Chapter 55

Guidelines for Assessment and Management of Nonalcoholic Fatty Liver Disease in Indians

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INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is today considered the most common cause of chronic liver disease in both the developed as well as developing countries. Studies from different regions of India[1-4] have shown that NAFLD is very common in Indians. Although NAFLD was recognized long ago by Zelman,[5] and Westwater and Fainer[6] it was blissfully ignored for almost a quarter of a century, until Ludwig et al. brought it into the limelight in the year 1980. Ludwig coined the term nonalcoholic steatohepatitis (NASH) for alcohol like liver disease that developed in persons who were not heavy drinkers (<20 grams/day for men and <10 grams/day for women).[7] Fatty liver disease is defined as more than 5% of the hepatocytes containing fat or more than 5% of the liver weight due to fat.[8] Nonalcoholic fatty liver disease has a wide histopathological spectrum ranging from simple, bland steatosis, which is usually associated with a benign prognosis, to NASH, which is believed to possess the potential for progress to cirrhosis, and its inherent complications of liver failure and liver cancer.[9,10] The risk factors which have been associated with NAFLD are obesity, type 2 diabetes mellitus (T2DM), dyslipidemia and metabolic syndrome; other conditions with emerging association include polycystic ovarian syndrome, hypothyroidism, hypopituitarism, hypogonadism, obstructive sleep apnea and pancreatoduodenal resection.

NATURAL HISTORY

Data on the natural history and mortality of NAFLD/NASH are contradictory and the studies available in the literature are not conclusive.[11,12] There is no definitive laboratory test for diagnosis, and various published studies have variable definitions. There are a limited number of prospective, longitudinal studies with long-term histologic follow-up of patients with NAFLD. While the short-term prognosis of NAFLD is largely excellent, the long-term prognosis depends crucially on histological stage at presentation.[12] In addition, even liver biopsies are not fully accurate in assessing the severity and progression of disease. One community-based cohort study of NAFLD subjects was noted to have a 34% increase in hazard ratio for overall mortality.[13] Liver-related mortality is the third most common cause of death in large cohorts of patients with NAFLD.[13,14] Ong et al on the basis of NHANES III data and other cohorts, reported that in patients with NAFLD, liver related mortality appeared to be higher than that in the general population, even when cofounders such as metabolic factors were adjusted.[15] A recent meta-analysis also demonstrated that NAFLD increased the risk for all-cause mortality.[16] True understanding of the natural history, however, is limited by lack of long-term follow-up, difficulties with diagnosis, under-diagnosis, and other confounding factors, particularly the greater risk of mortality imparted by the underlying metabolic syndrome prevalent in patients with NAFLD. Besides, most of the data published in literature stem from large tertiary care centers that routinely perform biopsy and have greater than typical follow-up and naturally it may not be representative of the population at large.[17] The natural history of NAFLD is summarized in **Flow chart 1**.

