the reversal of hepatic fibrogenesis.[14]

Alcoholic Liver Disease

Alcoholic liver disease (ALD) is due to chronic and excessive alcohol consumption and is a leading cause of liver disease worldwide.[15] In fact, ALD is the third highest risk factor for disease and disability globally with nearly 4% of the world's deaths attributed to

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Table 1. Etiology of Hepatic Fibrosis

Disease	Etiology
Major	
Alcoholic liver disease	Alcohol
Non-alcoholic fatty liver disease	Obesity, Diabetes, Metabolic Syndrome
Chronic viral hepatitis	Hepatitis B, Hepatitis C
Cholestatic liver disease	Biliary obstruction
Minor	
Autoimmune hepatitis	Inflammation
Wilson's disease	Copper overload
Hemochromatosis	Iron overload
Parasitic diseases	Schistosomiasis, Echinococcosis

alcohol consumption.[16,17] Per the National Institute on Alcohol Abuse and Alcoholism, the 12th leading cause of death in the United States is cirrhosis with 48% of those deaths due to alcohol.[18] Not only is there a high mortality associated with alcohol abuse, but it leads to increased social problems including violence, child neglect and abuse, and absenteeism in the workplace.[16]

By definition, ALD can occur when daily alcohol ingestion exceeds 20g in women or 30g in men. This number should not be taken as an absolute threshold as patients vary based on differences in genetic susceptibility and other risk factors.[19,20] Indeed, the spectrum of alcoholic liver disease is vast and includes simple steatosis or fatty liver, alcoholic hepatitis, end-stage cirrhosis, and HCC.[21] Of note, nearly 100% of heavy drinkers have fatty liver, but only 10-20% of them advance to alcoholic hepatitis or obtain the final pathologic changes of ALD associated fibrosis and cirrhosis.[15,22,23] In ALD-associated fibrosis, the major cell type that contributes to fibrogenesis is the activated hepatic stellate cell. While the underlying mechanism of fibrosis in ALD is very similar to the mechanisms seen in other chronic liver diseases, methionine metabolism abnormalities, hepatocyte apoptosis, oxidative stress, and endotoxin lipopolysaccharides which activate Kupffer cells may play special roles in ALD fibrosis.[16,22] In addition, emerging mechanisms underlying hepatic fibrogenesis in ALD include lipogenesis, cannabinoid receptor activation, and IL-1 signaling.[11,16]

Non-alcoholic Fatty Liver Disease (NAFLD)

As opposed to ALD, non-alcoholic fatty liver disease (NAFLD) occurs in the absence of chronic alcohol consumption (less than 20g of pure alcohol/day for women and less than 30g of pure alcohol/day for men) or other liver diseases and has emerged as the most common chronic liver disease in Western countries.[24-26] Obesity, unhealthy diet, sedentary lifestyle and genetic predisposition are all risk factors associated with the development of NAFLD. Higher rates of insulin resistance, diabetes mellitus, hypertension, dyslipidemia and the metabolic syndrome are associated with this disorder.[27] In fact, excessive food intake, especially high fructose corn syrup and saturated fats have been shown in numerous studies to contribute to the development of NAFLD.[28] NAFLD is thought to affect 30% of the general adult population and 70-80% of patients that are diabetic or obese.[29] Furthermore, the impact of NAFLD on society is significant since it is estimated that NAFLD increases healthcare costs by 26% and will be the leading cause of liver transplantation by 2020.[25]

NAFLD encompasses two clinicopathological entities that range from simple steatosis to non-alcoholic steatohepatitis (NASH). Simple steatosis accounts for 80-90% of NAFLD cases and is characterized by an excessive amount of fat in the liver, and is mostly benign and non-progressive. NASH constitutes the remaining 10-20% of NAFLD cases and is characterized by steatosis coupled with inflammation and fibrosis, and can progress to cirrhosis and HCC.[19] The development of NASH is often described by the "two-hit" mechanism with the "first hit" being the development of steatosis and the "second-hit" involving environmental factors such as oxidative stress and proinflammatory cytokines coupled with genetic factors leading to hepatic injury.[29-31] Once patients develop NASH, approximately one-third

