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NAFLD – Where Do We Stand Today

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INTRODUCTION

NAFLD is defined as the accumulation of fat in the liver (affecting more than 5% of hepatocytes) in the absence of significant intake of alcohol The spectrum of nonalcoholic fatty liver disese (NAFLD) ranges from simple steatosis (SS) that is relatively benign to NASH (nonalcoholic steatohepatitis) that has the potential to progress to cirrhosis with its subsequent complications including hepatocellular carcinoma. Ludwig in 1980 first time described "alcohol like liver disease that develops in people who are not heavy drinkers" and patients described in this study were females, obese and diabetic. In next two decades there was explosion of information on NAFLD in North America.

In the first two decades importance of NAFLD in east was not so well recognized. In 2003 Prof FARRELL emphasized the importance of NAFLD in Asia – Pacific region in his Ocuda Lecture. In 2007 Asia–Pacific working party was formulated for guidelines on NAFLD and the working party estimated the prevalence of NAFLD in adult population from 5% to 30. For all practical purposes obesity, type 2 diabetes, dyslipidemia and metabolic syndrome are universal risk factors for NAFLD throughout the world. Risk factors in non-obese population in Asia are visceral fat deposition, recent increase in weight, high cholesterol diet and genetic background. Central obesity poses a particular risk factor for NAFLD.

PATHOGENESIS (FIGURE 1)

The pathogenesis of NAFLD is closely linked to insulin resistance (IR) and to the development of metabolic syndrome. Insulin resistance contributes to increased delivery of fatty acids to liver because of increased lipolysis from expanded and inflamed adipose tissue. An excess of de novo fat synthesis in the liver, excess of dietary intake of fat, reduced –oxidation of fatty acids and decreased export of very low-density lipoprotein (VLDL) also contribute to the development of hepatic steatosis. Insulin resistance as studied by homeostasis model assessment for insulin resistance (HOMA-IR) has been shown in 83-98% of Indian patients with NAFLD . The development of NASH is believed to be due to a two-hit hypothesis of NAFLD, wherein hepatic steatosis is the "first hit", followed by a second hit which could be oxidative stress and cytokines producing inflammation/ fibrosis and progression to NASH. Recent concept of "multiple hits" with lipotoxicity, inadequate hepatocyte regeneration, apoptosis and other multiple events acting in parallel is evolving.