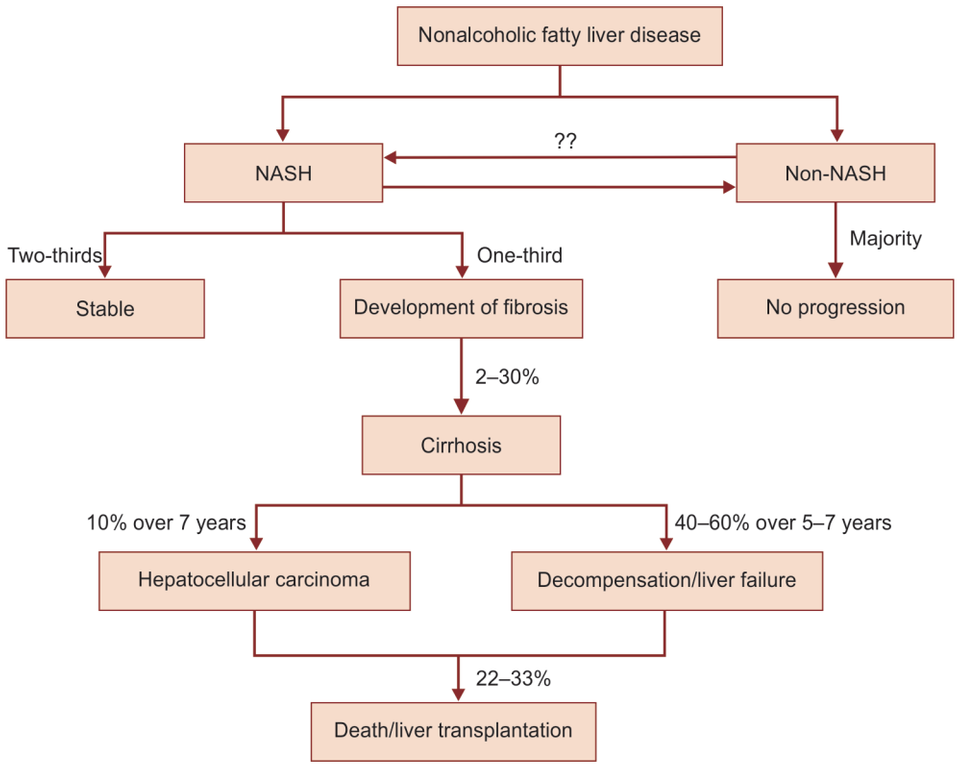
PATHOGENESIS

The pathogenesis of NAFLD is currently not well understood. It has been hypothesized that this involves complex interactions of genetic and environmental factors. The early "two-hit" model of NASH had proposed that the "first hit" involved accumulation of lipids specially triglycerides inside the hepatocytes.[18] The lipid-rich environment inside the hepatocyte then provided the setting for oxidative stress constituting the "second hit" that triggers hepatocellular injury, inflammation and fibrosis. Recently an alternative hypothesis has been proposed; the metabolites of fatty acids induce hepatocellular injury in NASH rather than the fatty acids themselves. The "lipotoxicity" model of NASH suggests that the accumulation of triglyceride in the liver is not a cause of liver injury but rather may paradoxically be protective. Excessive or inappropriate peripheral lipolysis, and excessive de novo lipogenesis exceeds the liver's ability to burn the fat or convert it to triglyceride which can be secreted.[19] The flux of free fatty acids from the liver forms metabolites that cause hepatocellular injury in the form of stress to the endoplasmic reticulum, inflammation, apoptosis and necrosis. Other contributors to the pathogenesis of NASH include mitochondrial dysfunction,[20,21] impaired adenosine triphosphate (ATP) production,[22] hypoxia due to impaired blood flow,[23,24] gut-derived endotoxin and ethanol,[25,26] and dysregulation of adipokine[27,28] and cytokine production.[29,30] While the exact etiology of NAFLD and NASH is unclear, insulin resistance appears to be central to the pathogenesis of NASH by allowing inappropriate levels of lipolysis and impairing peripheral glucose disposal. Besides insulin resistance, NAFLD is also closely associated with other characteristics of the metabolic syndrome including central obesity, hypertension and hyperlipidemia.[31] The obesity epidemic and increasing prevalence of the metabolic syndrome is predicted to be paralleled by an increasing prevalence of NAFLD in the future.

NONALCOHOLIC FATTY LIVER DISEASE BURDEN IN INDIA

Overall, the prevalence of NAFLD in India is around 10–32% based on the data on people undergoing master health check-up, ultrasonography for non-liver related causes, healthy relatives

Flow chart 1: Natural history of nonalcoholic fatty liver disease



of hospitalized patients, railway employees and their families.[1-4] Diabetes, central obesity and dyslipidemias are common predisposing factors. Insulin resistance is seen almost universally. India has the largest number of people with diabetes in the world.[32] Moreover, Asian Indians are more prone to insulin resistance and have increased waist circumference and body fat (particularly visceral fat), features that are described as the Asian Indian phenotype.[33] Presuming an overall NAFLD prevalence rate of 20% translates to a staggering 244 million with fatty liver in India. With increasing obesity and diabetes mellitus, there is the gloomy possibility of the prevalence of fatty liver increasing further. And if the implications are anywhere near what has been suggested by the data on natural history and association with coronary artery disease, then it is time to wake up and assess the enormous burden this disease can pose in Indians.

