REVIEW ARTICLE

# Nonalcoholic fatty liver disease: Synopsis of current developments

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## Abstract

Non-alcoholic fatty liver disease (NAFLD) which is defined as the accumulation of fat >5% of liver weight is increasingly becoming an important cause of chronic liver disease. This article tries to chronicle advances that have occurred in the understanding of the pathogenesis, pathology as well as the management of this disease. We have done a Medline search on published work on the subject and reviewed major conference proceedings in the preceding years. The Pathogenesis involves a multi-hit process in which increased accumulation of triglycerides in face of insulin resistance results in increased susceptibility to inflammatory damage mediated by increased expression of inflammatory cytokines and adipokines, oxidative stress and mitochondrial dysfunction, endoplasmic reticulum stress and gut derived endotoxemia. An interplay of multiple metabolic genetic expression and environmental factors however determine which patient with NAFLD will progress from simple steatosis to non-alcoholic steatohepatitis (NASH) and liver cirrhosis. The minimum criteria for diagnosis of NASH are steatosis, ballooning and lobular inflammation; fibrosis is not required. The NASH Clinical Research Network (CRN), histological scoring system is used to grade and stage the disease for standardization. The management of NAFLD consists of treating liver disease as well as associated metabolic co-morbidities such as obesity, hyperlipidaemia, insulin resistance and type 2 diabetes mellitus (T2DM). Patient education is important as their insight and commitment is pivotal, and lifestyle modification is the first line of treatment. Improvement in liver histology in non-diabetic NASH patients has been reported with use of Vitamin E. Other liver-related therapies under investigations include pentoxyfiylins, Caspar inhibitors, Resveratrol as well as probiotics. The prognosis (both overall and liver-related mortality) for simple steatosis is not different from that of the general population however.

**Key words:** Current development, nonalcoholic fatty liver disease, review, synopsis, update

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## Introduction

Nonalcoholic fatty liver disease (NAFLD) is defined strictly as fat accumulation of >5% of the liver weight on histology. However, in clinical practice and for epidemiological reasons, it is the presence of fatty liver at ultrasonography (USG) in the absence of known secondary causes of fatty liver[1] although this is associated with underestimation.[2] It is a spectrum of pathologic changes in the liver that ranges from simple steatosis to nonalcoholic steatohepatitis (NASH), early fibrosis, and cirrhosis and can progress to hepatocellular carcinoma (HCC). It is the third most common risk factor for HCC after viral infection and alcohol.[3] It is a major cause of chronic liver disease in the western society, and the burden is expected to increase with the increasing incidence of obesity and metabolic syndrome (MetS), which are closely associated with it. Factors that protect against the development of NAFLD include: Black race, low level of homeostasis model

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assessment of insulin resistance (HOMA-IR), low serum alanine aminotransferase (ALT).[3]

## Epidemiology

As our nations get heavier, our livers will get fattier. The prevalence of NAFLD has been rising in tandem with the rise in obesity ever since the term NASH, (a subtype of NAFLD) was coined by Ludwig *et al*. in 1980.[4] Reports of epidemiology also shows variation in prevalence relating to race (between 20% and 30% in the United States, Europe, Middle East and 9% in an African population)[5] with peaks in adolescent and elderly, and increases with presence of co-morbidities such as hypertension, obesity, diabetes mellitus and MetS. It is an increasing indication for liver transplantation, a risk factor for HCC and represents a major cause of elevated serum ALT in the absence of viral and alcoholic liver diseases (ALDs).[3] Large population-based surveys in China, Japan, and Korea indicate that the prevalence of NAFLD is now 12–24% in population subgroups, depending on age, gender, ethnicity, and location (urban versus rural)[6] while prevalence of ultrasonographic NAFLD was 69.4% among Type 2 diabetics in Brazil.[7]

## Pathogenesis of Nonalcoholic Fatty Liver Disease

Basically, the hallmark in the pathogenesis of the disease is the accumulation of triglycerides (TGs) in hepatocytes which is followed by increased susceptibility to hepatocyte injury. The pathogenesis is thought to involve the "two-hits" hypothesis proposed by day in 1998 [Figure 1].[8] The "first hit" is characterized by accumulation of TGs derived from the esterification of free fatty acid (FFA) and glycerol. The latter arises from an imbalance of supply, formation, consumption and hepatic oxidation and disposal of TG.[9] The sources of FFAs are diet, adipose tissue lipolysis, and *de novo* lipogenesis. Donnely *et al*.[10] demonstrated that in NAFLD, the major sources of FFA are adipose tissue lipolysis (59%) and *de novo* lipogenesis (26%) and less so from diet (15%). The increased influx of FFA from adipose tissue in NAFLD is attributed to impaired suppression of lipolysis in adipose tissue by insulin due to insulin resistance.[9] It has been shown that the type of fat and its location in the hepatocyte (usually the mitochondria) is important.[10]

