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Regression of Hepatic Fibrosis and Evolution of Cirrhosis: A Concise Review

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Abstract: Fibrosis is not a unidirectional, linear process, but a dynamic one resulting from an interplay of fibrogenesis and fibrolysis depending on the extent and severity of a biologic insult, or lack thereof. Regression of fibrosis has been documented best in patients treated with phlebotomies for hemochromatosis, and after successful suppression and eradication of chronic hepatitis B and C infections. This evidence mandates a reconsideration of the term "cirrhosis," which implies an inevitable progression towards liver failure. Furthermore, it also necessitates a staging system that acknowledges the bidirectional nature of evolution of fibrosis, and has the ability to predict if the disease process is progressing or regressing. The Beijing classification attempts to fill this gap in contemporary practice. It is based on microscopic features termed "the hepatic repair complex," defined originally by Wanless and colleagues. The elements of the hepatic repair complex represent the 3 processes of fragmentation and regression of scar, vascular remodeling (resolution), and parenchymal regeneration. However, regression of fibrosis does not imply resolution of cirrhosis, which is more than just a stage of fibrosis. So far, there is little to no evidence to suggest that large regions of parenchymal extinction can be repopulated by regenerating hepatocytes. Similarly, the vascular lesions of cirrhosis persist, and there is no evidence of complete return to normal microcirculation in cirrhotic livers. In addition, the risk of hepatocellular carcinoma is higher compared with the general population and these patients need continued screening and surveillance.

Key Words: cirrhosis, hepatocellular carcinoma, regression of hepatic fibrosis, vascular lesions, vascular remodeling, hepatic repair complex, the Beijing classification, chronic hepatitis, nonalcoholic fatty liver disease

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Like many radically disruptive ideas, the debate about regression of hepatic fibrosis and cirrhosis started in early 1960s. An early study on reversal of fibrosis was published by Hans Popper, one of the founders of hepatopathology.[1–4] The debate continued with much skepticism and little optimism over the next 4 decades,[5] culminating with the pioneering publication of Wanless et al.[6] The past 2 decades have however, provided substantial evidence for regression of hepatic fibrosis.[7–10] This new paradigm in the evolution of hepatic fibrosis led to development of the Beijing classification for systematic and reproducible documentation of regression versus progression of fibrosis.[11] Successful treatment of chronic liver diseases, accompanied by of regression of fibrosis, has additionally changed the diagnostic and therapeutic implications of the term "cirrhosis." Considered inevitably "end-stage" for almost 2 centuries, current evidence for regression of fibrosis begs us to reconsider the term "cirrhosis" in the face of timely diagnosis, accurate identification of the underlying etiologies, and effective therapies.[12]

In this review, we summarize the histopathologic parameters that have been demonstrated to support regression of fibrosis in chronic liver disease, elaborate the Beijing classification's relevance and clinical utility, and highlight the underexplored areas of inquiry such as the fate of vascular abnormalities associated with cirrhosis and the risk of hepatocellular carcinoma (HCC).

HEPATIC FIBROSIS: IS UNIDIRECTIONAL PROGRESSION INEVITABLE?

Hepatic fibrosis is defined as excessive deposition of collagen (type I and 1V) in the hepatic parenchyma. It is distinct from parenchymal collapse which results in approximation (collapse) of pre-existing reticulin network (collagen type III) when the intervening hepatocytes are lost in a disease process. Conventional systems for staging of fibrosis in chronic viral hepatitis, developed before effective therapies became available, considered fibrosis to be a linear, inevitably progressive process that proceeded from an early stage (portal fibrosis—Ishak stage 0 to 2, Metavir F0 to F1, Batts-Ludwig stage 0 to 2), through intermediate stages (fibrous septa, focal or frequent —Ishak stage 3 to 4, Metavir F2 to F3, Batts-Ludwig stage 3) to advanced stages of fibrosis (fibrous septa with diffuse nodularity/"established cirrhosis"—Ishak stage 5 to 6, Metavir F3 to F4, Batts-Ludwig stage 3 to 4).[13–15] However, fibrosis is not a unidirectional, linear process, but rather a dynamic one resulting from an interplay of fibrogenesis and fibrolysis depending on the extent and severity of a biologic insult, or lack thereof. In short, fibrosis of the liver parenchyma at any given time represents the balance between injury and repair. Thus, when an underlying injurious agent is removed, the balance shifts towards repair, with fibrolysis leading to regression of fibrosis.