DIAGNOSIS

Commonly, NAFLD is diagnosed incidentally as more than half of the patients are asymptomatic. One fourth to half of NAFLD patients may complain of right upper quadrant pain and an equal number of patients may complain of fatigue. On the contrary, at times, cirrhosis or its complications may be the initial presentation. Majority of the patients have normal physical examination. While a small proportion may have clinically identifiable hepatomegaly, mild to modest alanine transaminase (ALT), aspartate aminotransferase (AST) elevation is found in 25–50% of patients, and the remaining patients have normal liver enzymes.[34-36]

The diagnosis of NAFLD requires that:

- There is hepatic steatosis by imaging or histology;
- There is no significant alcohol consumption;
- There are no competing etiologies for hepatic steatosis and
- There are no co-existing causes for chronic liver disease.

Common alternative causes of hepatic steatosis are significant alcohol consumption, hepatitis C medications, parenteral nutrition, Wilson's disease and severe malnutrition.

Assessment of Nonalcoholic Fatty Liver Disease

All NAFLD patients should be assessed as follows:

- *Careful history:* This is mandatory especially for exclusion of alcohol consumption by history to rule out alcoholic liver disease.
- *Anthropometric evaluation:* In any patient with NAFLD, one must measure height (in meters), weight (in kilograms), BMI (kg/m^2), and waist circumference (in centimeters).

The patient should then be classified as:

Overweight: Body mass index (BMI) greater than equal to 23 but less than 25 kg/m^2,

or

Obese (BMI > 25 kg/m^2)

Central obesity should be as diagnosed by using the following Asia-Pacific criteria: Abnormal waist circumference greater than 90 cm (men) and greater than 80 cm (women).[37,38]

- Blood pressure should be measured not only because hypertension is common in NAFLD patients, but also because this is a criterion for metabolic syndrome and its presence has also been linked to presence of fibrosis in these patients.
- *Biochemical tests:* This must include serum bilirubin, serum AST, ALT, Gamma GT, albumin, globulin, fasting sugar and fasting lipid profile.
- *Hematological tests:* Complete blood count including total platelet count. A low platelet favors significant fibrosis or cirrhosis.
- *Serological and immunological tests:* Anti-HCV and HBsAg are essential in the work-up of a NAFLD patient.

- *Glycemic profile and insulin sensitivity:* Fasting blood glucose, 75 g oral glucose tolerance test (GTT) and fasting serum insulin.
- *Abdominal ultrasound:* Ultrasonographic evaluation should be performed particularly with reference to the liver echogenicity in comparison to the echogenicity of kidney and spleen, vascular blurring and deep attenuation of ultrasound signal in order to classify hepatic steatosis.[39] Fatty liver is diagnosed in the presence of two of the following three conditions:
  1. Bright hepatic echo texture as compared to kidney and spleen
  2. Blurring of hepatic veins
  3. Loss of deep echo-discontinuous diaphragm.

Ultrasonographically, hepatic steatosis can be further classified as:

- *Grade 1 (mild):* Normal visualization of diaphragm/intrahepatic vessels
- *Grade 2 (moderate):* Impaired visualization of diaphragm/intrahepatic vessels
- *Grade 3 (severe):* Poor visualization of diaphragm/intrahepatic vessels.

Optional Tests for Nonalcoholic Fatty Liver Disease Patients

When clinical profile dictates, Hepatitis B core antibody, ANA, ASMA, Anti-LKM, AMA may be done in NAFLD patients.

