Regression of liver fibrosis: evidence and challenges

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Abstract
It has been reported that liver fibrosis could be reversed after eliminating liver injuries. This article systematically summarizes the evidence of fibrosis regression based on histology, liver stiffness, and serum biomarkers, and discusses several clinically relevant challenges. Evidence from liver biopsy has been regarded as the gold standard in the assessment of fibrosis regression. Semi-quantitative staging and grading systems are traditionally and routinely used to define regression. Recently, the predominantly regressive, indeterminate, and predominantly progressive score was proposed, based on the regressive features from “hepatic repair complex”, to provide additional information regarding the quality of fibrosis. For non-invasive assessment, although liver stiffness and serum biomarkers could be applied to reflect the dynamic changes of liver fibrosis, other confounding factors such as liver inflammation have to be considered. In conclusion, both histology and non-invasive methods can provide evidence regarding fibrosis regression. The predictive value of fibrosis regression in long-term prognosis warrants further investigation.

Keywords: Liver fibrosis, Regression, Reversal, Liver biopsy, Liver stiffness, Serum biomarker

Introduction
Liver fibrosis is the chronic wound-healing process between fibrogenesis and fibrolysis.[1] Fibrosis, and compensated and decompensated cirrhosis were considered as a sequential process, which was previously thought to be irreversible. However, with the rapid advances in anti-viral therapy in chronic hepatitis B (CHB) and hepatitis C (CHC), effective and long-term viral suppression has led to fibrosis regression in many patients. Current clinical and histological evidence has revealed that liver fibrosis is reversible after the removal of underlying liver injuries.[12] In addition, fibrosis regression has been regarded as one of the critical endpoints to evaluate treatment response in clinical trials, particularly in the realm of new drugs against fibrosis and non-alcoholic fatty liver disease (NAFLD).[4]

Liver biopsy has been considered as the gold standard for assessing liver fibrosis. Staging and grading systems were proposed based on histological features in treatment-naive patients.[4] The stage of fibrosis was thought to be sufficient to evaluate disease severity; however, the widely adopted definition of fibrosis regression is insufficient to describe the healing features of fibrosis.[13] In addition, non-invasive methods, including liver stiffness and serum biomarkers, which were developed by considering histological staging systems as the reference standard, have been gradually used to assess the reversal of liver fibrosis.[16] Therefore, this study aimed to systematically review the evidence of fibrosis regression from liver biopsy and non-invasive methods, and to discuss several clinically relevant challenges.

Evidence-based Histological Assessment
Liver biopsy has been regarded as the gold standard for the assessment of fibrosis regression. Several studies have assessed the proportion of fibrosis and cirrhosis regression through paired liver biopsies before and after treatment.[7-35] It has been reported that 51% to 88% of patients with hepatitis B virus (HBV)-related liver fibrosis could achieve regression after long-term suppression of HBV replication.[17-19] Similarly, fibrosis induced by hepatitis C virus (HCV) infection could be regressed after viral eradication.[20-26]

Apart from viral hepatitis-related fibrosis and cirrhosis, regression was also observed in non-viral hepatitis. The fibrosis of patients with alcoholic fatty liver disease regressed after cessation of alcohol consumption.[27] Patients with NAFLD showed regression after losing
weight by lifestyle modification or bariatric surgery. Patients with autoimmune hepatitis were more likely to show fibrosis regression after achievement of biochemical remission. Patients with hemochromatosis could show regression of severe fibrosis to a milder stage with efficient treatment.

Detailed information regarding each study, including publications, etiologies, number of patients, treatment, duration of follow-up, and the definition of fibrosis is listed in Table 1. As shown in Table 1, fibrosis/cirrhosis induced by different etiologies could be reversed after effective causal treatment. The regression rates of both the entire cohort and patients with cirrhosis are also listed in Table 1.

In most of the previous studies, regression was defined as at least one-stage decrease of semiquantitative histological fibrosis staging systems, including the histology activity index, Ishak, and METAVIR scores [Table 1]. However, it has been recognized that some regressive histological features are not captured by traditional staging systems. After examining a series of cirrhotic explants, the regression parameters were proposed and well elucidated by Wanless et al in 2000. Collectively, the signs were referred to as the “hepatic repair complex” (HRC), including eight parameters in terms of septa/fibers, vascular changes, and hepatocyte regenerations. The HRC has been gradually accepted by pathologists and hepatologists, particularly in the era of anti-viral therapy.