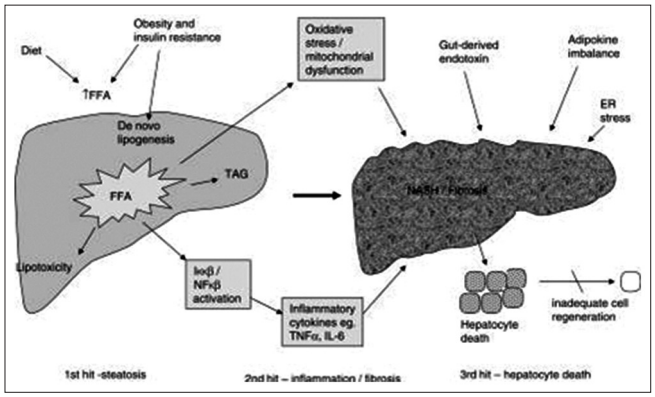


**Figure 1:** Pathogenesis of nonalcoholic fatty liver disease showing the multi-hit process

Following accumulation of TG in hepatocytes, there is increased susceptibility to inflammatory injury, and this constitutes the "second hit" in the pathogenetic pathway. The injury is mediated by increased expression of inflammatory cytokines and adipokines, oxidative stress and mitochondrial dysfunction, endoplasmic reticulum stress and gut-derived endotoxemia from bacterial overgrowth among others.[8,9] The cytokines include tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), IL-1β. TNF-α correlates with increased severity and promotes insulin resistance. Adipokines are produced from adipose tissue and include leptin and adiponectin. While leptin promotes inflammation and fibrogenesis, adiponectin is anti-inflammatory. In addition, adiponectin promotes insulin sensitivity and antagonizes TNF-α.[8,9]

Fibrosis is the final stage or the "third hit" resulting from an imbalance between the rate of hepatocyte death and hepatocyte regeneration. There is inhibition of hepatocyte proliferation due to oxidative stress. This results in activation of hepatic stellate cells and differentiation into myofibroblasts which in turn produce excessive matrix and also stimulate recruitment of hepatic progenitor cells.[11] The latter proliferate to differentiate into hepatocytes and cholangiocytes, and they can also produce chemokines, which attract inflammatory cells to the liver. This alternate repair response gives rise to distortion in liver architecture with presence of a variable fibrosis, regenerative nodules, and inflammatory cell infiltration.[8,9]

A complex interplay of multiple genetic predispositions and environmental factors determine which patient with NAFLD will progress from simple steatosis to NASH and liver cirrhosis.[12] Genetic factors have been suggested based on familial clustering, twin studies, and inter-ethnic differences; and the results of the large multi-center Flip GWAS study implicated three metabolic genes. These are Patatin-like phospholipase domain-containing 3, GCKR, and TRIBI.[13] Diet low in anti-oxidants and high in unsaturated fats is a risk factor. Coffee intake and little alcohol are thought to be protective while fructose probably due to the high carbohydrate intake is also a risk factor.[14] Toxins from gut microbes are thought to play a role as well.[15]

### Metabolic aspects, insulin resistance and iron deposition

Nonalcoholic fatty liver disease is considered to be the hepatic manifestation of the MetS and insulin resistance, the

pathophysiologic hallmark.[16] Insulin resistance in NAFLD encompasses reduced whole-body, hepatic, and adipose tissue insulin sensitivity.[17] Hyperinsulinemia promotes the transcriptional upregulation of genes that promote *de novo* lipogenesis in the liver. In the presence of insulin resistance, there also are greater uptake rates of plasma nonesterified fatty acids attributable to increased release from an expanded mass of adipose tissue all explained by diminished insulin responsiveness.[18] Other mechanisms underlying the accumulation of fat in the liver may include excess dietary fat, increased delivery of FFAs to the liver and inadequate fatty acid oxidation.[17]