Metabolic tests including serum ceruloplasmin, serum ferritin, abdominal CT scan, liver biopsy, magnetic resonance (MR) spectroscopy, MR elastography, fibroscan, and biomarkers for liver fibrosis are optional and not essential in the work-up for NAFLD patients.

Ultrasonographic Assessment of Fatty Liver

The sensitivity of ultrasonography (US) in detecting steatosis varies between 60% and 94%,[40] and also varies depending on the degree of steatosis. Sensitivity is very low when the degree of steatosis is less than 30%; this technique has important limitations. First, it is operator-dependent and subject to significant intra- and inter-observer variability;[41-43] second, US does not provide quantitative information of the degree of lipid accumulation. Another limitation is its inability to differentiate simple steatosis from steatohepatitis as both of them have similar appearance on ultrasound.

Optional Investigations

Noncontrast-enhanced CT is the most accurate CT technique to detect and characterize hepatic steatosis.[44] Magnetic resonance imaging provides an accurate and rapid assessment of hepatic steatosis to a lower limit of 3%. Magnetic resonance spectroscopy provides a sensitive, quantitative, noninvasive method to measure hepatic triglyceride content (HTGC) and when applied to a large urban US population, revealed a strikingly high prevalence of hepatic steatosis.[45] An MR equivalent of transient elastography (TE) has recently demonstrated excellent diagnostic accuracy with sensitivity and specificity of 98% and 99% respectively for detecting all grades of fibrosis.[46] Transient elastography (Fibroscan, Echosens, Paris, France) is a noninvasive method of assessing liver fibrosis which can be performed at the bedside or in the outpatient clinic. It employs ultrasound-based technology to measure liver stiffness and had shown good results in patients with NAFLD.[47] Liver biopsy is considered the gold standard for evaluating the degree of hepatic necroinflammation and fibrosis. However, several noninvasive investigations including serum biomarkers have been developed to establish the diagnosis and also to evaluate treatment response. These include noninvasive risk scores, biomarker panels and radiological modalities to identify at risk patients with NAFLD without recourse to liver biopsy on a routine basis. Examples include combination of serum markers like NAFLD fibrosis score (NFS), BARD score, fibrometer, FIB4, and noninvasive tools like fibroscan which assess fibrosis in patients with NAFLD. Other markers of fibrosis that have been evaluated include high-sensitivity C reactive protein, plasma pentraxin 3, interleukin 6 and cytokeratin 18.[48] Liver biopsy should be considered in situations when there is a diagnostic uncertainty, to assess histological disease severity in patients suspected to have advanced fibrosis, and in those undergoing laparoscopy, cholecystectomy, or bariatric surgery.

Liver Biopsy

In recent years many noninvasive investigations have been developed to assess liver fibrosis; however, liver biopsy still remains the gold standard for treatment and prognostication. NASH should ideally be differentiated from simple steatosis since the prognosis differs and liver biopsy is the only means to differentiate between them. Grading and staging of histology is done taking into consideration the degree of steatosis, lobular inflammation, ballooning degeneration and fibrosis; different systems used to stage/classify include the old Matteoni classification and Brunt's system, but recently the NAFLD activity score (NAS) has gained popularity and is followed by most pathologists all over the world.