Recently, in an attempt to evaluate fibrosis regression in a cohort of patients with CHB after anti-HBV therapy, we proposed a new classification, namely the “Beijing Classification.” This new classification not only simplified the traditional semi-quantitative staging and grading systems, but also comprised a novel and independent P-I-R score (predominantly regressive, indeterminate, and predominantly progressive). The P-I-R score was proposed according to the balance of progressing versus regressing septa. The regressing septa were one of the regressive parameters of HRC and were defined as thin/delicate stroma with few inflammatory cells. Therefore, if most (more than 50%) of the septa show the features of HRC, the fibrosis is considered “predominantly regressive.”

In the original study on P-I-R score, 71 paired liver biopsy tissues were performed before and after anti-HBV therapy. Among the patients with stable Ishak score, 25 (72%) could be further defined as “predominantly regressive,” based on the P-I-R score. The novelty of the P-I-R score is that it extends the conventional criteria of fibrosis regression, that is, decreasing of Ishak score, and dynamically reflects the fibrosis changes in one cross-sectional specimen. Therefore, the P-I-R score extends beyond the traditional staging systems and provides additional histological evidence that fibrosis could be reversed. Recently, results from a study involving a Korean CHB-related cohort with hepatocellular carcinoma (HCC) have revealed that the P-I-R score has been approved to predict the recurrence of HCC, indicating its predictive value for long-term clinical outcomes.

With the application of morphometry in pathology, subtle changes of collagen and improvements in fibrosis could be quantitatively and sensitively detected. The collagen proportionate area (CPA), measured using a partly automated technique, decreased in patients with HCV-related cirrhosis after sustained viral response (SVR). In addition, qFibrosis, a quantitative assessment of liver fibrosis by using second harmonic generation/two photon excitation fluorescence (SHG/TPEF) revealed decreased HBV-related fibrosis in patients after viral suppression. It has been demonstrated that the width of the fibrous septum detected by SHG/TPEF was the most predictive feature indicative of regression. Therefore, computer-aided morphometric measurement confirmed the decrease in collagen with the improvement of fibrosis.

Non-invasive Assessment in Fibrosis Regression

Although liver biopsy has been considered the gold standard for the evaluation of fibrosis regression, it remains an expensive and invasive method that is associated with sampling error and risk of rare but potential complications. These limitations have led to the development of non-invasive methods, including liver stiffness measurements and serum biomarkers. These methods have been widely used to determine or to exclude significant fibrosis and cirrhosis. However, in the assessment of fibrosis improvement, the decrease in liver stiffness and serum biomarker levels may result from not only the regression of fibrosis but also the remission of liver edema and inflammation. Detailed information regarding studies in which liver stiffness and serum markers were used to evaluate fibrosis regression is provided in Tables 2 and 3.

Measurement of Liver Stiffness is a Promising Method to Evaluate Fibrosis Regression

Liver stiffness measured by transient elastography (TE) is a feasible and repeatable method to monitor the improvements in fibrosis in patients on anti-viral therapy. Longitudinal studies have demonstrated significant improvements in liver stiffness of patients with CHB and CHC after anti-viral therapy. Interestingly, liver stiffness reduced rapidly in parallel with alanine aminotransferase (ALT) levels after treatment for 6 months; thereafter, it decreased slowly but continually after remission of necroinflammation, with normalization of ALT levels.

Based on this dynamic pattern of liver stiffness, Kong et al proposed a two-phase reduction in liver stiffness by the piecewise linear mixed-effects model: the fast-declining phase (from baseline to 6 months) and the slow-declining phase (after 6 months). They found that the rate of reduction in liver stiffness during the first 6 months (the fast-declining phase) was significantly higher in patients with histological fibrosis regression. Therefore, the early steep reduction in liver stiffness may predict the histological reversibility of liver fibrosis in patients with CHB who are undergoing treatment.

However, there are studies showing that the decrease of absolute liver stiffness after treatment could be related to
the remission of liver inflammation rather than fibrosis regression;[54,55] Wong et al.[54] recruited 71 patients with CHB and paired liver biopsy samples before and after 48 weeks of anti-viral therapy. They found that the proportion of patients who showed a >30% reduction in liver stiffness was not consistent with the proportion of patients who showed decreased histological fibrosis stages. A similar conclusion was reached in another study that enrolled patients with CHB whose paired liver biopsy samples before and after 78 weeks of anti-viral therapy were available.[55] Therefore, the reduction in liver stiffness should be interpreted with caution owing to the impact of normalization of ALT levels by anti-viral therapy.

