REVIEW ARTICLE

FATTY LIVER DISEASE: A WAKE UP CALL

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Non-alcoholic fatty liver disease (NAFLD) is now the commonest cause of chronic liver disease in many developed countries. [1] Up to a third of the population of some developed nation have evidence of steatosis on imaging,[2,3] with the majority (70%–90%) having simple steatosis. However, 10%–30% of subjects with NAFLD have non-alcoholic steatohepatitis (NASH) that can progress to cirrhosis, which puts patients at risk of liver-related complications.[4-6] Due to the metabolic risk factors that are common to both NAFLD and cardiovascular disease, patients with NASH have an increased risk of cardiovascular death as well as liver-related mortality.[7] Its Incidence is rising rapidly. In Japan its incidence rate is 86 persons per 100 persons yearly, and in England the figure is 29 per 1000 persons. Its prevalence widely varies in population to population.

Spectrum of Fatty Liver Disease

Fatty liver is the accumulation of triglycerides and other fats in the liver cells. The amount of fatty acid in the liver depends on the balance between the processes of delivery and removal. In some patients, fatty liver may be accompanied by hepatic inflammation and liver cell death (steatohepatitis). Fatty liver is called when fat makes at least 5% of liver. Simple fatty liver is completely benign. Alcoholic fatty liver is an early and reversible consequence of excessive alcohol consumption. Fatty liver develops in every individual who consumes more than 60 g of alcohol per day. This review highlights NAFLD because of its magnitude of the health problem and increasing prevalence. The definition of nonalcoholic fatty liver disease (NAFLD) requires that (a) there is evidence of hepatic steatosis, either by imaging or by histology and (b) there are no causes for secondary hepatic fat accumulation such as significant alcohol consumption, use of steatogenic medication or hereditary disorders. In the majority of patients, NAFLD is associated with metabolic risk factors such as obesity, diabetes mellitus, and dyslipidemia. NAFLD is histologically further categorized into nonalcoholic fatty liver (NAFL) and nonalcoholic steatohepatitis (NASH). NAFL is defined as the presence of hepatic steatosis with no evidence of presence of hepatic steatosis and inflammation with hepatocyte injury (ballooning) with or without fibrosis.

Other definitions

Nonalcoholic Fatty Liver Disease (NAFLD) Encompasses the entire spectrum of fatty liver disease in individuals without significant alcohol consumption, ranging from fatty liver to steatohepatitis and cirrhosis.

Nonalcoholic Fatty Liver (NAFL) Presence of hepatic steatosis with no evidence of hepatocellular injury in the form of ballooning of the hepatocytes or no evidence of fibrosis. The risk of progression to cirrhosis and liver failure is minimal.

Nonalcoholic steatohepatitis (NASH) Presence of hepatic steatosis and inflammation with hepatocyte injury (ballooning) with or without fibrosis. This can progress to cirrhosis, liver failure and rarely liver cancer.

NASH Cirrhosis Presence of cirrhosis with current or previous histological evidence of steatosis or steatohepatitis

Cryptogenic Cirrhosis Presence of cirrhosis with no obvious etiology. Patients with cryptogenic cirrhosis are heavily enriched with metabolic risk factors such as obesity and metabolic syndrome.

NAFLD Activity Score (NAS) An unweighted composite of steatosis, inflammation, and ballooning scores. It is a useful tool to measure changes in liver histology in patients with NAFLD in clinical trials.: Presence of hepatic steatosis with no evidence of hepatocellular injury in the form of ballooning of the hepatocytes or no evidence of fibrosis. The risk of progression to cirrhosis and liver failure is minimal.

Some Common causes of Secondary Steatohepatitis

Macrovesicular steatosis

- Excessive alcohol consumption
- Hepatitis C (genotype 3)
- Wilson's disease

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- Lipodystrophy
- Starvation
- Parenteral nutrition
- Abetalipoproteinemia
- Medications (e.g., amiodarone, methotrexate, tamoxifen, corticosteroids)

Microvesicular steatosis

- Reye's syndrome
- Medications (valproate, anti-retroviral medicines)
- Acute fatty liver of pregnancy
- HELLP syndrome
- Inborn errors of metabolism (e.g., LCAT deficiency, cholesterol ester storage disease, Wolman disease)

Prevalence of NAFLD

The prevalence of NAFLD in the general population is estimated at 20–30%; this figure is based largely on ultrasound studies in other similar populations. NASH is present in around 2–3% of the British population. NAFLD is more common in people who are overweight, hypertensive or have type 2 diabetes mellitus.