Initially limited to experimental animal studies, credible evidence now extends to human patients treated with phlebotomies for hemochromatosis, and after successful suppression and eradication of chronic hepatitis B and C infections.[2,4,16–20] Partial regression of cirrhosis has also been documented in patients with biliary obstruction, Wilson disease, intestinal bypass-related cirrhosis, Indian childhood cirrhosis, autoimmune hepatitis, primary biliary cholangitis, and alcoholic liver disease.[21–28] The earliest case reports and small case series documenting regression of fibrosis after therapeutic phlebotomies were published in 1950 to 1970s.[29–33] One of the largest series on regression of

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fibrosis in hemochromatosis documented regression of fibrosis using METAVIR staging system.[34] The study documented 36 patients, between the ages of 18 to 75 with homozygous C282Y mutation, METAVIR stage F3 or F4 on the initial liver biopsy, and a minimal interval of 2 years between cessation of phlebotomies and a second liver biopsy. The pretherapeutic and posttherapeutic biopsies were compared independently by 2 liver pathologists, who were blinded to the clinical and biochemical data. The histologic parameters studied included portal fibrosis (METAVIR grading system), quantity of iron (semiquantitative grading system of Deugnier et al[13]),[31] and amount of steatosis (a 4-grade scale). Regression of fibrosis, defined as a decrease of at least 2 METAVIR stages, was seen in 47% (17/36) patients. Among 23 patients with cirrhosis (F4) on their initial biopsy, fibrosis decreased in 10 (43.5%); from F4 to stage 0 in 1 patient, to stage 1 in 4 patients, to stage 2 in 3 patients, and to stage 3 in 2 patients. Among 13 patients with F3 fibrosis on initial biopsy, fibrosis decreased in 11 (84.6%); from F3 to stage 0 in 3 patients, to stage 1 in 6 patients, and to stage 2 in 2 patients.

DOES REGRESSION OF FIBROSIS IMPLY REVERSAL OF CIRRHOSIS?

Cirrhosis is not merely a "stage of fibrosis," but rather a diffuse process characterized by advanced fibrosis, regenerative nodule formation, and vascular remodeling. Vascular remodeling accompanies parenchymal damage and is fundamental to the progression of chronic liver diseases.

A hallmark of chronic liver diseases are regions of parenchymal extinction, originally defined as a parenchymal area with contiguous loss of hepatocytes.[35] The drop-out of hepatocytes is accompanied by loss of the local microvasculature, which causes vascular compromise and ischemia, leading to further parenchymal damage. A self-perpetuating cycle is set up with increasing vascular compromise, involving progressively larger branches of the hepatic and portal vein thus escalating the congestion and ischemia,[36] and leading to ever larger areas of parenchymal collapse and extinction. Therefore, Wanless et al[36] proposed a revised definition of parenchymal extinction as "a region with focal loss of contiguous hepatocytes and adjacent microvascular structures." The fate of vascular abnormalities in cirrhosis is an underexplored area and there is lack of substantial evidence to support the idea of complete regression of these lesions. Thus, regression of fibrosis does not equate to reversal of cirrhosis as vascular abnormalities persist in livers with regressed fibrosis.