In addition to TE, liver stiffness measured by acoustic radiation force impulse imaging gradually decreased during anti-HBV therapy. It decreased more significantly in regressive patients than in those with stable histological fibrosis stages.[56] Whether the decrease in liver stiffness, as observed using magnetic resonance elastography and other imaging-based methods, is correlated with histological improvement in fibrosis is yet to be determined.[37,38]

Serum Biomarkers Were Sensitive but not Specific to Define Fibrosis Reversal

Aspartate aminotransferase-to-platelet ratio index (APRI) and fibrosis index based on four factors (FIB-4) are the two commonly used serum biomarkers for CHC.[59,60] These markers could successfully identify significant fibrosis and cirrhosis in patients infected with HCV. However, APRI and FIB-4 are unsuitable for monitoring fibrosis improvement in patients with CHB who are on anti-viral therapy. Kim et al.[61] analyzed APRI and FIB-4 in 575 patients with CHB who received paired liver biopsy samples before and after 240 weeks of therapy. They found that reduction in

| Table 1: Studies of liver fibrosis/cirrhosis regression by histology. |
|---------------------------------------------------------------|
| **Studies (authors, year)** | **Etiology** | **Patients, n** | **Biopsy interval** | **Treatment** | **Definition of regression** | **Regression rate** | **Total** |
|-----------------------------|-------------|----------------|------------------|-------------|----------------------------|-------------------|----------|
| Demist et al.[29] 2003     | HBV         | 63             | 2 years          | LAM         | Knodell score ≥1            | 67% (advanced fibrosis + cirrhosis) | 73% (8/11) |
| Papatheodoridis et al.[1] 2005 | HBV       | 147            | 24 months        | IFN (n = 120) | Ishak score ≥1              | IFN18%            | IFN14% (4/28) |
| Hadziyannis et al.[3] 2006 | HBV         | 125            | 48 weeks; 192 weeks; 240 weeks | ADV         | Ishak score ≥1              | No treatment: 4% | Ishak ≥ 2, 58% (7/12) |
| Schiff et al.[4] 2008      | HBV         | 245            | 48 weeks         | ETV/LAM    | Ishak score ≥1              | 35% (58/162) | 77% (13/17) |
| Chang et al.[5] 2010       | HBV         | 57             | 48 weeks; 1-7 years | ETV        | Ishak score ≥1              | 33%–59% (advanced fibrosis + cirrhosis) | 100% |
| Marcellin et al.[6] 2013   | HBV         | 346            | 240 weeks        | TDF        | Ishak score ≥1              | 32% (8 weeks) | 100% |
| Hou et al.[10] 2015        | HBV         | 57             | 5 years          | LDT/LAM    | Ishak score ≥1              | 51% (74%)        | 72% (11/16) |
| Sun et al.[11] 2017        | HBV         | 71             | 78 weeks         | ETF-based  | Ishak score ≥1              | 33% (27/81) | 60% (33/55) |
| Wang et al.[12] 2018       | HBV         | 117            | 78 weeks         | ETF-based  | Ishak score ≥1              | 35% (58/162) | 77% (13/17) |
| Kong et al.[13] 2019       | HBV         | 212            | 78 weeks         | ETF-based  | Ishak score ≥1              | 35% (58/162) | 77% (13/17) |
| Shiratori et al.[14] 2000  | HCV         | 593            | 3.7 years        | IFN; n = 487 | Ishak score ≥1              | 29% (32/111) | 46% (29/63) |
| Poynard et al.[15] 2002    | HBV         | 3010           | 20 months        | IFN+IFN+ BBV | Ishak score ≥1              | 43% (11/25) | 55% (92/172) |
| George et al.[16] 2008     | HBV         | 49             | 62 months        | IFN+ADV    | Ishak score ≥1              | 45% (92/172) | 55% (92/172) |
| Mallet et al.[17] 2008     | HCV         | 96             | 118 months       | IFN+IFN+ BBV | Ishak score ≥1              | 73% (91/123) | 91% (91/123) |
| Tack et al.[18] 2016       | HCV         | 130            | 5.5 ± 1.2 years  | IFN+ADV    | Ishak score ≥1              | 44% (1735) | 49% (1735) |
| Mauro et al.[19] 2018      | HCV         | 112            | 12 months        | DAAs/ADV    | Ishak score ≥1              | 60% (63%)        | 60% (63%) |
| Serpaggi et al.[20] 2006   | HCV/HBV/ALD/ AHD | 113           | 0.6–4.4 years   | Specific treatment | Ishak score ≥1 | 60% (63%) |
| Glass et al.[21] 2015      | NASH        | 45             | 4.6 ± 1.4 years  | Body weight loss/bariatric surgery | Ishak score ≥1 | 60% (63%) |
| Vij-Kumar et al.[22] 2015  | NAFLD       | 293            | 52 weeks         | Weight loss through lifestyle modification | Ishak score ≥1 | 60% (63%) |
| Dubuc et al.[23] 1997      | AIH         | 84             | 47 months        | Glucocorticoids, immunosuppressive drugs, or both | Ishak score ≥1 | 60% (63%) |
| Grasso et al.[24] 2004     | NAFLD       | 87             | 63 ± 6 months    | Predominant in combination with azathioprine/ higher dose prednisone alone | Ishak score ≥1 | 60% (63%) |
| Harrl et al.[25] 2017      | AIH         | 60             | At least 1 year  | Corticosteroids/ azathioprine/ combination therapy | Ishak score ≥1 | 60% (63%) |
| Bardos-Jacquet et al.[26] 2019 | NAFLD     | 106            | 9.5 (3.5–15.6) years | Venesection | Ishak score ≥1 | 60% (63%) |
| Himmel et al.[27] 2003     | Chronic stenosis of the common bile duct due to chronic pancreatitis | 25.5 (2.5–7.5) years | Bilary drainage | Ishak score ≥1 | 60% (63%) |