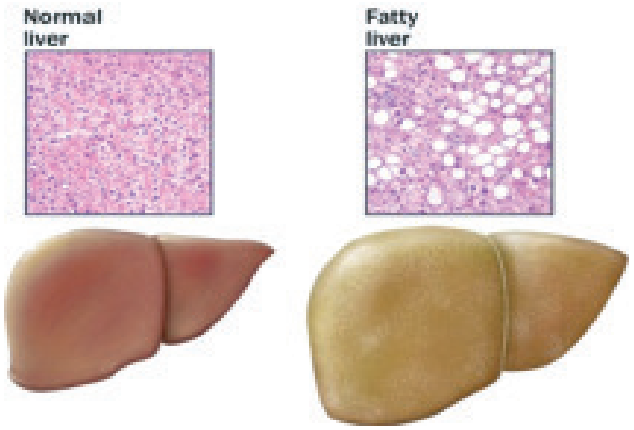

Fig.-1: *Comparison between histology of normal and fatty liver. Courtesy Mayo Foundation for medical Education and Research*

Both excessive BMI and visceral obesity are recognized risk factors for NAFLD. There is high prevalence of NAFLD in persons with type 2 Diabetes[4]. High serum triglyceride levels and low serum HDL levels are very common in patients with NAFLD. The prevalence of NAFLD in individuals with dyslipidemia attending lipid clinics was estimated to be 50%.[7] Age, gender and ethnicity are also associated with a differential prevalence for NAFLD. NAFLD is more common in certain ethnic groups including people of Latin American and South Asian family origin.[4] Many recent studies have reported that male gender is a risk factor for fatty liver disease. 4 For example, in a study of 26,527 subjects undergoing medical checkups, the prevalence of NAFLD was 31% in men and 16% in women.[8] There are data to suggest that hypothyroidism, hypopituitarism, hypogonadism, sleep apnea, and polycystic ovary syndrome independent of obesity are important risk factors for the presence of NAFLD.

Natural course of NAFLD

The long term outcomes of patients with NAFLD and NASH have been reported in several studies.[9,10,11] Their detailed discussion is beyond the scope of this guideline, but their findings can be summarized as follows; (a) patients with NAFLD have increased overall mortality compared to matched control populations, (b) the most common cause of death in patients with NAFLD, NAFL and NASH is cardiovascular disease, and (c) patients with NASH (but not NAFL) have an increased liver-related mortality rate. Another piece of indirect evidence that supports the progressive nature of NASH is in the features of cryptogenic cirrhosis which is closely related to NAFLD. [12,13]

Patients with cryptogenic cirrhosis have disproportionately high prevalence of metabolic risk factors (T2DM, obesity, metabolic syndrome) typical of patients with NAFLD, their liver biopsies frequently show one or more features of NASH, and studies have demonstrated the loss of histological features of NASH with the development of cirrhosis. [12,13]

Patients with NAFLD are at increased risk for HCC, but this risk is likely limited to those with advanced fibrosis and cirrhosis. [14-18]

Screening for NAFLD

It's still in controversy. Screening for NAFLD, at least among higher-risk individuals attending diabetes and obesity clinics. However, at present there are significant gaps in our knowledge regarding the diagnosis, natural history, and treatment of NAFLD. As liver biochemistries can be within normal ranges in patients with NAFLD and NASH, they may not be sufficiently sensitive to serve as screening tests, whereas liver ultrasound is potentially more sensitive but it is expensive and cumbersome as a screening test.

Diagnosis of NAFLD

The diagnosis of NAFLD requires that (a) there is hepatic steatosis by imaging or histology, (b) there is no significant alcohol consumption, (c) there are no competing etiologies for hepatic steatosis, and (d) 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. When evaluating a patient with newly suspected NAFLD, it is important to exclude co-existing etiologies for chronic liver disease including hemochromatosis, autoimmune liver disease, chronic viral hepatitis, and Wilson's disease.

Mildly elevated serum ferritin is common in patients with NAFLD and it does not necessarily indicate increased iron stores. Elevated serum ferritin and

transferring saturation in patients with suspected NAFLD should lead to testing for genetic hemochromatosis. Mutations in the HFE gene occur with variable frequency in patients with NAFLD and their clinical significance is unclear.[20]

One should consider a liver biopsy to assess hepatic iron concentration and to exclude significant hepatic injury and fibrosis in a patient with suspected NAFLD with elevated serum ferritin and a homozygote or compound heterozygote C282Y mutation in the HFE gene.[21]

Elevated serum autoantibodies are common in patients with NAFLD and are generally considered to be an epiphenomenon.

In a recently published large study from the NASH Clinical Research Network, positive serum autoantibodies, defined as ANA>1:160 or ASMA>1:40 were present in 21% of patients with well-phenotyped NAFLD and were not associated with more advanced histologic features.[22]

liver disease with very high aminotransferases and high globulin should prompt a more complete work-up for autoimmune liver disease. Serum aminotransferase levels and imaging tests such as ultrasound, CT, and MR do not reliably assess steatohepatitis and fibrosis in patients with NAFLD. There has been intense interest in non-invasive methods to identify advanced fibrosis in patients with NAFLD [7];these include the NAFLD Fibrosis Score[23],Enhanced Liver Fibrosis (ELF) panel70and transient elastography. The NAFLD Fibrosis Score is based on six readily available variables (age, BMI, hyperglycemia, platelet count, albumin, AST/ALT ratio) and it is calculated using the published formula (http://nafldscore.com). In a meta-analysis of 13 studies consisting of 3,064 patients,[7] NAFLD Fibrosis Score has an AUROC of 0.85 for predicting advanced fibrosis (i.e., bridging fibrosis or cirrhosis) and a score<1.455 had 90% sensitivity and 60% specificity to exclude advanced fibrosis whereas a score >0.676 had 67% sensitivity and 97% specificity to identify the presence of advanced fibrosis. The ELF panel consists of plasma levels of three matrix turnover proteins (hyaluronic acid, TIMP-1, and PIIINP) had an AUROC of 0.90 with 80% sensitivity and 90% specificity for detecting advanced fibrosis. [24]

