

a series of fact sheets written
by experts in the field of liver
disease

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Disease Progression: What is Fibrosis?

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Chronic infection with hepatitis C or hepatitis B virus (HCV or HBV) can lead to long-term liver damage including fibrosis, cirrhosis, and hepatocellular carcinoma (liver cancer). It is estimated that about 10-25 percent of people with chronic hepatitis C will develop cirrhosis, a process that usually takes 20-30 years. This fact sheet will discuss fibrosis.

The Fibrosis Process

Liver fibrosis refers to the accumulation of tough, fibrous scar tissue in the liver. Formation of scar tissue is a normal bodily response to injury, but in fibrosis this healing process goes awry. When hepatocytes (functional liver cells) are injured due to viral infection, heavy alcohol consumption, toxins, trauma, or other factors, the immune system is activated and the repair process swings into gear. The injury or death (necrosis) of hepatocytes stimulates inflammatory immune cells to release cytokines, growth factors, and other chemicals. These chemical messengers direct support cells in the liver called hepatic stellate cells to activate and produce collagen, glycoproteins (such as fibronectin), proteoglycans, and other substances. These substances are deposited in the liver, causing the build-up

of extracellular matrix (nonfunctional connective tissue). At the same time, the process of breaking down or degrading collagen is impaired. In a healthy liver, the synthesis (fibrogenesis) and breakdown (fibrolysis) of matrix tissue are in balance. Fibrosis occurs when excessive scar tissue builds up faster than it can be broken down and removed from the liver.

Fibrosis Risk Factors

Liver fibrosis does not occur at the same rate in all individuals, and in some people with chronic hepatitis C or B fibrosis remains stable or may even regress over time. Several factors influence fibrosis progression. Fibrosis occurs more rapidly in men than in women, and also in older people—particularly those over age 50. Progression does not seem to be linear; that is, the process appears to accelerate later in the course of disease. Immune system compromise, for example due to coinfection with HIV or use of immunosuppressive drugs after a liver transplant, also has been shown to accelerate fibrosis. Heavy alcohol consumption is strongly associated with worsening fibrosis and cirrhosis. Finally, studies indicate that steatosis (fatty liver) and insulin resistance are associated with more rapid and severe fibrosis. In contrast, HCV viral load does not appear to have much effect on fibrosis progression. There is some evidence that HCV genotype 3 may play a role in the formation of steatosis, but the exact mechanism of action is not completely understood.

Grading Fibrosis

Early fibrosis can be difficult to diagnose because it is often asymptomatic. Various techniques are under study to detect fibrosis using noninvasive blood tests, for example by measuring markers of fibrogenesis and fibrolysis. But the current “gold standard” for determining the extent of liver disease is the liver biopsy, in which a small sample of tissue is removed with a needle, stained, and examined under a microscope. In order to monitor progression in a timely manner, most experts recommend repeat biopsies every 5-7 years.

Various systems are used to grade fibrosis and cirrhosis. These include the Knodell Histological Activity Index (HAI), a modified HAI known as the Ishak system, and the METAVIR system.

For more information about grading fibrosis and cirrhosis, refer to the HCSP Fact Sheet *Grading and Staging a Liver Biopsy*.

Effects of Fibrosis

In the early stages of fibrosis, the liver functions relatively well and few people experience symptoms. But as the inflammation and liver injury continue, scar tissue builds up and connects with existing scar tissue, which can eventually disrupt the metabolic functions of the liver. If the disease progresses, it can lead to cirrhosis, a condition in which the liver is severely scarred, its blood flow is restricted, and its ability to function is impaired.

Treatment and Future Prospects

It was once thought that fibrosis was irreversible, but more recent research indicates that treatment for hepatitis C can slow or halt fibrosis progression, and potentially even reverse existing liver damage. Studies have shown that fibrosis stabilization and regression are most likely when HCV positive individuals treated with interferon-based therapy achieve a sustained virological response (SVR, continued undetectable HCV viral load six months after the completion of therapy), but improvement has also been seen in some partial responders and nonresponders.

The final results of four large on-going clinical trials (HALT-C, EPIC-3, COPILOT, PROFI-C) using pegylated interferon monotherapy, pegylated interferon with placebo or colchicines, and interferon with and without silymarin for 2-4 years in patients with advanced liver disease will hopefully answer some important questions about fibrosis progression and treatment.

It is very important to know the fibrosis stage or health of the liver so that the appropriate decisions can be made for managing hepatitis C. There are many steps people can take to help slow down HCV disease progression:

- Consider HCV medical treatments, which can slow disease progression and possibly reverse fibrosis.
- Get regular exercise and rest
- Learn about and practice stress reduction measures.
- Eat a healthy, well-balanced diet that follows the *new* Food Guide Pyramid. This diet is low in fat and salt,

high in whole-wheat products, and has enough protein. Protein is in most meats, chicken, turkey, cheeses, nuts and beans (www.mypyramid.gov).

- Don't use recreational drugs.
- Don't drink alcohol, or at the very least, limit how much you drink.
- Take your prescriptions as instructed by your doctor.
- Be careful when mixing over the counter drugs, prescription drugs, herbal supplements, street drugs and/or alcohol.
- Stay away from poisonous liquids and fumes including solvents, paint thinners, and bug killers. If you have to use such chemicals, cover your skin, wear gloves and a mask and keep the windows open to allow air in.
- Do not eat raw or undercooked shellfish, which may have diseases that can be harmful to the liver.
- Ask your doctor to give you both the hepatitis A and the hepatitis B vaccinations.
- Become a strong self-advocate by learning as much as you can about hepatitis C.

For more information about hepatitis C, hepatitis B and HCV coinfections, please visit www.hcvadvocate.org.

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