HISTOLOGIC FEATURES OF FIBROSIS REGRESSION

The Hepatic Repair Complex

The "hepatic repair complex" defined by Wanless et al[6] describes the elemental microscopic features that signal regression of fibrosis: delicate perforated septa, isolated thick collagen fibers, delicate periportal fibrous spikes, portal tract remnants, hepatic vein remnants with prolapsed hepatocytes, hepatocytes within portal tracts or splitting septae, minute regenerative nodules, and aberrant parenchymal veins. These features form the basis of the Beijing classification (discussed below), which broadly classifies them into 3 categories; fragmentation and regression of scar, vascular remodeling (resolution), and parenchymal regeneration (Fig. 1).[11]

Fragmentation and Regression of Scar

An established cirrhotic nodule is a "regenerative" nodule surrounded completely by thick fibrous septae containing inflammatory infiltrate, ductular proliferation, and edema. The central hepatic veins are compressed, obliterated, thrombosed, and often extinct, with concomitant development of vascular collaterals shunts. The vascular shunts in the cirrhotic nodule act as independent microcirculatory units. With regression, the fibrous septa start to lose inflammatory infiltrates and edema thus becoming more compact, thin, delicate, and less cellular or completely acellular. Thinning of septa leads to perforation and fragmentation and eventual interruption by regenerating hepatocytes. The hepatocytes can often be seen splitting the septa. Other features suggestive of regressing fibrosis are the presence of periportal delicate fibrous spikes or "adhesions," and reduction in the amount of collagen in the portal tracts.

Vascular Remodeling

With resorption of collagen, the portal tracts at the periphery of cirrhotic nodules start losing collagen resulting in appearance of "portal tracts remnants"—paired artery/arteriole and bile duct with a thin, delicate rim of collagen. The small veins are often obliterated. As repair/regeneration persists, hepatocytes migrate into the portal tract stroma and can be seen in the proximity of ducts/arteries and even in the lumen of portal vein remnants. Partially or completely recanalized large hepatic veins can be seen with regression, however most veno-occlusive disease lesions persist as fibroelastotic cords of collagen. Migration of regenerating hepatocytes into these lesions is also seen. Other features include presence of telangiectatic sinusoids and unpaired arteries in the regions of parenchymal extinction. These "arterialized sinusoids" and "capillarized channels" representing vascular shunts persist even when much of the fibrosis has regressed (Fig. 2).[37–39]

Parenchymal Regeneration

Suppression of the underlying injurious agent (viral infection, autoimmune hepatitis, alcohol etc.) tilts the balance in favor of hepatocellular regeneration. Hepatocytes proliferate and repopulate foci of parenchymal extinction, hitherto rich in proliferating ductules and inflammatory cells. Resorption of sinusoidal collagen results in remodeling of these areas and appearance of "near-normal" hepatic plates. However, large regions of parenchymal extinction persist, thus a complete regression of cirrhosis is almost never seen (Fig. 2).[35]

Incomplete Septal Cirrhosis

Incomplete septal cirrhosis, an enigmatic entity first described by Popper,[40] is a type of cirrhosis characterized by vaguely macronodular appearance delineated by delicate, incomplete septa. It is often associated with portal hypertension.[41] Although incomplete septal cirrhosis has been a perplexing entity, there are documented reports of partially resolved cirrhosis following suppression of liver injury that appear as incomplete septal fibrosis.[42,43] Wanless et al,[6] based on a study of 52 cases, proposed that incomplete septal cirrhosis, in fact represents a stage of regression of cirrhosis. With regression of fibrosis, the septa around the cirrhotic nodules become thin and delicate with time, and with migration of hepatocyte buds are split apart and eventually fragmented, imparting the appearance of an "incomplete" nodule. This observation was supported by