MANAGEMENT

The management of patients with NAFLD consists of treating liver disease as well as the associated metabolic comorbidities such as obesity, hyperlipidemia, insulin resistance and T2DM. As patients with NAFLD without steatohepatitis have excellent prognosis from a liver standpoint, treatments aimed at improving liver disease should be limited to those with NASH.[49]

Lifestyle Intervention

Currently lifestyle modifications including dietary restrictions and exercise should be recommended as the cornerstone of NAFLD management. Patients should be set a target weight of 22 x (Height in meters)^2 since a BMI of 22 has been shown to be the critical BMI for development of fatty liver.[1] Many studies have shown that lifestyle modification may reduce aminotransferases and improve hepatic steatosis when measured either by ultrasound[50-52] or MR imaging and spectroscopy.[53,54] Study from India has also shown that lifestyle modification improves insulin resistance and liver histology in patients with NAFLD,[55] and also helps in normalizing serum aminotransferase level in patients of NASH.[56] The general recommendations for the diet are individualized, and one should aim to achieve energy deficit of 500–1000 kcal/day depending on the patient's BMI. Reduced saturated fat and total fat should constitute less than 30% of the total energy intake, and intake of refined sugars should be decreased with an increase in soluble fiber intake. Physical activities recommended is 60 minutes/day for at least 3 days a week and progressively exercise should be increased to five times a week.[36,37] The degree of hepatic fat reduction is proportional to the intensity of the lifestyle intervention and generally requires a body weight loss between ~5 and 10%.[57,58] The effect of exercise without dietary modification on hepatic steatosis was investigated in four studies using MR spectroscopy.[59-62] Exercise programs consisted of 2–3 sessions a week of 30–60 minutes over a period of 6–12 weeks. In all but one study liver fat content diminished without a significant change in body weight.[63] Pharmacological and surgical methods of weight loss should be used in morbidly obese patients or moderately obese patients with significant risk factors.

PHARMACOTHERAPY

Metformin belongs to the class of medication called the biguanides and is a widely used oral medication for the treatment of T2DM. The insulin-sensitizing effect of metformin is attributed to its ability to activate the AMP activated protein kinase pathway which switches cells from the anabolic to catabolic pathways. There are numerous studies assessing the effects of metformin in NASH[64-71] but except two,[65,68] none of the studies have shown improvement in liver histology. A study from India[72] showed metformin to be effective in achieving biochemical response in patients with NAFLD not responding to lifestyle interventions. However, a recent meta-analysis[73] concluded that 6–12 months of metformin plus lifestyle intervention did not improve aminotransferases or liver histology, compared with lifestyle intervention alone, independently of metformin dose or the presence of diabetes. Currently there is weak support for evidence based recommendations of metformin use for management of NAFLD.

The thiazolidinediones (TZDs) currently in clinical use include rosiglitazone and pioglitazone. This class of oral medications works by activating the PPAR-γ, a nuclear receptor expressed in the liver, muscle, and adipose tissue that regulates adipocyte differentiation, fat metabolism, and inflammation. Activation of the receptor leads to multiple potential beneficial effects for NASH including inhibiting hepatic fatty acid synthesis,[74] remodelling adipose tissue to sequester fatty acids,[75] promoting an insulin sensitive profile by increasing adiponectin levels,[76] and decreasing proinflammatory cytokines. Several studies investigated the effect of pioglitazone and rosiglitazone on aminotransferases and liver histology in adults with NASH[77-82] and showed improvement except one study[82] which showed improvement in liver histology only. TZDs appear to have a promising role in the treatment of NASH but there is considerable debate about the long term safety of TZDs regarding cardiovascular adverse effects including congestive heart failure, bladder cancer and bone loss.

Oxidative stress is considered to be a key mechanism of hepatocellular injury and disease progression in subjects with NASH. Vitamin E is an antioxidant and has been investigated for treatment of NASH.[83-86] Therapy with vitamin E is associated with a decrease in aminotransferases in subjects with NASH, and improvement in steatosis, inflammation, ballooning and resolution of steatohepatitis in adults with NASH, but it does not have any effect on hepatic fibrosis. In the largest clinical trial (PIVENS)[86] reported to date, the pure form of rrr α-tocopherol was orally administered at a dose of 800 IU/day for 96 weeks. The primary endpoint, i.e. improvement of liver histology was achieved in a significantly greater number of participants receiving vitamin E compared to placebo (42% vs 19%, $p < 0.001$). However, one concern with vitamin E therapy is the controversial issue of whether it increases all-cause mortality.