CLINICAL FEATURES

NAFLD is usually asymptomatic, and is an incidental

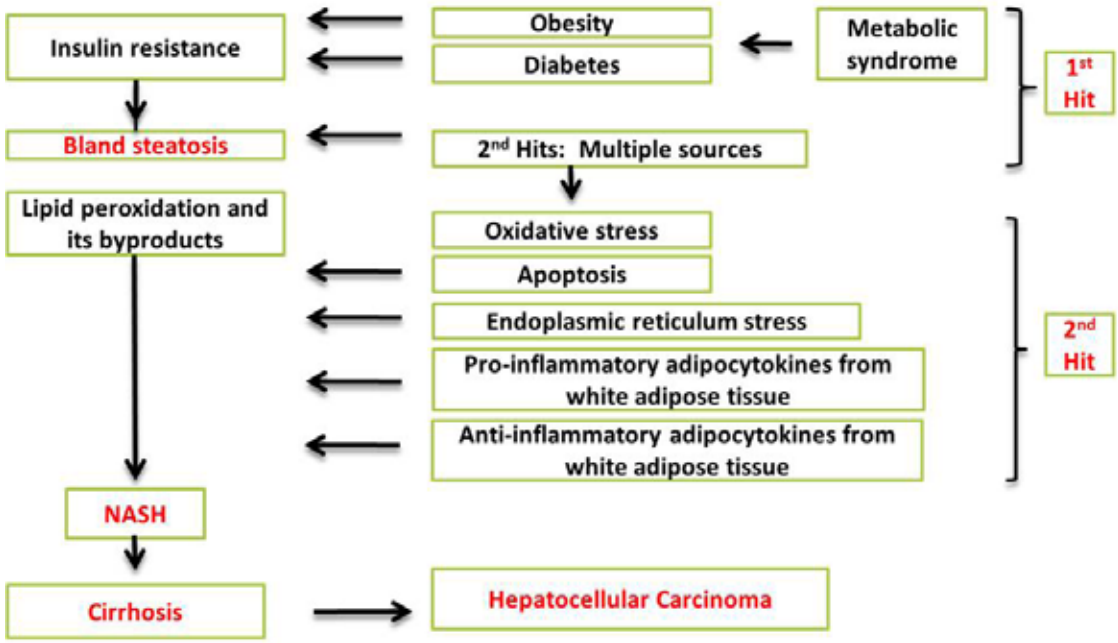

Fig. 1: Pathogenesis of NAFLD

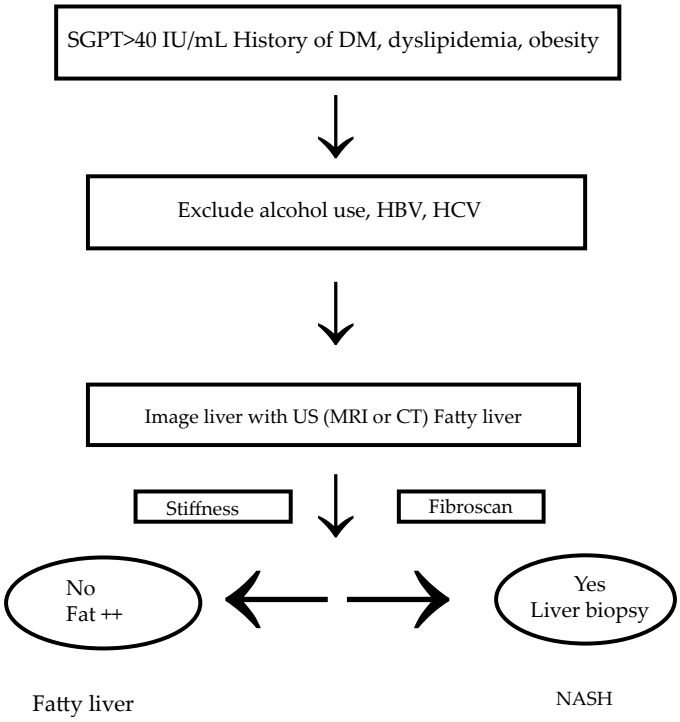

Fig. 2: Diagnosis of NAFLD

diagnosis on ultrasonography or asymptomatic elevation of transaminases in the presence of metabolic features. Most patients being investigated for dyspepsia or abdominal discomfort find themselves getting diagnosed to have fatty liver on ultrasound. Ultrasound of abdomen performed for investigation of asymptomatic elevation of liver enzymes also may reveal fatty liver and point towards the existence of NASH. A palpable liver may be found on physical examination apart from overweight/obesity and elevated waist circumference (central obesity). Signs of hepatocellular failure may be discernible if cirrhosis ensues with its attendant complications. Extrahepatic associations of NAFLD are as follows:- CVD mortality, malignancies, PCOD, obstructive sleep apnea, metabolic syndrome, diabetes and hypothyroidism.

NATURAL HISTORY

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 HCC has been predicted for steatohepatitis. In patients with simple steatosis progression to cirrhosis may occur in 4-5% over a period of 8-15 years while NASH can progress to cirrhosis in over 25% patients over similar follow-up period; at initial biopsy 5-20% patients with NAFLD may have cirrhosis. Risk factors showing rapid progression in NAFLD are T2DM, obesity, older age and metabolic syndrome. NAFLD is important cause of cryptogenic cirrhosis and may not be appreciated in histology as with disease progression steatosis may disappear. NAFLD and cryptogenic cirrhosis have been shown to have increased risk of HCC. Recently, 2 studies have shown increased cv risk in patients with NAFLD.

