Brief Communication

NAFLD current concepts

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Introduction

Fatty liver disease was defined as more than 5% of the hepatocytes containing fat or more than 5% of the liver weight due to fat. The term non alcoholic steatohepatitis (NASH) was developed by Ludwig in 1979 to describe an 'alcoholic – like liver disease that develops in people who do not drink alcohol. [1].

The pathological spectrum of Non Alcoholic Fatty Liver Disease (NAFLD) ranges from simple steatosis to steatohepatitis and cirrhosis.. [1-3] .The risk factors for the development of NASH were identified as metabolic syndrome, obesity, type II diabetes mellitus (T2 DM), and dyslipidemia. By the late 1990s, NASH was conceptualized as part of metabolic syndrome. [1-5] NAFLD is becoming a major public health problem due to the rising prevalence of obesity and T2DM worldwide.[6] NAFLD/NASH are now considered to be common causes of chronic liver disease, and increasing indication of liver transplantation and a possible cause of hepatocellular carcinoma (HCC) [2]

Natural history of NAFLD is quite variable. There are some inherent draw backs in studying natural history of NAFLD. [6,7] Firstly there is no definitive laboratory test for diagnosis. Various studies published have different definitions. Published series using serial biopsies for histological progression have limitation of short follow up and selection bias. While cohort studies examining clinical outcomes have remarkably varied definition of NAFLD and clinical outcome may be shadowed by other diseases. Due to these conflicting results many workers considered NAFLD as a medical curiosity.[6-11.] While others consider it as major cause of chronic liver disease with impending epidemic.[12-16] Over the last 5 years there is addition of valuable information on NAFLD. NAFLD is considered as a liver manifestation of a generalized fat storage disorder (metabolic syndrome).[17]

NAFLD patients may have increased risk of cardiovascular events, extra hepatic malignancies as compared to liver related mortality. [12-16]

NAFLD is histologically categorized into simple steatosis and steatohepatitis with dichotomous natural history. Relatively benign prognosis for steatosis while progressive liver disease leading to cirrhosis and hepatocellular carcinoma (HCC) has been predicted for steatohepatitis. [6, 10,18-22]. Unfortunately there is no good non invasive marker which separates steatosis from steatohepatitis and hence liver biopsy still remains gold standard for prognostication of NAFLD based on serial biopsies [20-23.] Studies disease progression in NAFLD is a) In patients with simple steatosis progression to cirrhosis may occur in 4 to 5% over a period of 8 to 15 years while steatohepatitis can progress to cirrhosis in over 25% patients over similar follow up period. B) At initial biopsy 5 to 20% patients with NAFLD may have cirrhosis c) Once cirrhosis develops cumulative probability of complications and need for the transplantation and mortality is just the same as hepatitis C related cirrhosis. Risk for factors rapid progression in NAFLD are type II diabetes, obesity, older age and metabolic syndrome.[24] NAFLD is important cause of cryptogenic cirrhosis and may not be appreciated on histology as with disease progression steatosis may disappear. Many studies have shown that cryptogenic cirrhotics have the same risk profile as NAFLD and higher incidence of NAFLD is noted in these patients after liver transplantation.[25] NAFLD and cryptogenic cirrhosis have been shown to have increased risk of HCC. Risk factor for HCC in NAFLD are liver cirrhosis, type II diabetes, obesity, metabolic syndrome, insulin resistance, older age and male gender.[26-27.] Association of diabetes with cryptogenic cirrhosis and HCC is well established HCC arising from NASH related cirrhosis and NASH without significant fibrosis has been documented in several case reports. [28-36]

Clinical manifestations of NAFLD

NAFLD is a silent disease more than half of the patients are diagnosed accidentally without any symptoms. 25 to 50 %patients may complain of right upper quadrant pain and equal no of patients may complain of fatigue. Some patients can present directly with development cirrhosis and it complications. Majority of the patients have normal physical examination. 25-50% may have clinically identifiable hepatomegaly. Mild to modest ALT, AST elevation is found in 25-50% of patients, remaining patients have normal liver enzymes. [37-45]