Liver fat is highly correlated with all the components of the MetS, and this is independent of the presence of obesity or glucose intolerance. This statement is corroborated by the findings by Marchesini *et al*.[19] who measured anthropometric and metabolic variables in persons with NAFLD. Their results showed that NAFLD was associated with insulin resistance and hyperinsulinemia even in lean subjects with normal glucose tolerance.[19] These findings should however not obviate the need for screening for glucose intolerance in persons with NAFLD. In a recent study on glucose intolerance in young Koreans aged <30 years with NAFLD, a surprising 48% had abnormal glucose tolerance of which 15% had frank diabetes mellitus.[20] It is pertinent to note that oral glucose tolerance test, which is the most sensitive test for detecting glucose intolerance was administered to the study group. It is safe, therefore, to deduce from the foregoing that an even higher proportion of persons with previously undiagnosed glucose intolerance may be detected or uncovered in people older than 30 years of age with NAFLD especially given the fact that ageing is a well-documented risk factor for T2DM. The MetS is a cluster of cardiovascular risk factors that is characterized by obesity, central obesity, insulin resistance, atherogenic dyslipidemia and hypertension.[21] There is a plethora of definitions of the Mets, but the common denominator of these definitions is insulin resistance which is also a feature of NAFLD.[21] The MetS being a feature of NAFLD does not necessarily translate into it occurring more in persons with NAFLD than in persons without NAFLD. Onyekwere *et al*.[5] in their report on NAFLD in persons with DM, documented comparable prevalence rates of the Mets between diabetic patients with NAFLD and those without NAFLD.

Hepatic iron deposition has been noted to occur in parenchymal and/or nonparenchymal cells of the reticuloendothelial system (RES) in a third of persons with NAFLD.[22] In NAFLD, iron may potentiate the onset and progression of the disease by increasing oxidative stress and altering insulin signaling and lipid metabolism.[22] The presence of iron in liver RES cells occurring in association with NASH is also a marker for increased apoptosis and increased oxidative stress which in turn may potentially promote hepatocyte necrosis in this disease.[23]

There is an increasing barrage, albeit conflicting, of data[24-27] on the possible relationship between thyroid dysfunction and NAFLD. Some Reports have demonstrated a higher prevalence of thyroid dysfunction in the form of overt or subclinical hypothyroidism among patients with NAFLD/NASH.[26,27] Several studies that had healthy controls showed significantly higher prevalence rates of hypothyroidism in patients with NAFLD/NASH compared to the controls. However, the results of a Chinese study[28] that evaluated the relationship between serum thyroid stimulating hormone (TSH) level and NAFLD showed that although serum TSH level was significantly higher in persons with NAFLD compared to those without NAFLD, TSH level was not found to be an independent risk factor.

A popular proffered mechanism for the possible relationship between hyothyroidism and NAFLD is hypothyroidism induced oxidative stress.

Further studies are required on this entity especially in the sub-Sahara Africa to further evaluate a possible relationship between this two all-important clinical entities.

## Pathology of Nonalcoholic Fatty Liver Disease

The pathologic lesions differ between adults and children. The spectrum of lesions ranges from the most benign form; simple steatosis to cirrhosis in its most advanced form and NASH as the intermediate form[29,30] Hashimoto *et al*.[31] classified NAFLD into two entities based on clinical outcome: The more benign nonprogressive NAFL and the most severe NASH. They reported that the latter is more likely to progress to liver cirrhosis and HCC. Another study however showed that 16 of 25 patients with an earlier diagnosis of NAFL followed-up for 3.7 years progressed to NASH with bridging fibrosis, especially if metabolic risk factors deteriorate.[30] NAFLD is, therefore, a spectrum of disorders which at the earliest stage appears benign but over a period develops into a more advanced irreversible liver damage.

The earliest lesion in NAFLD is simple steatosis present in >5% of hepatocytes; it is typically perivenular, macrovesicular with or without foci of mild lobular or portal inflammation or lipogranuloma. The extent of steatosis is usually graded into mild (0–33%), moderate (34–66%) and severe (>66%).

Simple steatosis can progress to a more severe lesion NASH. The lesions that have been reported in NASH are: Steatosis, hepatocyte ballooning with or without Mallory–Denk bodies (MDB), necroinflammation and perisinusoidal fibrosis.[31,32] However, the minimum

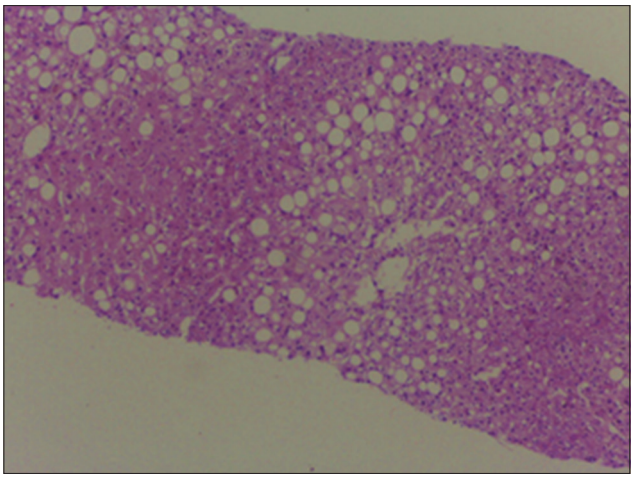

**Figure 2:** Photomicrograph of liver in a 34 yrs male showing features of NASH (steatosis+ballooned hepatocytes, H and E ×10)