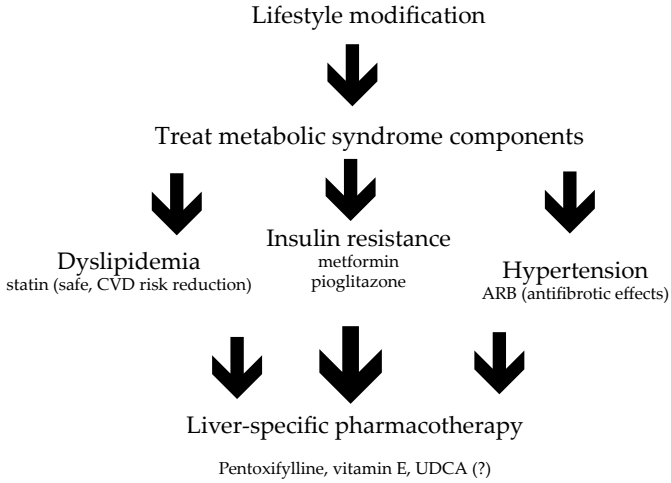

Fig. 3: Treatment of NAFLD

DIAGNOSIS (FIGURE 2)

Elevated transaminases may or may not be seen in NAFLD. It has poor correlation with histological severity and, therefore, it is not appropriate to make the diagnosis of NASH. Ultrasound, CT scan, MRI have good sensitivity and specificity around 85% in detecting steatosis but can not detect inflammation and fibrosis which are characteristic of NASH. Fibroscan (transient elastography) has been evaluated for detecting liver fibrosis in NAFLD and has a good correlation with liver histology. It is therefore being increasingly used as a marker of fibrosis and NASH. NAFLD fibrosis score (a computer calculated score based on age, BMI, impaired fasting glucose or diabetes, AST-ALT ratio, albumin and platelets), is helpful in predicting NASH and fibrosis in patients with NAFLD. Other causes of hepatic steatosis such as use of certain drugs, chronic viral infection(HBV / HCV) surgical bypass procedures, total parenteral nutrition, coeliac disease, haemochromatosis or Wilson's disease need to be excluded befere making diagnosis of NAFLD. As liver fat tends to diminish with increasing hepatic fibrosis, liver histology is not very helpful in making the diagnosis of NASH related cirrhosis or HCC. It is usually diagnosed on the presence of metabolic risk factors and exclusion of other causes of cirrhosis and HCC.

TREATMENT (FIGURE 3)

NAFLD patients who loose 10% of baseline body weight by a combination of diet and an intense exercise program achieved resolution of NASH and regression of fibrosis in 90% and 45% respectively.Adopting a Mediterranian diet has also been shown to reduce steatosis and insulin sensitivity. In addition to lifestyle interventions, there have been a number of drugs that have been tested in NAFLD patients with variable success. Please refer to the flow chart below. Emerging drug therapies include GLP 1 agonist and DPP 4 inhibitors, anti-fibrotic like simtuzumab and Nuclear Receptor Ligands like OCA. A small open label case series found that GLP 1 agonist and DPP 4 inhibitors improved grade of ballooning and fibrosis score in diabetic patients with NASH. A large phase IIb trial of

simtuzumab versus placebo in adults with compensated NASH related Cirrhosis is currently underway. Bariatric surgery in obese patients with BMI >30 is associated with significant improvement of NASH. But then, it should not be considered a primary treatment of NAFLD. Liver transplantation is an option for management of NASH related cirrhosis and HCC. Fatty liver is almost universal after 5 years of liver transplantation but recurrence of NASH, advanced fibrosis or cirrhosis is infrequent.

CONCLUSION

NAFLD is a major public health problem especially in patients of metabolic syndrome. Incidence is progressively rising and NAFLD/NASH will become leading cause of liver disease, cirrhosis and hepatocellular carcinoma in our country as well. The ideal management strategy has not yet been defined but lifestyle modification holds the key in combating the epidemic of this disease. Metformin, Statins, Vitamin-E and Pentoxyfyline are preferred pharmacotherapy in different guidelines for management of NAFLD. Bariatric surgery can be considered in refractory patients. Recently, global guidelines have been published by World Gastroenterology Association. And that is where we stand today.

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