Approach to patients with NAFLD in clinical practice is as follows :

Fatty Liver can be defined on ultrasonography characteristics as given below in day to day clinical practice [46-47]

Ultrasonographic criteria:

- Presence of 2 of the following 3 with or without elevated ALT
- A) Bright hepatic echo texture as compared to kidney and spleen
- B) Blurring of hepatic veins
- C) Loss of deep echo- discontinuous diaphragm.

Magnetic resonance spectroscopy and liver histology may be more accurate than ultrasound but their utility in daily clinical practice remains unclear.

Defining NASH

Diagnosis of NASH should be based on liver histology. Liver biopsy should be done in patients with NFALD in whom suspicion of NASH is raised. Presence of high risk factors for progression of the liver disease. [BMI >23Kg/m2 for Asians, Age >50 yrs, raised AST, type2 DM, raised TG >150mg/dl)].

Liver biopsy should be graded and staged.(AASLD composite criteria, Hepatology2003)[12]
Currently no imaging modalities can differentiate NASH from NAFLD but in future fibro scan and serological markers may be able to obviate the need of liver biopsy,

Defining NAFLD associated cirrhosis

a) Clinical, biochemical, imaging and endoscopic evidence of cirrhosis liver.
b) Presence of at least 2 factors of metabolic syndrome.
c) Exclusion of other known etiologies of cirrhosis of liver.

Exclusion of other causes of liver diseases

a) Alcohol consumption <20 gm/d (men), and 10gm/d (women).
b) Exclusion of HBV and HCV infections (HBsAg, Anti-HCV).
c) Exclusion of Wilson and Autoimmune liver disease using appropriate tools.
d) Absence of ingestion of Indigenous treatment in recent past (6 months).

Who should be screened for NAFLD?

NAFLD screening is recommended for patients with diabetes, obesity, dyslipidemia, patients with unexplained elevation of transaminases. Ideal screening tool for NAFLD is ultrasound Patients who are accidentally diagnosed to have fatty liver on ultrasound should undergo evaluation for obesity, central obesity, dyslipidemia and glucose intolerance and metabolic syndrome.[47]

What should be minimal assessment for patients with NAFLD?

Once a patient is found to have suspected NAFLD, further evaluation including clinical examination and baseline investigations should be done to confirm the diagnosis of NAFLD, identify any underlying metabolic disorder, exclude other disorders and make an assessment of disease severity.

The assessment of NAFLD patients should include the following:

- A careful history and physical examination (specially look for drugs, surreptious alcohol abuse, use of complementary and alternative medicine)
- Hematological tests complete blood count including platelet count.
- Anthropometry
- Biochemical tests including liver function test, serum creatinine
- Serological and immunological tests including tests for hepatitis B & C, ANA, serum ceruloplasmin
- Metabolic tests including glucose tolerance test, lipid profile, Insulin sensitivity
- Abdominal ultrasound
- Optional tests: Abdominal CT scan, Liver biopsy, biomarkers for liver fibrosis

These tests have been divided in to those which are essential for minimal assessment and those which are optional [47]

Liver biopsy: it 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

Management of NAFLD

All patients diagnosed to have NAFLD after evaluation should be treated for abnormalities if present e.g. diabetes, and dyslipidemia and glucose intolerance. In case of doubt of severity of liver disease, patients should undergo liver biopsy. In the absence of diabetes and dyslipidemia but presence of NASH on histology, with abnormal glucose tolerance tests or presence of insulin resistance should be considered for treatment with insulin sensitizers. Treatment modalities are still evolving and no drug has been proved useful in the treatment of NAFLD in the absence of predisposing conditions.