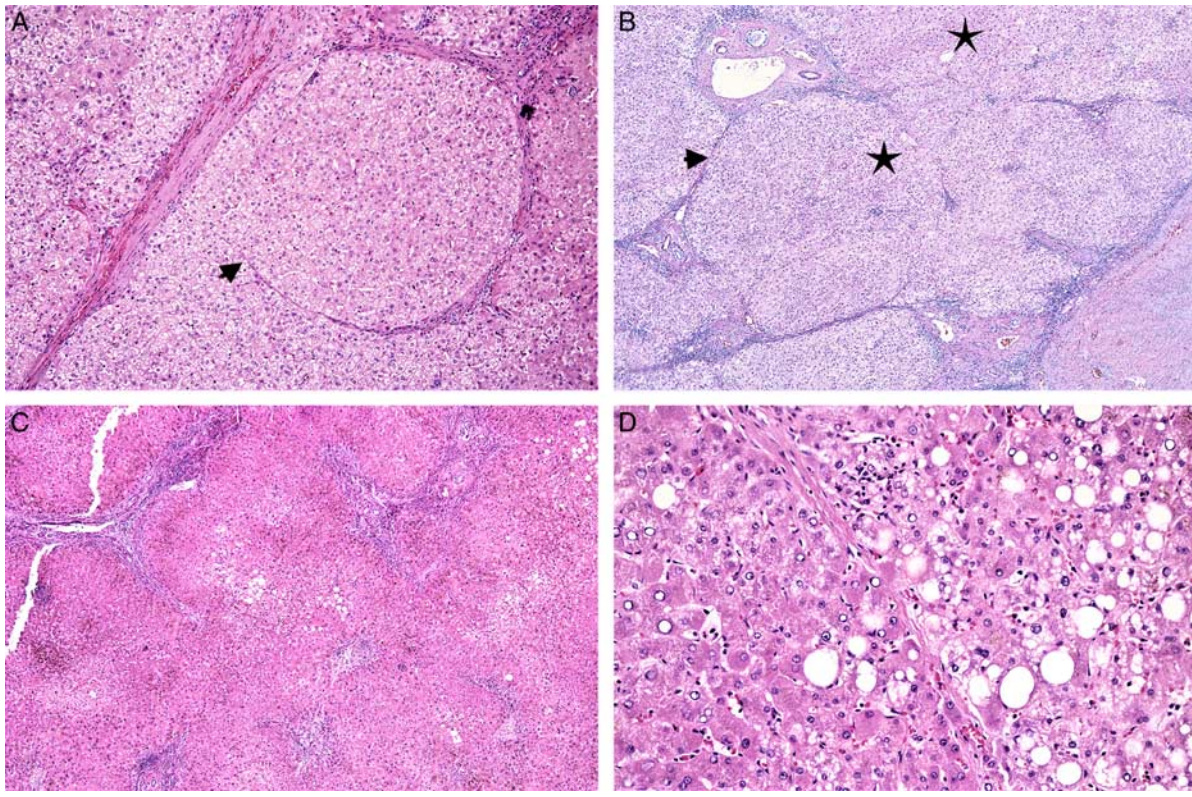

FIGURE 1. A, Regressing fibrosis seen as an incomplete nodule with progressively thinning septum (arrowhead) and regeneration of hepatocytes in a patient with cirrhosis due to nonalcoholic steatohepatitis. Hematoxylin and eosin ×100. B, Nodular liver parenchyma with incomplete septa. Compared with the portal tracts, fibrosis has regressed significantly with one thin septum (arrowhead) and aberrant vein remnants (stars) in a patient with cirrhosis due to nonalcoholic steatohepatitis. Hematoxylin and eosin ×100. C, Vaguely nodular liver parenchyma characterized by absence of complete septa and presence of portal tract remnants. Mild steatosis persists without ballooned hepatocytes or Mallory-Denk bodies in a patient with cirrhosis due to nonalcoholic steatohepatitis. Hematoxylin and eosin ×40. D, Hepatocyte buds are seen splitting the thin septum; the collagen band is significantly thinned out in the center compared with the periphery in a patient with cirrhosis due to nonalcoholic steatohepatitis. Hematoxylin and eosin ×100.

Theise et al[11] after assessment of 71 cases of treated chronic viral hepatitis B cirrhosis.

THE BEIJING CLASSIFICATION[11]

The advent and wide-spread availability of successful therapies for suppression of hepatitis B viral replication and eradication of hepatitis C virus has compelled a re-examination of existing staging systems. Contemporary practice requires a staging system that take into consideration the bidirectional nature of evolution of fibrosis with the potential ability to predict if the disease process is progressing or regressing. The Beijing classification proposed by Theise and colleagues attempts to fill this gap by devising a method to assess whether fibrosis is progressing or regressing at a given period in time, as captured in a liver biopsy.