criteria for diagnosis are steatosis, ballooning and lobular inflammation [Figures 2 and 3]. The lobular inflammatory infiltrate is mild with acinar zone 3 accentuation. Fibrosis is not required for diagnosis of NASH. Ballooning is an important feature; its presence indicates aggressiveness and heralds increased risk of cirrhosis. Fibrosis starts from acinar zone 3, has a typical chicken wire pattern with pericellular/perisinusoidal emphasis. Bridging fibrosis and macronodular cirrhosis can develop in advanced cases.

Other lesions are MDB, megamitochondria, glycogenated nuclei and mild periportal siderosis. Although MDB is not required for diagnosis, its presence correlates with increased necroinflammation and cirrhosis. Matteoni *et al*.[33] had demonstrated that patients in which liver biopsy showed ballooning and Mallory hyaline or fibrosis tend to have poor outcomes.

The histology of pediatric NAFLD differs from that of adults. Zone 3 steatosis, ballooning and zone 3 perisinusoidal fibrosis are less common in children. Brunt described type 1 and 2 with an overlap. The type 1 is more common in girls and resembles the adult type with zone 3 accentuation of steatosis while type 2 is more common in boys with zone 1 (portal) accentuation of steatosis and inflammation.[34]

Differential diagnosis of NASH includes ALD, chronic hepatitis C virus infection. Most of the lesions described in NASH can also be present in ALD and differentiating these entities may be difficult in the absence of reliable history of alcohol. However, canalicular cholestasis, marked ductular reaction and acute portal inflammatory infiltrate are more common in ALD while in NASH, steatosis is more severe, and necro-inflammation tends to be milder.[35,36] Also presence of glycogenated nuclei in periportal hepatocytes on the other hand is supportive of NAFLD while MDB can be found in both ALD and NAFLD. Other diseases in which steatohepatitis has

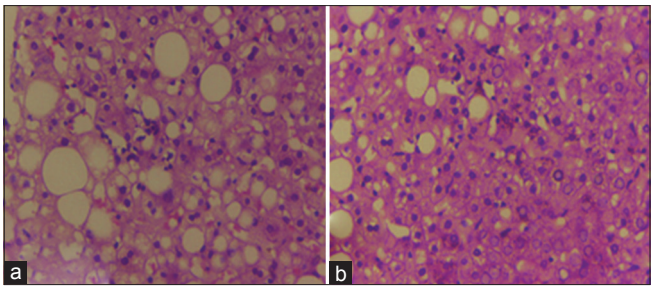


**Figure 3:** Photomicrographs of liver in a 34 yrs male showing features of NASH (steatosis with ballooned hepatocytes, a focus of mild lobular lymphocytic infiltrate in (a) and few glycocylated nuclei in (b) – H and E, ×40

been documented are primary biliary disease, α-1-anti-trypsin deficiency, and chronic hepatitis B virus infection.

## Histologic grading of nonalcoholic fatty liver disease

In view of the need for standardization in the criteria used in histologic diagnosis of NASH, grading and staging have been introduced similar to the one used for chronic hepatitis. The NASH Clinical Research Network, histological scoring system is the one that is most widely used [Table 1].[37] Grading is based on the three parameters of steatosis (S), lobular inflammation (L) and ballooning (B) which represent the important features that contribute to the severity of NAFLD. These are assessed to produce a three-tier global grade of activity [Table 1].

The sum of the scores of (S + L + B) gives a total of NAFLD Activity Score of 8. Score of 1–2 implies definitely not NASH, 3–4 means borderline and 5–8 is definite NASH.

## Staging of fibrosis in nonalcoholic fatty liver disease

Staging is based on the characteristic pattern and evolution of fibrosis ranging between perisinusoidal involvement to portal/periportal, bridging fibrosis and cirrhosis at the extreme. These are:

- Stage 0: None
- Stage 1a: Mild zone 3 perisinusoidal fibrosis
- Stage 1b: Moderate zone 3 perisinusoidal fibrosis
- Stage 1c: Portal/periportal fibrosis only
- Stage 2: Zone 3 perisinousoidal and portal/periportal fibrosis
- Stage 3: Bridging fibrosis
- Stage 4: Cirrhosis.