Several studies[87-90] investigated ursodeoxycholic acid (UDCA) (conventional and high doses) to improve amino-transferases and steatosis in patients with NAFLD and liver histology in patients with NASH. A single large multicenter randomized clinical trial (RCT) convincingly showed that UDCA offers no histological benefit over placebo in patients with NASH.[89] Several other agents like Pentoxifylline (PTX), omega-3 fatty acids, S-adenosylmethionine (SAM), Alpha-glucosidase inhibitor, Incretin analogs, Obeticholic acid, Statins, Bile acid sequestrants, angiotensin-converting enzyme inhibitors (ACEI) or angiotensin-II receptor blockers (ARBs) have been tried for NAFLD in some preliminary studies, but there is no evidence for their use in clinical practice.

Bariatric surgery for weight loss has been shown to be effective in improving NASH. Two meta-analyses[91,92] evaluated the effect of bariatric surgery on the liver histology in patients with NAFLD. The meta-analysis by Mummadi et al.,[91] showed that steatosis, steatohepatitis, and fibrosis appear to improve or completely resolve after bariatric surgery. However, a recently published Cochrane review[92] concluded that lack of RCTs or quasi-randomized clinical studies prevents definitive assessment of the benefits and harms of bariatric surgery as a therapeutic approach for patients with NASH. Hence this form of therapy too cannot be routinely advocated for treatment of NASH.

DOS AND DON'TS FOR PATIENTS WITH NONALCOHOLIC FATTY LIVER DISEASE

Alcohol Consumption

It is not clear as to what amount of alcohol can safely be ingested by a patient with NAFLD. A recent report has even extolled the benefits of modest consumption of alcohol.[93] However, until further studies clearly show how much is right, and define the upper limit of alcohol which can be safely ingested, it would be prudent to advise our NAFLD patients to limit their alcohol consumption to no more than an occasional drink a month.

Use of Statins

Nonalcoholic fatty liver disease patients are often on statins which are prescribed for dyslipidemia before a diagnosis of NAFLD is made; on the other hand majority of the NAFLD patients are found to have dyslipidemia when this is looked for and need statin prescription. There was some confusion earlier regarding safety of statins in this setting. However, statins have been found to be safe in patients with NAFLD even in the presence of raised liver enzymes hence can be prescribed safely without frequent liver function test monitoring.[49]

Use of Hepatotoxic Drugs

Though there is no data on the use of hepatotoxic drugs like antitubercular drugs and paracetamol, but it is better to be cautious while using these drugs and other hepatotoxic drugs in patients with NAFLD, and when these are prescribed, frequent, periodic biochemical monitoring should be advised. Besides, patients should also avoid nonesteroidal anti-inflammatory drugs and aspirin.

Vaccination for Hepatitis A and B

All patients with NAFLD and NASH related cirrhosis should be vaccinated for hepatitis A and B.