The Beijing classification was developed on a study of paired pre and post treatment biopsies from 71 patients successfully treated for chronic hepatitis B virus (HBV) infection. In addition to grading of necroinflammatory activity and staging of fibrosis, it provides a P-I-R (Progressive-Indeterminate-Regressive) score to evaluate the predominant pattern and quality of fibrosis: predominantly progressive, predominantly regressive or indeterminate for cases in which the pattern is not straightforward one way or the other.

Evaluation is performed on a routine hematoxylin-eosin stain, combined with a trichrome or reticulin stain for assessment of fibrosis. Grading and staging are simplified into 3 grades of necroinflammatory activity and 3 stages of fibrosis, respectively. The 3 grades of necroinflammatory activity are "inactive" (portal inflammation only or rare foci of interface or lobular hepatitis; no confluent necrosis), "active, nonsevere" (varying degrees of interface and lobular hepatitis easily identified at low power; no confluent necrosis), and "active, severe" (confluent necrosis, perivenular drop out, bridging necrosis or parenchymal collapse). The 3 stages of fibrosis are "early" (no fibrosis or portal fibrosis), "intermediate" (fibrous septa, focal or frequent), and "advanced" (fibrous septa with focal or diffuse nodularity).

The defining histologic features of the progressive pattern are broad fibrous septa with loosely aggregated collagen fibers, edema, congestion, and inflammatory cells. In progressive disease, as parenchymal extinction evolves, the inflammatory activity is initially marked but gradually decreases and is masked by activation of macrophages and hepatic stellate cells, increasing deposition of collagen with broad fibrous septa formation, and appearance of ductular reactions. The predominantly regressive pattern is characterized by presence of thin, compact relatively acellular septa without edema, inflammation and other cellular infiltrates.