Currently life style modifications including dietary restrictions and exercise should be recommended as cornerstone of the therapy. The general recommendations for the diet are individualized to achieve energy deficit of 500 to 1000 kcal per day depending on the patients BMI, reduced saturated fat and total fat less than 30% of the total energy intake, reduced refined sugars and increase soluble fiber intake. Physical activities recommended 60 minutes per day at least 3 days a week and progressively increase the exercise to five times a week. Pharmacological and surgical methods of weight loss should be used in morbidly obese patients or moderately obese patients with significant risk factors.[46-47]

Bariatric surgery for the weight loss has been shown to be effective in improving NASH. Some preliminary data shows efficacy of metformin and glitazones in improving liver histology in patients with non diabetic NASH but still their routine use cannot be recommended at present. Various cytoprotective drugs like UDCA, antioxidants like vitamin E, probiotics, anti TNF alpha agents like pentoxiphylene, antifibortic drugs like losartan have been used in some preliminary studies but there is no evidence for their use in clinical practice. [46,47,48]

What are dos and don'ts for patients with NAFLD?

We should advise our patients with NAFLD to limit their alcohol consumption no more than occasional drink a month.

What is risk of statins in patients with NAFLD?

Statins (HMG-CoA reductase inhibitors) are prescribed in patients with NAFLD to treat associated hyperlipidemia and for the prevention of cardiovascular disease. 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 LFT monitoring.

Patients with NAFLD should avoid crash diet, herbal medicines, cannabises and nicotine. Patients with NAFLD related cirrhosis should be vaccinated for hepatitis A & B and should be screened for hepatocellular carcinoma. 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 patients age, family history, extent of obesity and previous findings

Cardiovascular disease is commoner than liver disease as a cause of death in patients with NAFLD because of increased cardiovascular risk factors like metabolic syndrome and its components (obesity, type 2 DM, hypertension dyslipidemia). Evaluation of cardiac risk in patients with NAFLD is highly recommended.

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Brief Communication

Rationality and designing immune therapy against chronic hepatitis B virus infection

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Hepatitis B virus (HBV)-induced chronic hepatitis B (CHB) and subsequent complications (liver cirrhosis and hepatocellular carcinoma) represent major threats to human health worldwide. About 370 million people are chronically infected with the HBV worldwide. Several antiviral drugs are now used in patients with CHB, however, a well-designed study for a National Institutes of Health (NIH, USA) consensus development conference that analyzed all randomized clinical trials with antiviral drugs in CHB patients from 1989 to 2008 have shown that no single drug treatment improved ultimate clinical outcomes or all intermediate outcomes of CHB, although improvements of some intermediate outcomes have been seen. However, adverse events during antiviral treatment occurred in about 50% patients. In addition, patients taking antiviral drugs should be periodically checked for viral, biochemical and immunological aspects of the HBV before, during and after cessation of therapy. However, the health care delivery system of developing country is unable to accomplish these. In this situation, mutant HBV may spread in community that may cause a devastating outcome.

The concept of immune therapy originated due to better understandings of pathogenesis of CHB and inefficacy of commercially-available antiviral drugs. Host immunity plays a pivotal role during induction, maintenance, and progression of liver damages in these patients. Again, the replication of the HBV can be minimized by host immune response. Thus, proper manipulation of host immunity may have therapeutic implications. Now, controversy remains about the design immune therapy in CHB patients. Studies have revealed that non antigen-specific immune modulators (gamma-interferon, interleukins, and growth factors) that upregulate or down regulate host immunity do not seem to be able stand the test of time as a better therapeutic endeavor in CHB patients (2).

A new mode of immune therapeutic strategy surfaced in early 1990s in which hepatitis B vaccine containing HBsAg were used as a therapeutic vaccine for containment of HBV and reduction of liver damages by inducing HBV-specific immune responses in CHB patients. To optimize the therapeutic regimen, vaccine therapy was applied in murine model of HBV carrier state, HBV transgenic mice (HBV