Transient elastography, which measures liver stiffness non-invasively, has been successful in identifying advanced fibrosis in patients with hepatitis B and hepatitis C. Although a recent meta-analysis showed high sensitivity and specificity for identifying fibrosis in NAFLD.[7]

Management

Lifestyle modification

Physical activity and losing weight is the cornerstone of the management. Weight loss generally reduces hepatic steatosis, achieved either by hypocaloric diet alone or in conjunction with increased physical activity.[17] Loss of at least 3-5% of body weight appears necessary to improve steatosis, but a greater weight loss (up to 10%) may be needed to improve necroinflammation.[18]. Exercise alone in adults with NAFLD may reduce hepatic steatosis but its ability to improve other aspects of liver histology remains unknown.

Metformin

Several studies investigated the effect of metformin on aminotransferases and liver histology in patients with NASH. Early small, open-label studies demonstrated a reduction in insulin resistance and aminotransferases [26,27,28] but no significant improvement in liver histology. Metformin has no significant effect on liver histology and is not recommended as a specific treatment for liver disease in adults with NASH.

Vitamin E

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.[29,30,31,32] Vitamin E (a-tocopherol) administered at daily dose of 800 IU/day improves liver histology in non-diabetic adults with biopsy-proven NASH and therefore it should be considered as a first-line pharmacotherapy for this patient population.

Ursodeoxycholic acid (UDCA), Omega-3 fatty acids Several studies[32,33-37] investigated UDCA (conventional and high doses) to improve aminotransferases and steatosis in patients with NAFLD and liver histology in patients with NASH.

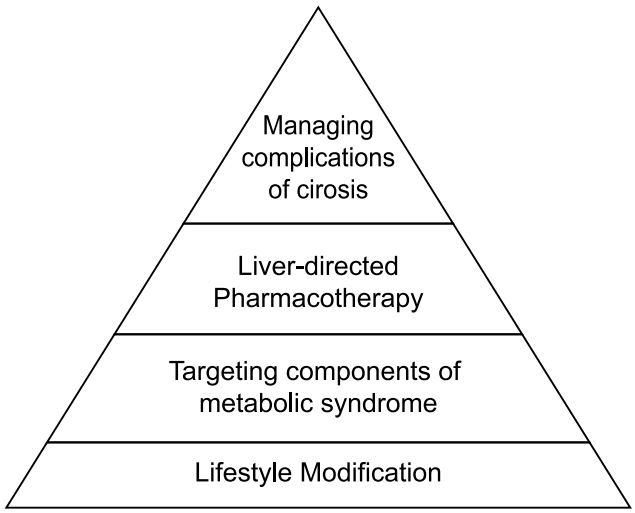

Fig.-1: *Management trategies in NAFLD (Dyson JK,et al. Frontline Gastroenterology 2014;0:1–10. doi:10.1136/flgastro-2013-100404)*

Table-I

Management of Hypertension and Dyslipidaemia in NAFLD.

Risk Factor	Indication	Outcome
Hypertension	ACEI and ARBs first-line if BP >140/90 mm Hg Escalate treatment according to NICE hypertension guidelines	Blocking RAS reduces hepatic fibrosis ARBs improve transaminase levels and insulin sensitivity20% reduction in new onset T2DM with ACEI or ARBs
Dyslipidaemia	Primary prevention with statin if 20% 10-year risk of developing cardiovascular disease. If secondary prevention, aim total cholesterol<4 mmol/L	Statins reduce 5-year incidence of all-cause mortality, major coronary events,coronary revascularisation and stroke by about 20% per mmol/L reduction in LDL. May reduce incidence of HCC

Pentoxifylline

Some studies shows that pentoxifylline is associated with histologic improvement probably by declining the oxidative process.[37]

Probiotics

Synbiotic supplementation in addition to lifestyle modification is superior to lifestyle modification alone for the treatment of NAFLD, at least partially through attenuation of inflammatory markers in the body. Whether these effects will be sustained with longer treatment durations remains to be determined. [38]

Bariatric Surgery

As the majority of patients undergoing bariatric surgery have associated fatty liver disease, there has been an interest in foregut bariatric surgery as a potential treatment option for NASH. There are no RCTs that evaluated any type of foregut bariatric surgical procedure to specifically treat NAFLD or NASH. [39]

Future Hope and Limitation

NAFLD is increasingly being identified through case finding in hospital outpatient departments for people with associated conditions such as diabetes, obesity or hypertension. Early detection and intervention will certainly improve the outcome. Newer treatments including Batriatric surgery and Probiotics are being evolved in the management of NAFLD. Physicians are more conscious to deal the situation. Mass awareness regarding the lifestyle modification will reduce the incidence and prevalence of NAFLD.

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