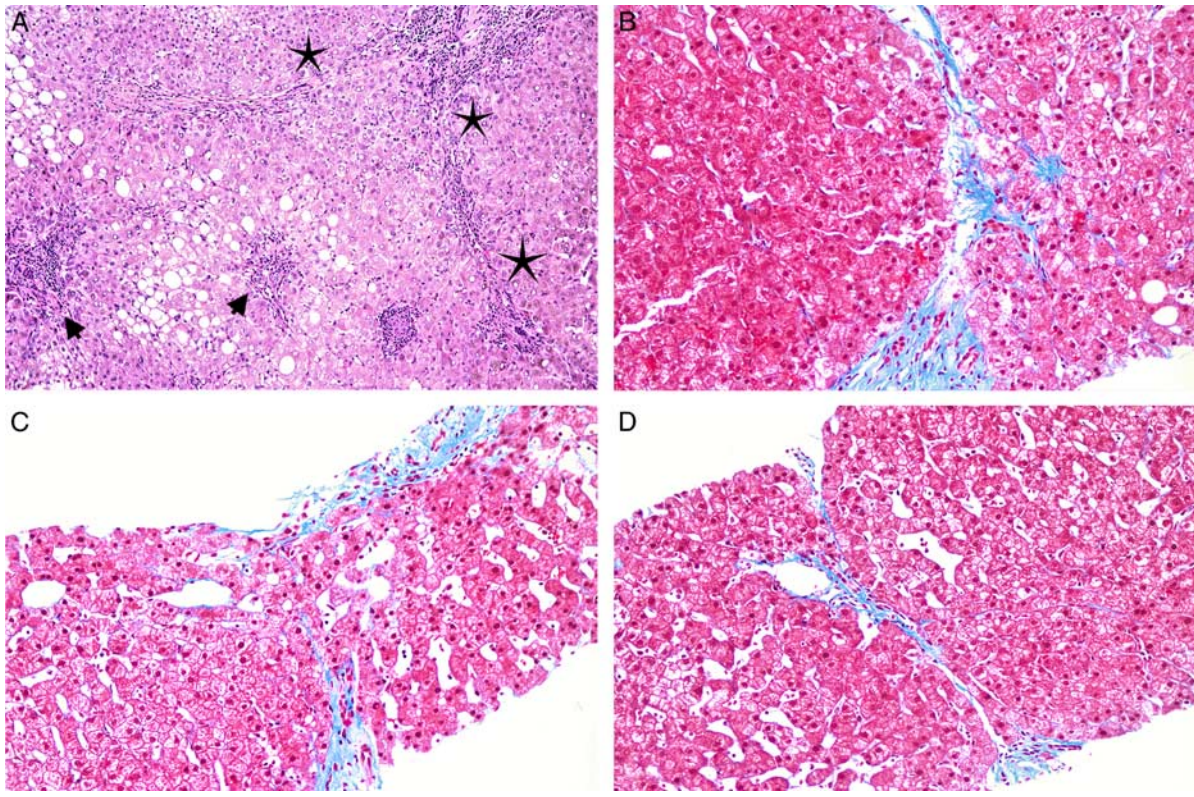

FIGURE 2. A, Regressed fibrous septa seen as periportal fibrosis (arrowheads) and regenerating hepatocytes splitting the septa (stars) in a patient with cirrhosis due to nonalcoholic steatohepatitis. Hematoxylin and eosin ×100. B, Fragmentation of septa and regression of scar seen as thinning of septae leading to perforation and fragmentation and eventual interruption by regenerating hepatocytes in a patient with cirrhosis due to chronic hepatitis C infection. Trichrome stain ×100. C, As repair/regeneration continues, hepatocytes migrate into the portal tract stroma and can be seen in the proximity of bile ducts and hepatic arteries in a patient with cirrhosis due to chronic hepatitis C infection. Trichrome stain ×40. D, Resorption of a bridging septum between 2 portal tracts with negligible inflammatory infiltrate and resorption of sinusoidal collagen resulting into remodeling and appearance of "near-normal" hepatic plates. Trichrome stain ×40.

Septal fragmentation, recanalization of vascular thrombosis, and foci of disintegrating scar tissue become evident as regenerating hepatocytes begin to grown into and replace the scar tissue.

The prognostic value of the P-I-R score lies in its strong clinical correlations. In the pilot study, the P-I-R score reflected the prognosis of the disease, independent of necroinflammatory activity, fibrosis severity, or treatment experience. The score showed strong correlation with the treatment; *P*/I before treatment versus R after treatment. It also correlated with the 4 stage Laennec system for staging of cirrhosis, and thus may potentially serve as a surrogate marker for hepatic venous wedge pressures for risk stratification of portal hypertension. The Laennec system implies a sequential progression of cirrhosis from 4A to 4B to 4C; the Beijing classification's P-I-R score reflects the dynamic evolution between Laennec stages 4A, 4B, and 4C, thus incorporating the probability of regression from 4B and 4C to 4A.

DOES REGRESSION OF FIBROSIS DOWNGRADE THE RISK FOR HCC?

Pathogenesis of HCC is the result of accumulative mutational burden resulting from factors that affect the tumor and its microenvironment, the tumor microenvironment (TME). Different etiological factors [HBV, hepatitis C viral (HCV), non alcoholic steatohepatitis, etc.] may elicit different pathways leading to hepatocarcinogenesis. The fibrous stroma, cellular elements, and vascular abnormalities in cirrhosis constitute the TME. When the injurious trigger is removed by effective therapies, the TME landscape changes due to decrease in inflammation and downregulation of the fibrogenic pathways. Despite this resolution, however, the driver mutations already imparted to hepatocytes in early disease, for instance, in HBV infection, do not vanish. The mutational burden rather becomes more complex and biodiverse with repeated cycles of injury and repair, resulting in genomic instability.[44–47] Furthermore, hypoxia-induced vascular endothelial growth factor (VEGF) expression is linked to tumor diversity and TME polarization.[48–51] With persistence of vascular lesions in cirrhosis, the hypoxic injury persists despite elimination of inflammation and regression of fibrosis.