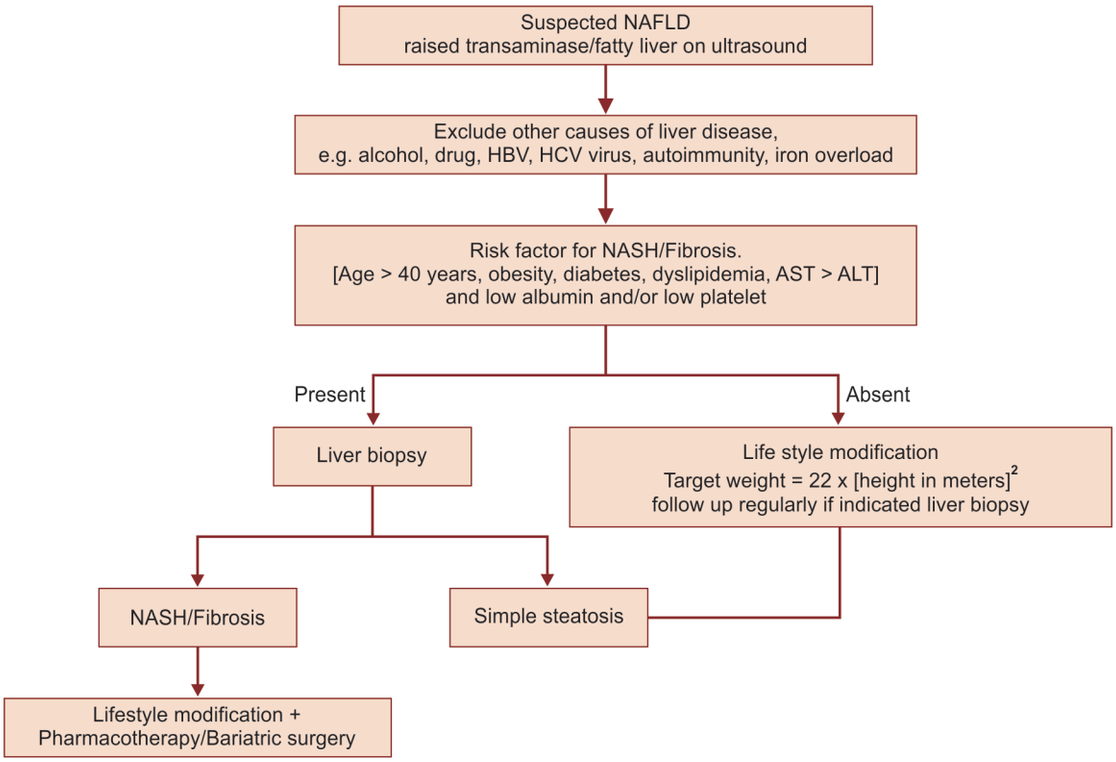
Nonalcoholic Steatohepatitis Patients with Cirrhosis or Advanced Fibrosis

All NASH patients with cirrhosis or advanced fibrosis should be periodically screened for hepatocellular carcinoma as for chronic hepatitis B patients with cirrhosis, and also should be examined by endoscopy for appearance of varices too. Once varices are diagnosed, they should be managed in future just like any other cirrhotic with portal hypertension.

Evaluation for Metabolic Factors and Cardiovascular Risk

Patients should be monitored for metabolic abnormalities like fasting blood sugar, lipid profile and clinical parameters like height, weight and waist circumference to follow-up intervals depending upon the patient's age, family history, extent of obesity and previous findings. Cardiovascular disease is more common than liver disease as a cause of death in patients with NAFLD because of increased cardiovascular risk factors like metabolic syndrome and its components. Evaluation of cardiac risk in patients with NAFLD is highly recommended.

Flow chart 2: Management algorithm for nonalcoholic fatty liver disease in Indians



General

Patients with NAFLD should avoid crash diets, herbal and other obscure medicines, smoking and cannabis.

CONCLUSION

Nonalcoholic fatty liver disease is a very common problem which physicians encounter in their daily practice. Hence Indian physicians need to be aware about the approach to a patient with NAFLD. The management algorithm for NAFLD patients has been elegantly shown in **Flow chart 2**. Since NAFLD is considered a hepatic manifestation of metabolic syndrome, it is also imperative for the treating physician to evaluate not only the liver, but also components of the metabolic syndrome and related comorbidities. All patients with NAFLD/NASH should be counseled regarding the benefits of lifestyle modification including dietary manipulation and regular exercise which would not only improve liver function but also result in surrogate benefits vis-a-vis metabolic syndrome and related cardiac ond other problems. Finally, there is urgent need for research on the natural history of NAFLD in Indians and NAFLD epidemiology and disease burden including morbidity and mortality in Indians, besides developing effective treatment strategies for prevention of NAFLD in India.

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