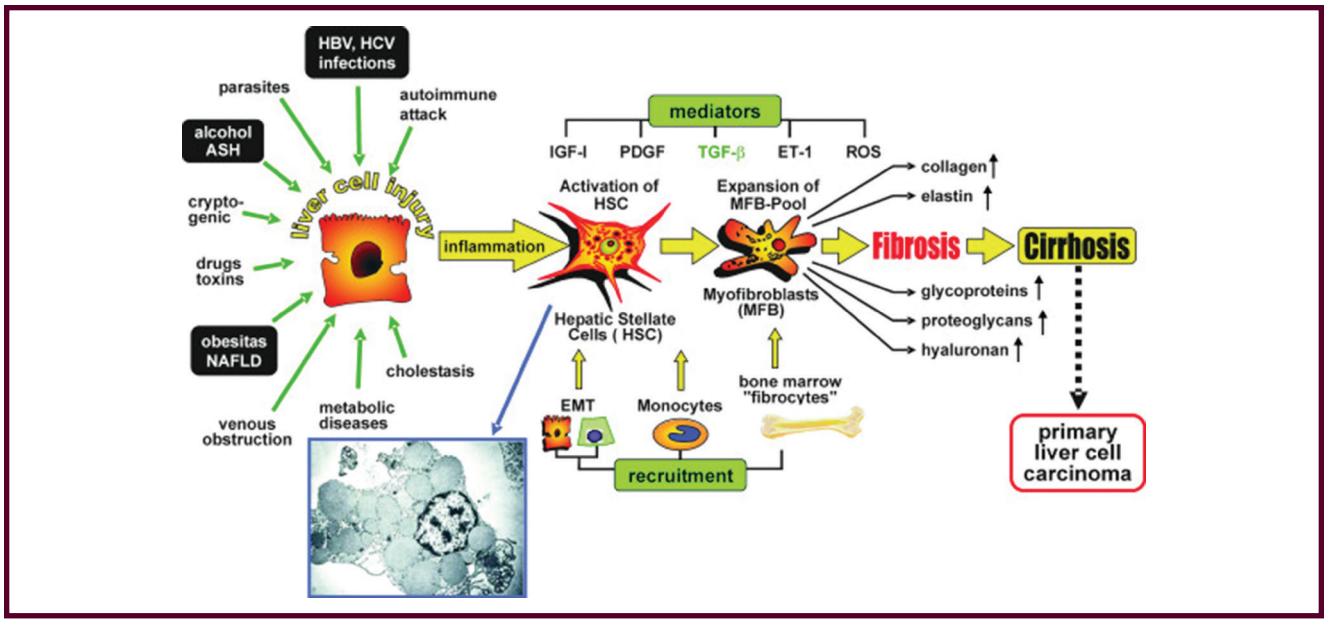

Figure 1. Formal pathogenesis of liver fibrosis (fibrogenesis). The "canonical principle" of fibrogenesis starts with necrosis or apoptosis of hepatocytes and inflammation-connected activation of hepatic stellate cells (HSC triggering), their transdifferentiation to myofibroblasts with enhanced expression and secretion of extracellular matrix and matrix deposition (fibrosis). The latter is a precondition for cirrhosis. New pathogenetic mechanisms concern the influx of bone marrow-derived cells (fibrocytes) and of circulating monocytes and their TGF-β driven differentiation to fibroblasts in the damaged liver tissue. A further new mechanism is epithelial-mesenchymal transition (EMT) of bile duct epithelial cells and potentially of hepatocytes. All three complementary mechanisms enlarge the pool of matrix-synthesizing (myo-)fibroblasts in the damaged liver. The most important fibrogenic mediators are transforming growth factor (TGF)-β, platelet-derived growth factor (PDGF), insulin-like growth factor 1 (IGF-1), endothelin-1 (ET-1), and reactive oxygen species (ROS including hydroxyl radicals, superoxid anions). Abbreviations: ASH - alcoholic steatohepatitis; NAFLD - non-alcoholic fatty liver disease. Inset shows an electron micrograph of HSC with numerous lipid droplets indenting the nucleus. *This article was copyrighted in 2007 by Comparative Hepatology and permission was obtained to reproduce this figure by SpringerOpen.*