The use of liver biopsy seems unpopular in the diagnosis of NAFLD, because it is considered to be invasive, lack of effective treatment even after diagnosis, only a small percentage of patient progress to NASH and the fact that noninvasive tests are improving in their sensitivity and specificity. In spite of all these, however, liver histology is still the gold standard used to validate other noninvasive tests, and it is the only way to distinguish simple steatosis from NASH

and fibrosis. The challenges of liver biopsy can be overcome by ensuring sample adequacy with the use of large gauged needle biopsy as against wedged biopsy, a tissue core that is >1.5 cm in length and interpretation should be carried out preferably by a trained specialist liver pathologist. This will improve the diagnostic yield and limit errors of interpretation.

## Natural History and Prognosis

The natural history is as depicted in Figure 4. The prognosis (both overall and liver-related mortality) for simple steatosis is not different from that of the general population. However, this is not the case in NASH as the risk of disease progression is very high (2.8 vs. 0.2) with associated increased cardiovascular events (15 vs. 7) due to endothelial dysfunction, intima media thickness, abnormalities of cardiac structure and risk of future cardiovascular events including in the posttransplant period.[38]

### Clinical features

A number of cases of NAFLD are asymptomatic, and when symptomatic, the commonest manifestation is fatigue with documented fatigue scores worse than in other liver diseases. It is thought to be related to autonomic dysfunction, as well as ventricular dysfunction.[39] Other manifestations include right hypochondrial discomfort/pain and elevated liver enzymes. Typically serum ALT is usually greater than AST and rarely more than 3 times the upper limit of normal. An AST, ALT ratio >1 is indicative of severe disease.[40]

**Table 1: NASH CRN NAFLD activity scoring system**

| Steatosis (s) (%) | Lobular inflammation (L) | Hepatocyte ballooning (B) |
|---|---|---|
| 0: <5 | 0: None | 0: None |
| 1: 5-33 | 2: In<2 foci | 1: Few ballooned cells |
| 2: 34-66 | 3: 2-4 foci | 2: Many ballooned cells |
| 3: >66 | 3>4 foci | |

CRN=Clinical Research Network; NASH=Nonalcoholic steatohepatitis; NAFLD=Nonalcoholic fatty liver disease

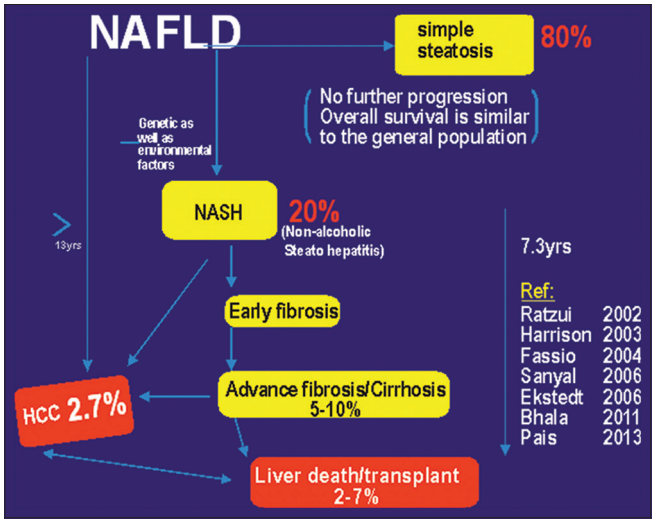


**Figure 4:** Natural history of nonalcoholic fatty liver disease

## Radiological Aspects of Nonalcoholic Fatty Liver Disease

The limitations of liver biopsy have prompted investigators to devise noninvasive, "painless" reliable alternatives to detect and quantify liver fat. There are a host of imaging modalities including ultrasonography (USG) with extra edge of elastography, computed tomography (CT), and magnetic resonance imaging (MRI) with chemical shift imaging (CSI) and spectroscopy to provide an estimation of hepatic fat content.[41]

## Ultrasonography

USG is a safe, radiation-free, readily available and cost effective way of determining fatty infiltration of the liver. The liver shows parenchymal echogenicity higher than the renal cortex and spleen due to fatty infiltration.[42] This may be diffuse or focal. The latter appears as areas of increased echogenicity in the liver with geographic or straight borders [Figure 5].[42] Various (0–3) grades of steatosis have been proposed based on visual analysis of the intensity of the echogenicity, provided the gain setting is optimum. When the echogenicity is just increased, it is Grade 1: When the echogenic liver obscures the echogenic walls of the portal vein branches, it is Grade 2, and when the echogenic liver obscures the diaphragmatic outline, it is Grade 3 fatty infiltrations.[2] These are, however, subject to inter/intra-observer variations. The sensitivity of USG in detecting hepatic steatosis ranges from 60% to 94% and the specificity from 84% to 95%.[43-46] There is also a sensitivity and specificity of 77% and 89% respectively in detecting the fibrosis.[43] Hepatorenal sonographic index, which is the ratio between the mean brightness level of the


