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Liver Fibrosis: Patients Can Be At Risk Of Death Even Without Exhibiting Symptoms

1 in 5 advanced fibrosis patients evolves to cirrhosis in as little as two and a half years.

The liver is the largest gland in the human body and, weighing roughly two kilograms, it is the second largest organ after the skin. Its varied functions include supplying the brain with glucose, filtering toxins out of the blood, producing proteins, and much more. This means that a well-functioning liver is of vital importance. Yet diseases of the liver are among the top five causes of death among the middle-aged in many industrialized countries today. Liver cirrhosis and liver tumors are even among the ten most frequent causes of death worldwide.[1]

Liver fibrosis – how does the disease progress and who does it afflict?

In most cases, fibrosis is preceded by an inflammatory liver disease. Inflammations of this kind can arise, for example, as a consequence of overconsumption of medications. They can also result from fatty liver disease, which is linked to obesity or excessive consumption of alcohol. Such inflammations can also occur as severe side effects, for example, of diabetes or hepatitis infections. Genetic metabolic or autoimmune disease are also among the frequent triggers.

In view of the growth in liver diseases worldwide, fibrosis has long been considered a serious global health risk given its impact on society as a whole. Let us look at the figures: According to the World Health Organization (WHO), two billion people have had a hepatitis B infection.[2] Furthermore, non-alcoholic fatty liver disease (NAFLD) has been underestimated as a serious disease. This has led to a steadily increasing need for liver transplants in the U.S. By 2010, the need for NAFLD-related liver transplants had increased ten-fold to 1 in 10, and by 2013, to 1 in 3. Experts claim that by 2030 the leading indication for liver transplant in the U.S. will be due to the consequences of NAFLD or the more serious form, non-alcoholic steatohepatitis (NASH). Although liver diseases are a global phenomenon, their causes and courses differ from region to region: In the Western world, nutrition, alcohol, and medications are a major factor; in newly industrialized and developing countries, it is the increased risk of infectious diseases that impacts the liver.

The consequences are enormous, not only for sufferers and the healthcare systems. The economic damage is also vast: In Germany alone, diseases of the liver cost the national economy around five billion euros per year.[3]

Fig. 1: Causes of liver diseases. Weight loss and lifestyle modifications can help reverse disease, compliance can be a challenge.

How does fibrosis develop?

The liver is one of a few human organs to have an extraordinary ability to regenerate itself: For example, if half the liver is removed as an organ donation, it rarely takes longer than ten weeks for it to grow back to its original size. The liver benefits from the complex biological process of regeneration after diseases, too. Liver diseases such as hepatitis, however, pose a direct danger to the organ because the resulting inflammations attack healthy cells. The hepatocytes then die due to either immediate damage (necrosis) or programmed cell death (apoptosis). This triggers an immune response that fights the inflammation and starts the healing process. If massive fibrous connective tissue then forms instead of healthy liver tissue, the organ becomes scarred – fibrosis begins to develop (Fig. 2).

Fig. 2: Lobular structure of the liver

Why is fibrosis so dangerous?

Probably one of the most deceptive dangers of liver fibrosis is that, even with severe scarring, symptoms do not necessarily present in the patient. Most cases are not detected until the fibrosis becomes cirrhosis at a late stage – or liver tumors additionally form. On the other hand, anomalies like bleeding gums, loss of appetite or alcohol intolerance do not necessarily indicate the presence of fibrosis. Only very late in the course of the disease are signs of liver damage more typical, for example, yellowing of the skin and eyes or itching over the entire body. These are clear signals that the liver function is already severely impaired by proliferation of connective tissue. If the liver is unable to compensate for the imbalance between functional and scar cells, the entire organ shrinks and hardens. The typical lobular structure risks collapsing, circulation stops and pressure builds in the portal veins. The stage of cirrhosis has been reached, providing all the conditions required for the formation of malignant tumors, such as hepatocellular carcinoma (HCC). One in five advanced fibrosis patients advance to cirrhosis in as little as two and a half years.[4]

Diagnosis – what examination methods are available?

The liver does not have pain receptors. Patients cannot feel inflammation. This means the fibrosis of the liver usually remains undetected and early diagnosis is a challenge. Strictly speaking, fibrosis is not a disease in its own right as it only occurs as a symptom of other diseases. Its gradual progression is critical because medical research has previously assumed that scarring of the liver is irreversible once it has become advanced. Modern treatment methods, however, provide grounds for hope, but early diagnosis is a decisive precondition for their application.

Diagnosis by surgical intervention: biopsy

For a long time, the most reliable way of detecting incipient fibrosis and assessing its extent was biopsy (Fig 3a). The liver was punctured and the samples taken were examined for scar tissue. This method does, however, have decisive drawbacks: One is that a biopsy shows only a very small section of the real condition of the liver. The scar tissue, connective tissue, and functional organ tissue are not necessarily evenly distributed. A further drawback is the invasive nature of the procedure: Biopsies are painful, cannot be repeated often, and the risk of hospitalization after infection is between one and five percent.[5]

Fig. 3a: How diagnosis works: biopsy

An established diagnostic method: examination by ultrasound

Ultrasound elastography using acoustic radiation force impulse (ARFI) is an ultrasound-based quantitative elastography technology that has its major clinical application in the noninvasive assessment of liver fibrosis in real time. Shear wave elastography relies on the principle that with increasing liver fibrosis there is increasing liver stiffness and decreasing liver elasticity (Fig. 3b).

Fig. 3b: How diagnosis works: elastography

A noninvasive test method: diagnosis by blood sampling

A low-cost and gentle alternative to biopsy and elastography are blood tests including liver function tests and other biomarker tests for liver fibrosis: Without risk of complication, the proportion of scar tissue and therefore the severity of a liver fibrosis is detected from a blood sample (Fig. 3c). Growing data shows noninvasive testing could help supplement biopsy results. This direct assessment of fibrosis has proven valuable for identifying patients at risk of progressing to cirrhosis and/or liver-related events.

Fig. 3c: How diagnosis works: biomarker test

The treatment objective is to maintain the status quo

The prospects of healing of fibrosis have been poor so far. There is, therefore, no established standard therapy method. Since regression, that is a decline in the cicatrized tissue, is generally not possible, treatments are only intended to maintain the present condition. This makes it all the more important to detect prior liver diseases in good time, diagnose them reliably, and treat them with lasting success. This often stops all further fibrosis. If symptoms occur in a severe course of the disease, interventions promise relief in individual cases, such as displacement of the bile ducts as part of a papillotomy. To stop, or at least slow, further progression, patients must have plenty of exercise and a balanced diet.

If the fibrosis causes cirrhosis ultimately leading to complete liver failure, the only therapy remaining is organ transplantation because, unlike the heart, kidney and lung, there is no machine to perform the function of the liver. Even a liver transplantation involves risks of complications. At present, one-year survival rates of 90 percent, 5-year survival rates of 80 percent and 10-year survival rates of 70 percent are achieved. The chances of survival depend very much on the primary disease of the patient.[6]

Is there hope for the future?

More recent research suggests that the liver is indeed capable of compensating for advanced scarring and can even regenerate. Many new approaches in hepatology research are based on this hope: For example, it was observed in a series of experiments with vesicular stomatitis viruses that liver tumors disappear and fibrosis is reduced.[7]
According to the current state of knowledge, the most promising method is preventive care of our own liver. Caution in the consumption of alcohol and medications, regular preventive exams, and prompt treatment when the first signs appear are still the most effective weapons in the fight against fibrosis, cirrhosis, and most other liver diseases.

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