go on to develop hepatic fibrosis.[32] In addition to obesity and sedentary lifestyle, NAFLD increases with age, central obesity, and has a strong genetic predisposition with several affiliated gene polymorphisms.[33] The renin-angiotensin system (RAS) seems to play an important role in the development of NASH, as does the bacterial endotoxin within the gut-liver axis.[34-36]

Chronic Viral Hepatitis

Hepatitis B (HBV) and Hepatitis C (HCV) viruses are leading causes of chronic liver disease. It is estimated that over two billion people have been infected with HBV, of which over 300 million are chronic carriers.[37] On average only about 10% of patients with HBV progress to chronic disease.[38] Of the chronic HBV patients, about 20% will develop liver cirrhosis.[39] The risk of HCC is about 100 times greater than the general population.[40] HBV promotes liver fibrosis via expression of the hepatitis B virus X (HBx) protein. This particular protein increases the expression of type 1 collagen, TGF-beta and increases the cell proliferation rate.[41] Studies have also shown that the HBx protein accelerates proliferation of HSC cells thereby facilitating liver fibrosis.[42]

It is estimated that over 185 million people worldwide are infected with HCV. Eighty percent of those infected progress to chronic infection.[44] Furthermore 20% of patients with chronic HCV will develop cirrhosis within 25 years and 25% of these patients develop HCC or decompensated liver disease.[45] HCV is the primary cause of liver transplantation in the United States.[46] There are a total of 6 identified genotypes of HCV. In the United States, 97% of all infections are from genotype 1, genotype 2 and genotype 3.[47] The inflammatory cascade that leads to cirrhosis is likely initiated by HCV core and NS3 proteins.[48] The subsequent cytokine and chemokines generated lead to increased recruitment of inflammatory cells such as macrophages, dendritic cells, natural killer cells and cytotoxic T cells. HCV activated Kupffer cells release

ROS and other proinflammatory mediators thus leading to the common hepatic fibrosis pathway.

Cholestatic Liver Disease

Cholestatic liver disease primarily results from an impairment of hepatobiliary production and excretion of bile. Cholangiocytes and hepatocytes proliferate in response to injury leading to biliary damage, periductular fibrosis and cirrhosis.[49] The two most common causes of chronic cholestatic liver disease are primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC). PBC is a progressive autoimmune condition with an incidence of approximately 100 cases per million people.[50] It primarily affects women in the fifth decade of life and is associated with an increased incidence of HCC.[51,52] The pathogenesis of PBC is an autoimmune mediated process and can be divided into several stages. The initial stage involves infiltration of the portal triad by lymphocytes, plasma cells and eosinophil granulocytes.[53] As PBC progresses fibrotic septa extend from the portal tracts and link them together. This is called "bridging fibrosis" and is the characteristic finding in PBC.[53] Eventually the hepatic architecture becomes distorted leading to cirrhosis and the formation of regenerative nodules. Diagnosis of PBC is made when 2 of the following 3 criteria are met: presence of anti-mitochondrial antibodies, elevation serum alkaline phosphatese > 1.5 times the upper limit of normal and consistent histologic findings on liver biopsy.[51]