**Figure 5:** Focal fatty infiltration of the liver (arrow). Transverse image shows geographically shaped echogenic area

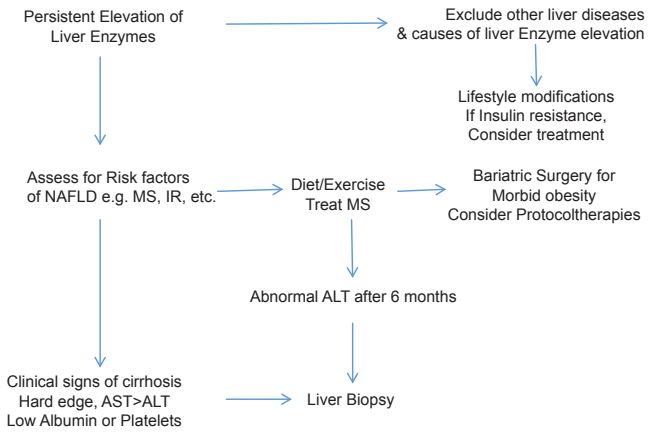


**Figure 6:** Algorithm for evaluation and treatment of NAFLD (modified from JK Dowman; Alimen pharm Therapeut)

liver and the right kidney has also been proposed as a measure of hepatic steatosis with a cut-off of 1.49, yielding a very high sensitivity and specificity for the diagnosis of more than 5% fat accumulation in liver.[47] Sonoelastography provides an estimation of the liver stiffness that in turn is affected by fat infiltration and includes techniques such as acoustic radiation force impulse and transient elastography/fibroscan which has been integrated into the convectional USG system.[41]

## Computed Tomography

Steatosis causes reduced attenuation of the liver on CT, which can be represented quantitatively by comparing it with the attenuation of spleen on unenhanced scans. A liver-to-spleen attenuation ratio of <0.8 has a high specificity (100%) for diagnosis of moderate to severe steatosis. In calculating the difference between the attenuation of spleen and that of the liver in a normal individual, a liver-to-spleen attenuation difference >10 HU is a strong predictor of hepatic steatosis.[48]

Dual-energy CT can also be used to quantify hepatic fat. It involves the acquisition at two tube potential (80 kVp and 140 kVp). The estimation of tissue composition is possible due to the difference in the attenuation characteristics of different substances. In hepatic steatosis, there is a decrease in CT attenuation of liver at low energy level. As the tube potential increases, the fat attenuation increases. Studies have found an attenuation change of >10 HU with increase in tube potential from 80 kVp to 140 kVp suggestive of fatty infiltration of >25%.[49]

## Magnetic Resonance Imaging

Magnetic resonance imaging is a radiation-free modality for detecting hepatic fat even in microscopic quantity. Various techniques like CSI, proton spectroscopy, and MR elastography can be utilized. The sensitivity and specificity of CSI are 90% and 91%, while that of spectroscopy is 91% and 87%, respectively.[50] MR elastography can be used to measure liver stiffness. However, MRI is a relatively time-consuming and costly procedure. Steatosis is hyperintense on T1 and mildly hyperintense on T2.

Chemical shift imaging is based on the fact that during echo time, the transverse magnetization vectors of fat and water develop a phase difference which results in decreased overall length of the magnetization vector under opposed phase conditions. The limitation of this technique was its long acquisition time and sensitivity to the magnetic field inhomogeneities.

Modified GRE techniques have been developed to decrease acquisition time and to eliminate misregistration and susceptibility to the magnetic field inhomogeneities.[4]

Magnetic resonance spectroscopy (MRS) shows an increase in the intensity of the lipid resonance peak in the presence of steatosis. MRS allows the direct measurement of the area under the lipid resonance peak. It can be used to provide a quantitative assessment of fatty infiltration of the liver. It is also unaffected by confounding factors like fibrosis, iron overload, and glycogen. However, it is a complex technique that requires patient co-operation and samples only a small portion of the entire liver.[41]

## Diagnosis

Nonalcoholic fatty liver disease remains a diagnosis of exclusion as many other causes of hepatic steatosis which include hepatitis C virus infection, Wilson's disease and especially ASH need to be excluded from detailed history, thorough physical examination and essential sensitive and specific investigations.