HBV predisposes to hepatocarcinogenesis through direct and indirect mechanisms. One of the earliest direct mechanisms is HBV DNA integration into the host genome resulting in direct insertional mutations, leading to high levels of HBV replication, genomic instability and subsequent clonal expansion of tumor cells. In chronic HBV infection, HBV-encoded oncoproteins like hepatitis B virus

X protein and truncated preS2/S proteins impair control of proliferation and transcription, thus contributing to malignant hepatocyte transformation. Hepatitis B virus X protein is also responsible for epigenetic changes of tumor suppressor genes, thus HBV associated HCCs have a higher rate of chromosomal alteration including TP53 mutations and relatively low rate of activating β-catenin mutations. HBV-related HCCs can arise in noncirrhotic livers, further supporting the direct role of the virus in hepatocarcinogenesis. Chronic high viral load and specific genotypes initiate a cascade of host immune response leading to recurrent necroinflammation, fibrosis, accelerated hepatocyte turnover and accumulation of mutations.[52,53]

The principal oncologic drivers in chronic HCV infection are core protein and NS3 and NS5A proteins. HCV core is an RNA-binding protein, that is singularly capable of inducing hepatic steatosis, insulin resistance and HCC.[54–56] It also promotes hepatocyte proliferation and its distinct mutations in genotype 1 patients confer a higher HCC risk, even after elimination of HCV.[57,58] The NS3 protein of HCV promotes hepatic fibrosis in chronic liver disease while NS5A has a central role in viral replication and assembly, is capable of inducing hepatic steatosis, is protective against apoptosis and confers resistance against interferon α.[59–64] The key cellular and molecular pathways underlying progression of chronic HCV infection to HCC are: the epidermal growth factor,[65–70] signal transducer and activator of transcription 3[71,72] transforming growth factor beta[73–76] and VEGF.[77,78] In its evolution, HCV infection is also associated with higher microvessel density compared with chronic hepatitis B patients.[79]

In the face of ever-growing obesity epidemic in the developed and developing world, nonalcoholic fatty liver disease (NAFLD) has become one of the leading causes of end-stage liver disease.[80] Furthermore, it is the fastest growing cause of HCC.[81] Inflammation in non alcoholic steatohepatitis is "metabolic" in nature[82]; several pathways including insulin resistance, lipotoxicity, lipid peroxidation, and necroinflammation precipitate steatohepatitis.[83] With regression of fibrosis, most of the risk factors for development of HCC persist in NAFLD; lipid metabolic reprogramming involving carnitine palmitoyl transferase and fatty acid β-oxidation, being key mechanisms.[84] Similarly, the risk of HCC persists in cirrhosis secondary to hemochromatosis even after "clinically successful" therapeutic phlebotomies.[85–90]

FUTURE PERSPECTIVE

With better understanding of the underlying cellular and molecular mechanisms of fibrosis, novel therapeutic strategies are under investigation to target these pathways.[91–93] Although the significance of vascular lesions in the progression of liver disease is quite underappreciated, there is evidence to support and explore the potential role of anticoagulants, statins, and VEGF modulators as protective agents that can either slow down the progression or even reverse the vascular abnormalities.[94–99]

CONCLUSIONS

The evidence in favor of regression of fibrosis in chronic liver disease is substantial and irrefutable. However, complete resolution of cirrhosis is yet to be demonstrated. So far, there is little to no evidence to suggest that large regions of parenchymal extinction can be repopulated by regenerating hepatocytes. Similarly, the vascular lesions of cirrhosis persist, and there is no evidence of complete return to normal microcirculation in cirrhotic livers. Despite regression of fibrosis, adequate suppression of viral load in chronic HBV infection, and successful treatment of chronic HCV infection, the risk of HCC is higher compared with the general population and these patients need continued screening and surveillance.[100–103]

There is need for reassessing the timing of protocol biopsies for chronic viral hepatitis (HBV, HCV) and more studies are needed to explore the clinical utility and reproducibility of the Beijing classification. The vascular lesions of cirrhosis need to be studied and explored for their natural history and evolution. Cirrhosis, as a term either needs to be revised or discontinued as its historical diagnostic connotations and clinical implications would be increasingly less relevant in the face of modern therapeutic strategies.[12] And last but not the least, given the burden of NAFLD and a multitude of ongoing clinical trials, there is a need for documenting the regression of fibrosis and cirrhosis in a systematic, reproducible, and clinically relevant manner.

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