Primary sclerosing cholangitis (PSC) is a progressive inflammation and fibrosis of the intra and extra hepatic bile ducts. It is estimated that 1 in 100,000 people will be affected. Most are males and the median age of diagnosis is 40.[54] Of note, 75% of patients with PSC have inflammatory bowel disease (IBD).[55] PSC leads to cholestasis, progressive hepatic fibrosis and decompensated cirrhosis over the course of 10-15 years.[56] PSC increases the risk for hepatobiliary and colorectal cancer.[57] The pathogenesis of PSC is poorly understood. It is believed to be a complex immune mediated disease. There is likely a genetic predisposition that is subsequently triggered by an environmental component.[58] Diagnosis is primarily made through liver tests and imaging. [59] No auto-antibody has been found that is specific to PSC.[60] Cholangiography shows short, multifocal, annular strictures alternating with normal and slightly dilated intervening segments leading to the classic "beads-on-a-string" appearance.[61]

Diagnosis of Hepatic Fibrogenesis

Liver biopsy with histologic examination has been the gold standard for diagnosis and staging of hepatic fibrogenesis. However several non-invasive methods also are available to assist in diagnosis. Ultrasound (US) is the first modality as it is non-invasive, cost-effective and does not expose patients to radiation. Characteristic findings of cirrhosis on US include a coarse nodular appearance of hepatic parenchyma, hepatomegaly, ascites and caudate lobe atrophy.[62] Computer tomography (CT) is also a commonly used modality in the evaluation and diagnosis of liver fibrogenesis. CT is believed to have sensitivity of 77.1% and specificity of 67.6%.[63] Magnetic resonance imaging (MRI) has been used to quantify fibrosis with a sensitivity of 85% and specificity of 100%.[64] More recently a new method called transient elastography (TE) has been developed. It relies on the principle of shear waves. A transducer emits a 50MHz pressure wave through the liver and the resulting shear wave is measured by US. The shear wave velocity is correlated with liver stiffness, which in turn estimates liver fibrosis. For the diagnosis of cirrhosis, TE has a sensitivity of 83% and a specificity of 89%.[65] Several serum biomarkers are also available in the non-invasive diagnosis of liver fibrogenesis. Often these biomarkers are described as direct, which reflect extracellular turnover, or indirect, which reflect overall liver function. AST-Platelet Ratio Index (APRI) is a common biomarker used in the estimation of fibrosis. A higher APRI value is indicative of worsening fibrosis. APRI score of 1.0 had a sensitivity and specificity of 76% and 72% respectively for the prediction of cirrhosis.[66] Fibrotest is a another biomarker panel that uses alpha-2 macroglobulin, haptoglobin, total bilirubin, apolipoprotein-A, GGT, age and gender to calculate score between 0.0 to 1.0, with 1.0 meaning significant fibrosis.[67] Direct biomarkers include hyaluronic acid (HA), amino terminal of serum procollagen III peptide (PIIINP), tissue inhibitors of metallopreinase-1 (TIMP-1). HA is a glycosaminoglycan found in the extracellular matrix. It enters circulation during matrix turnover and is degraded in the liver through hepatic endothelial cells. High levels of HA can be due to increased matrix turnover or reduced clearance. PIINP is a marker of collagen turnover with increased levels correlated with tissue repair and fibrosis. PIINP has been found to accurately predict fibrosis in the setting of PBC, NAFLD and viral hepatitis.[68-71] TIMP-1 is an enzyme that inactivates chollagenase with levels found to be

Table 2. Recommendations for the Primary Care Provider

1. Recommend alcohol cessation
2. Screen for viral hepatitis, vaccinate, and treat where appropriate
3. Measure waist circumference, BMI and screen for diabetes and dyslipidemia
4. Counsel on regular moderate physical activity (3 to 5 days per week)
5. Avoid high calorie diets rich in trans/saturated fats and high fructose-sweetened beverages
6. Encourage low fat, low calorie diets
7. Consider supplementation with omega-3 fatty acids, probiotics, ginger, and curcumin
8. Consider ARB if medication is needed for hypertension
9. Consider statin with close monitoring of LFTs if dyslipidemic
10. Consider metformin or pioglitazone if medication is needed for diabetes
11. Vitamin E and pentoxifylline may have a role in NASH but needs further study
12. In cholestatic liver disease, refer to GI to relieve any biliary obstruction