Although liver biopsy remains the gold standard for diagnosis, its limitations have already been stressed necessitating the use of imaging modalities. However, a major limitation of radiological diagnosis is the inability to distinguish between simple steatosis and steatohepatitis.[2] Report of a review of the literature has suggested that serum ALT is not an ideal biomarker for either diagnosis of NAFLD or distinguishing simple steatosis from NASH.[51] Also, a detailed patient history of alcohol consumption is critical as no diagnostic test can reliably distinguish between ASH and NASH. These have prompted the use of validated questionnaires, surrogate biomarkers, fibrosis prediction panels as well as algorithm in evaluation and follow-up of patients with NAFLD. Several panels of biomarkers in variable combination have been developed for the detection of either NASH and/or advanced liver fibrosis. Most of the panels have not been validated in longitudinal studies. The study cohorts in most of the reports are heterogeneous in characteristics and sometimes highly selected.[51]

## Biomarkers for evaluating nonalcoholic fatty liver disease

### *Serum biochemical marker*

Traditionally serum ALT has been used as a marker of hepatic necro-inflammmation as hepatic ALT is >3000 × serum ALT but its utility is limited as the serum ALT varies with some demographic variables including age and sex. Also, report of serum ALT in subjects with NAFLD diagnosed using MRS as well as incidentally diagnosed during surgery have not shown a consistent pattern or trend of serum ALT within the histologic spectrum of NAFLD.[51]

## The fatty liver index

The fatty liver index (FLI) is a validated instrument that was first introduced by Bedogni *et al*.[52] and consists of a multivariate model which includes biomarkers that can accurately estimate the presence of fatty liver. Several investigators have applied the FLI sometimes in large population settings to determine the prevalence of FLI.[53-55] The index used an algorithm based on body mass index (BMI), waist circumference (WCF), TGs, gamma glutamyl transferase (GGT) and natural logarithm (In) as follows:

FLI = Exp (0.953 × In[TG] +0.139 × BMI + 0.718 × In[GGT] +0.053 × WCF − 15.745)/(1 + Exp[0.953 × In[TG] +0.139 × BMI + 0.718 × In[GGT] +0.053 × WCF − 15.745]) × 100 ng.

The accuracy of FLI in detecting fatty liver is estimated to be 0.84 at 95% confidence interval (0.81–0.87).

Markers of steatohepatitis (NASH test); though not validated in longitudinal study are calculated using an original combination of ten highly concentrated biochemical markers, which are easy to assess. The NASH test offers a noninvasive alternative for diagnosing NASH in patients with metabolic steatosis (overweight, diabetes, and hyperlipidemia). The NASH test combines α 2-macroglobulin, haptoglobin, apolipoprotein A1, total bilirubin, GGT, fasting glucose, TGs, cholesterol, ALT and AST, with parameters adjusted for patient's age, gender, weight and height.[56]

### *Markers of apoptosis-cytokeratin-18 fragments*

Plasma CK18 fragments were found to be markedly increased in patients with NASH ($n$ = 21) than those with simple steatosis ($n$ = 8) or normal controls ($n$ = 10) (median [interquartile range]: 765.7 U/L [479.6–991.1], 202.4 U/L [160.4–258.2], 215.5 U/L [150.2–296.2], respectively; $P < 0.001$).[41] A cut-off value of 395 U/L performed excellently for the diagnosis of NASH (AUROC 0.93, sensitivity 85.7, specificity 99.9%). For every 50 U/L increase in CK18 levels, the likelihood of having "definitive NASH" increased 86%.[57]

### *Markers of insulin resistance*

The HOMA-IR[58] is an easy method that provides an estimate of insulin resistance based on fasting serum glucose and serum insulin levels. It estimates steady state beta cell function and insulin sensitivity, as percentages of a normal reference population. HOMA-IR is calculated according to the formula: Fasting insulin (μU/L) × fasting glucose (nmol/L)/22.5. HOMA-IR values above or equal to 2.0 or 2.5 show enhanced diagnostic value in distinguishing NAFLD carriers from control group individuals.[59] It also correlates well with other methods of assessment of insulin resistance such a quantitative insulin sensitivity check index and McAuley index.

### *Markers of fibrosis*

A number of fibrosis prediction panels have been advocated for assessing extent and degree of fibrosis including NAFLD fibrosis score,[60] Original European Liver Fibrosis panel (OELF), enhanced liver fibrosis score (ELF score), Mayo score + ELF score as well as transient elastography. The OELF consists of age and three serum markers, HA, TIMP1, and PIIINP. For NAFLD, fibrosis Stage 3 or 4 was detectable using a threshold value of 0.375 with a sensitivity of 89%, specificity of 96%, PPV of 80%, and NPV of 98%.[61] The ELF panel differs from the OELF by simply removing age from the panel.

