

## NON-ALCOHOLIC FATTY LIVER DISEASE

**Non-alcoholic fatty liver disease** (NAFLD), a term used for *steatosis* (fatty liver), **non-alcoholic steatohepatitis** (NASH) and **cirrhosis** secondary to NASH. It is the most common reason for **abnormal liver function tests** among adults all over the world, and is on the rise here in Pakistan as well. It affects 30 million of the US population, and of these, 8.6 million have NASH, with nearly 20% having signs of advanced disease (i.e., bridging fibrosis, cirrhosis) on histologic examination. NAFLD is most commonly seen in persons who are overweight / obese (40%), have diabetes mellitus ( $\geq 20\%$ ) and hyperlipidemia – triglyceridemia (20%) in association with insulin resistance as part of metabolic syndrome.

The patients with NAFLD/NASH even have increased risk of developing diabetes when combined with obesity or insulin resistance. Even people of normal weight can develop NAFLD. Risk of NAFLD with metabolic syndrome is 4 to 11 times higher than that of persons without insulin resistance and coffee consumption ion appears to reduce the risk. Risk of NAFLD is also increased in persons with active psoriasis, soft drink consumption, cholecystectomy, drugs like corticosteroids, amiodarone, diltiazem, tamoxifen, irinotecan, oxaliplatin, highly active antiretroviral therapy (HAA-RT), toxins (vinyl chloride, carbon tetrachloride, yellow phosphorus), various endocrinopathies such as Cushing syndrome and hypopituitarism, polycystic ovary syndrome, hypothyroidism, hypobetalipoproteinemia, obstructive sleep apnea (with chronic intermittent hypoxia), excessive dietary fructose consumption-ion, starvation and refeeding syndrome and total parenteral nutrition. Other liver diseases that can present with steatosis are Hepatitis C, Acute hepatitis D, Wilson disease, Hemochromatosis, Lipodystrophy, Lysosomal acid lipase deficiency.

Most patients are asymptomatic or have mild right upper quadrant discomfort. Hepatomegaly is present in up to 75% of patients, but stigmata of chronic liver disease are uncommon. Signs of portal hypertension of advanced liver fibrosis or cirrhosis can occasionally occur in patients with mild and no fibrosis and severe steatosis. Persistently elevated ALT can be associated with disease progression. Patients with normal ALT levels can also develop progressive disease. Up to 80% of NAFLD patients can have normal ALT. In contrast to alcoholic liver disease, the ratio of ALT to AST is

almost always greater than 1, but it decreases to less than 1 as advanced fibrosis and cirrhosis develop. Antinuclear or smooth muscle antibodies and an elevated serum ferritin level may each be detected in one fourth of patients with NASH. Elevated serum ferritin levels may signify so - called dysmetabolic iron overload syndrome and mildly increased body iron stores, which may play a causal role in insulin resistance and oxidative stress in hepatocytes and correlate with advanced fibrosis. Iron deficiency is also common and associated with female sex, obesity, increased waist circumference, diabetes mellitus, and black or Native American race.

Ultrasound examination usually reveals bright liver with increased echotexture vs. kidney, vascular blurring, and macrovascular steatosis. Ultrasound findings for fatty liver cannot be distinguished from those of early cirrhosis. CT or MRI Imaging does not distinguish steatosis from steatohepatitis or detect fibrosis. Changes consistent with NAFLD may not be detected if  $< 20 - 30\%$  of liver contains fat.

Noninvasive assessment of liver fibrosis to guide treatment and monitor progression requires a risk score for predicting advanced fibrosis, known as **BAR-D**, based on **B**ody mass index  $>28$ , **A**ST/**A**LT **R**atio  $\geq 0.8$ , and **D**iabetes mellitus; it has a 96% negative predictive value (i.e., a low score reliably excludes advanced fibrosis). Another risk score for advanced fibrosis, the **NAFLD Fibrosis Score** based on age, hyperglycemia, body mass index, platelet count, albumin, and AST/ALT ratio, has a positive predictive value of over 80% and identifies patients at increased risk for liver-related complications and death. A **clinical scoring system** to predict the likelihood of NASH in morbidly obese persons includes six predictive factors: hypertension, type 2 diabetes mellitus, sleep apnea, AST greater than 27 units/L (0.54 mckat/L), ALT greater than 27 units/L (0.54 mckat/L), and non-black race.

Liver biopsy is the gold standard to make the diagnosis of NASH, initiate drug therapy, assess prognosis: liver, cardiovascular, etc, stage fibrosis (if imaging or tests are indeterminate), rule out concomitant liver disease like autoimmune, Wilson disease, Drug Induced Liver Injury (DILI), iron overload (ferritin can be high in NAFLD in absence of iron overload).

Lifestyle modifications in NAFLD are difficult to achieve and sustain, and will not be enough for morbidly obese patients. Limiting total caloric intake is ideal and more important than aiming for a specific nutrient composition. Processed carbohydrates like white / brown bread, rice, white / orange potatoes, flour / corn tortillas, pizza / pasta, chips, and fructose-containing sodas and juices should be limited significantly. Physical inactivity is strongly linked to increased body weight, central adiposity, insulin resistance, increased risk of metabolic syndrome, NAFLD and severity of NASH. Exercise associated with a reduction in hepatic fat even in the absence of weight loss, and small studies had suggested that resistance training reduces hepatic fat, improves other metabolic parameters. Current evidence reinforces utility of aerobic or resistance exercise for improving steatosis.

Still no FDA-approved therapies for NASH are available but there are some therapeutic options with proven efficacy like vitamin E, Pioglitazone, Pentoxifylline and Liraglutide. In case of vitamin E therapy liver enzymes are not reliable to assess quiescence or progression and there is increased risk of hemorrhagic stroke as well.

Gastric bypass may be considered in patients with a body mass index greater than 35 and leads to histologic regression of NASH in most patients. Liver transplantation for NASH with advanced cirrhosis may be associated with increased mortality from cardiovascular disease and sepsis compared with liver transplantation for other indications.

Fatty liver often has a benign course and is readily reversible with discontinuation of alcohol or treatment of other underlying conditions; if untreated, fibrosis progresses at an average rate of 1 stage every 14 years, with a subset progressing more rapidly. In patients with NAFLD, the likelihood of NASH is increased by the following factors: obesity, older age, non-African American ethnicity, female sex, diabetes mellitus, hypertension, higher ALT or AST level, higher AST/ALT ratio, low platelet count, elevated fasting C-peptide level, and a high ultrasound steatosis score. NASH may be associated with hepatic fibrosis in 40% of cases with progression at a rate of 1 stage every 7 years; cirrhosis develops in 9 – 25%; and decompensated cirrhosis occurs in 30 – 50% of cirrhotic patients over 10 years. Course may be more aggressive in diabetic persons than in nondiabetic persons. Mortality is increased in patients with NAFLD, correlates with fibrosis stage, and is more likely to be the result of malignancy and ischemic heart disease than liver disease. Risk factors for mortality are older age, male sex, white race, smoking, higher body mass index, hypertension, diabetes mellitus, and cirrhosis. Steatosis is a cofactor for the progression of fibrosis in patients with other causes of chronic liver disease, such as hepatitis C. Hepatocellular carcinoma is a

complication of cirrhosis caused by NASH, as it is for other causes of cirrhosis, and has been reported even in the absence of cirrhosis. NASH accounts for a substantial percentage of cases labeled as cryptogenic cirrhosis and can recur following liver transplantation. Central obesity is an independent risk factor for death from cirrhosis of any cause.

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