Abbreviations: BMI: body mass index; ARB: angiotensin receptor blocker; LFT: liver function test; GI: gastroenterology.

higher in patients with liver fibrogenesis.[72] Enhanced liver fibrosis (ELF) test uses a combination of PIIINP, HA and TIMP-1. It has been found to have a sensitivity and specificity of 90% and 69% respectively in those with chronic liver disease.[73]

Recommendations for the Primary Care Provider

From this overview on the basics of hepatic fibrogenesis, several recommendations can be made for the primary care physician when co-managing these patients (see table 2). First should be the removal of any liver injury-causing factors such as viral agents, alcohol, toxins and medications. This not only halts the progression of hepatic fibrosis, but it often leads to its regression.[3] Alcohol abstinence is the most effective treatment for ALD, and this should be enforced at every encounter as it may completely reverse steatosis.[16,17] Viral hepatitis screening, vaccination, and treatment is paramount since even cirrhosis has been reversed in several patients, when HBV and HCV have been treated.[9]

When it comes to NAFLD, generalists can screen for risk factors of the metabolic syndrome by measuring waist circumference, obtaining body mass index (BMI), and screening for insulin resistance and dyslipidemia.[33] Obesity, especially central obesity, is a major risk factor for NASH and BMI is a good marker for predicting NAFLD.[74,75] Counseling on regular moderate physical activity for 3 to 5 days per week should be recommended.[27,76,77] In addition, high calorie diets that are rich in trans/saturated fat and high fructose-sweetened beverages should be avoided, while low calorie diets supplemented with monounsaturated fatty acids, omega-3 fatty acids, and probiotics should be encouraged.[78] 6-gingerol, a key component of ginger, and curcumin, a bioactive component in turmeric have both been shown to have anti-inflammatory and antioxidant properties that may be hepatoprotective.[79,80] Pharmacotherapy should include an angiotenstin receptor blocker (ARB) for hypertension, statin therapy, with close monitoring of liver tests, for dyslipidemia, and metformin or pioglitazone for diabetes.[24,25,34] Vitamin E and pentoxifylline may have a role for NASH, but need further study.[20]

The advent of antiviral therapy has revolutionized the management of viral hepatitis. In managing HBV there is now strong evidence that antiretroviral therapy lowers disease progression and the incidence of HCC in patients with high serum HBV DNA levels and advanced liver disease.[81] Recently several oral direct acting antiviral medications that target different stages of the HCV life cycle have become available. Treatment using these agents is genotype specific. Treatment of HCV in HIV coinfected patients can be a challenge as there are extensive drug interactions with HIV antiretrovirals.[82,83]

Treatment of PBC and PSC are limited. For

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patients with PBC, treatment with ursodeoxycholic acid (ursodiol) has been shown to delay progression of hepatic fibrosis.[84] Other medications such as colchicine and methotrexate may be effective.[85,86] There are no medical therapies that alter the natural course of PSC. Liver transplant is the only definitive treatment for patients with advanced disease. Overall prognosis in PSC remains poor with a 12 year median time from diagnosis to death or liver transplant.[87] Acute decompensation can occur in patients with PSC due to sudden obstruction of the hepatobiliary system. Relieving obstruction can improve outcomes.

CONCLUSION

Hepatic fibrogenesis is a dynamic process with a multitude of etiologies. In the United States there are over 100,000 hospitalization and 36,000 deaths from liver disease.[88] Etiologies include ALD, NAFLD, viral hepatitis and cholestatic liver disease. Diagnostic modalities ranging from invasive liver biopsy to non-invasive imaging and serum markers provide physicians with an array of options for further evaluation of suspected liver disease. In addition to the etiology specific treatments available, general measures can be taken to prevent and arrest the progression of hepatic fibrogenesis. ■

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