# Treatment

The management of patients with NAFLD consists of treating liver disease, as well as the associated metabolic co-morbidities such as obesity, hyperlipidemia, insulin resistance, and T2DM. The most important aspect of managing NASH is to educate patients about its potential gravity. Patient insight and commitment are pivotal in the control of NASH, and lifestyle modification is the first line of treatment.

Lifestyle modification has been shown to be a key component of the management of NAFLD.[62] Weight loss is an essential for persons with NAFLD who are obese with central obesity also included in this category. Successful weight loss either achieved via lifestyle modification/behavior therapy or surgery but not pharmacotherapy especially orlistat has been demonstrated to improve both metabolic parameters and liver histology. A report on testing the effects of weight loss on this disease entity showed that a 1-year period of lifestyle adjustment resulted in a 7–10% weight loss with significant histological improvement of liver disease.[63]

Given the pivotal role that insulin resistance is considered to play in the pathogenesis of NAFLD, the potential role of insulin sensitizers such as biguanides, thiazolidinediones (TZDs), glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase four inhibitors cannot be

overlooked. Of the insulin sensitizers, metformin is the one that is widely studied as regarding its role in the management of NAFLD. In the majority of trials on the use of metformin in the management of NAFLD, it was observed that whilst liver enzymes were improved, there was no effect on liver histology.[64] It remains uncertain if metformin is used in persons with sole NAFLD/NASH in the absence of DM. Given the role of metformin in the management of the prediabetic state in the absence of overt DM, there may be a potential role for metformin in this condition when there is concomitant NAFLD/NASH.

Thiazolidinediones a class of oral anti-diabetic drugs that induces a nuclear transcription factor, peroxisome proliferator activated receptor-γ, which is predominantly expressed, in adipose tissue. The use of TZDs thus leads to decreased hepatic fat content and improves glycemic control with insulin sensitivity. Trials on the impact of TZDs on NAFLD showed no improvement in liver histology and reversible changes in liver enzymes.[64] From the foregoing, and also in light of the issues on possible hepatotoxicity and cardiotoxicity associated with its use, patient selection would definitely be imperative. The glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase four inhibitors have not been widely studied in this regard.

Patients with NAFLD often have dyslipidemia characterized by increased serum TGs, increased small, dense low-density lipoprotein (nontype A) particles, and low high-density lipoprotein cholesterol. There is unequivocal evidence that cardiovascular disease is the most common cause of mortality in patients with NAFLD.[65] Aggressive treatment of dyslipidemia plays a critical role in the overall management of patients with NAFLD especially in the presence of compelling data that point to cardiovascular disease as the commonly documented cause of mortality in this group of patients. Statins are effective in the management of dyslipidemia in NAFLD and the risk for serious liver injury from statins is quite rare, and patients with NAFLD are not at increased risk for statin hepatotoxicity.[65] Hypertriglyceridemia should, however, be treated with omega-3 fatty acids as they not only reduce TG levels but also improve liver disease.

Hyperferritinemia, an occasional feature of NAFLD is associated with the severity of liver disease and the development of HCC. In a randomized trial of iron depletion in NAFLD, results showed that phlebotomy was likely to be associated with a higher rate of improvement of histological liver damage compared to lifestyle changes alone.[66]

### Role of vitamin E in management of NAFLD

Oxidative stress is considered to be a key mechanism of hepatocellular injury and disease progression in subjects with NASH. Vitamin E is an anti-oxidant and has been investigated to treat NASH. Vitamin E (α-tocopherol) administered at daily dose of 800 IU/day improves liver histology in nondiabetic adults with biopsy-proven NASH and therefore it should be considered as a first-line pharmacotherapy for this patient population.[67] However, with concerns about the side-effect profile of high-dose vitamin E (a slight increase in long-term all-cause mortality and risk for prostate cancer), the risk of vitamin E therapy has to be weighed against the risk for NASH progression. Other liver-related therapies that have investigated include Pentoxyfiylins, Caspar inhibitors, Resveratrol as well as probiotics.

## Conclusion

Nonalcoholic fatty liver disease is fast emerging as an important cause of liver disease and is likely to assume greater contributory role in morbidity and mortality from liver disease following control measures for viral hepatitis B and cure for hepatitis C. It beholds clinicians and policy makers to update their knowledge of this metabolic disorder in order to stem the tide.

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