HBV: Hepatitis B virus; HCV: Hepatitis C virus; AIH: Autoimmune hepatitis; NASH: Non-alcoholic steatohepatitis; NAFLD: Non-alcoholic fatty liver disease; SVR: Sustained viral response; EOT: End of treatment; LDT: Telbivudine; LAM: Lamivudine; IFN: Interferon; ADV: Adefovir dipivoxil; ETF: Entecavir; TDF: Tenofovir disoproxil fumarate; DAAs: Direct-acting anti-viral agents; NA: Not applicable; RBV: Ribavirin; P-I-R: Predominantly regressive, indeterminate, and predominantly progressive score.
APRI and FIB-4 were sensitive but not specific to accurately evaluate fibrosis reversal.

### Challenges

**Could distorted lobular architecture be restored after fibrosis regression?**

Advanced liver fibrosis and cirrhosis are characterized by the loss of normal lobular metabolic zonation, with numerous shunting neovessels along the fibrous septa. D’Ambrosio et al. assessed the changes of metabolic zonation in patients with HCV-related cirrhosis after achieving SVR. They found that the metabolic zonation was lost before treatment and was restored in most patients after SVR. In this study, the severity of abnormal metabolic zonation was scored semi-quantitatively as 0 to 2 according to the expression of glutamine synthetase (GS) and CYP2E1. As GS is expressed in the hepatocytes surrounding hepatic veins in the normal liver, in one study, GS positivity adjacent to portal tracts has been used to quantitatively evaluate the metabolic zonation.

However, data from paired liver biopsy samples before and after treatment are still limited.

The restoration of altered blood flow is also a clinical issue. It has been shown that the hepatic venous pressure gradient decreased in 18 out of 19 patients with CHB-related cirrhosis with significant portal hypertension...
after 12 months of lamivudine therapy, suggesting that vascular remodeling may be reversible after viral suppression.

**Could fibrosis regression improve clinical outcomes?**

Viral suppression in HCV and HBV infection was associated with the reversal of fibrosis and cirrhosis. It has been proved that viral suppression was also associated with better clinical outcomes, including reducing the incidence of HCC, preventing decompensations, and improving survival.[71] However, the long-term prognosis results of fibrosis regression are still unclear. In addition, whether the better clinical outcome is the result of effective causal treatment or fibrosis regression needs to be confirmed. Wu et al.[26] studied patients with HBV-related compensated cirrhosis and found that dynamic changes of liver stiffness in the first 26 weeks could predict decompensations and HCC during anti-viral therapy. This might suggest the fibrosis regression could translate into clinical benefits. Moreover, a retrospective study on HCV has revealed that cirrhosis regression was related to decreased morbidity and improved survival.[24] However, there is still a lack of direct and solid evidence to demonstrate that biopsy-proven fibrosis regression could contribute to clinical outcomes.

**Could the decompensated cirrhosis turn into “re-compensation”?**

The clinical outcomes of some patients with decompensated cirrhosis could be improved after the suppression of etiological factors and by targeting the key factors of pathogenesis.[73] Those patients may become “re-compensated,” which means that decompensated complications may not occur in these patients a long period, particularly in patients with alcoholic and viral-related decompensations.[73] However, the definition and stability of “re-compensation” are still unclear.

In conclusion, compelling clinical and histological evidence states that liver fibrosis and even cirrhosis could be reversed after eradication of liver injuries. Liver biopsy remains the gold standard and the most robust evidence to assess fibrosis regression. With regard to non-invasive assessment, ALT normalization, and liver inflammation remission confirmed the results. Further clinical research is warranted to elucidate the long-term benefits of fibrosis regression.

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**Conflicts of interest**

None

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