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Quarterly Review

Nonalcoholic Fatty Liver Disease - The Clinician's Perspective

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ABSTRACT

Non alcoholic fatty liver (NAFLD) is a common cause of liver disease worldwide with prevalence ranging from 10-30%. It encompasses a spectrum ranging from simple steatosis to non-alcoholic steatohepatitis (NASH) which can progress to cirrhosis and hepatocellular carcinoma (HCC) in some patients. The diagnosis of hepatic steatosis can be made reliably by imaging. Differentiating simple steatosis from NASH usually requires liver biopsy although various non-invasive methods are under evaluation. Similarly, liver biopsy is the gold standard for staging of fibrosis but NAFLD fibrosis score and transient elastography are now validated for non-invasive assessment of fibrosis in patients with NAFLD. Liver biopsy should be reserved for patients at high risk of having NASH or advanced fibrosis, those needing evaluation of competing diagnoses or those enrolled in therapeutic trials. Treatment can be directed against various pathophysiological aspects of NAFLD and includes management of obesity, insulin resistance, hyperlipidemia and oxidative stress, suppression of inflammation and modulation of gut bacteria. Lifestyle modification with diet, exercise and weight loss is the cornerstone of therapy. Pharmacological treatment of NAFLD is still evolving with vitamin E and pioglitazone being the only approved drugs as of now. Bariatric surgery can lead to improvement in NASH in morbidly obese patients. Optimal therapy of NAFLD includes a multidisciplinary approach involving management of metabolic syndrome and cardiovascular disease. Management of NASH related cirrhosis and HCC is like that of other etiologies. Indications and outcomes of liver transplantation in patients with NASH are same as for other etiologies of liver disease.

KEYWORDS: NAFLD, NASH, nonalcoholic steatohepatitis, hepatocellular carcinoma, bariatric surgery, insulin sensitizers, vitamin E

Introduction

The term non-alcoholic fatty liver disease (NAFLD) was coined by Ludwig to a condition characterised by excess fat accumulation in the liver in the absence of significant amounts of alcohol consumption, usually defined as less than 20g of ethanol per day.[1] It includes patients with simple steatosis (SS) and nonalcoholic steatohepatitis (NASH). While SS is usually benign and non-progressive, NASH has propensity of progressing onto cirrhosis and hepatocellular carcinoma (HCC).[2]However, all patients of SS do not progress to NASH or cirrhosis and patients with NASH may spontaneously revert back to SS or even to a normal liver.[3] The amount of steatosis does not correlate with the degree of liver injury and in fact steatosis decreases with advanced fibrosis and cirrhosis.[4] General population prevalence of NAFLD and NASH is 10-

24% and 3-4% respectively in the West.[2] Prevalence of NAFLD in India ranges from 9-32%. The lower end of the spectrum of 9% was seen in a rural community based study[5] whereas figures from urban centres are higher and similar to that seen in the West.[6-8]

In the absence of alcohol intake, patientsdevelop hepatic steatosis due to increased free fatty acid deposition in the liver which is then converted to triglycerides. This may be as a result of increased delivery of fatty acids from adipose issue due to increased lipolysis or because of excess dietary intake or de-novo synthesis of free fatty acids in the liver. Some of these patients may further develop hepatic oxidative stress and recruitment of various cytokines which lead on to hepatic inflammation and/or fibrosis in addition to steatosis resulting in the progression of simple steatosis to NASH which can further develop into cirrhosis and HCC. Now, there is data on the role of genetic polymorphisms in predisposing to NAFLD. Polymorphisms of the Patatin-like phospholipase domain-containing protein 3 (PNPLA3) gene have been conclusively linked not only to the development of NAFLD across all ethnicities but with more severe disease with 3.24 times higher risk of high necro-inflammatory scores and liver fibrosis in patients with unfavourable genotypes.[9]

While the diagnosis of hepatic steatosis is relative straightforward and based on non-invasive test like imaging, differentiation of SS from NASH requires liver biopsy. As the prognosis and management of patients of SS and NASH differs greatly it is important to make this distinction. Over 8 years of follow-up, 11% of NASH patients developed liver-related mortality compared to 2% of patients with SS.[10] After 18.5 years of follow-up, liver-related mortality increases to 18% for NASH and whereas it is only 3% for patients with SS.[11]Patients with NAFLD are not only at risk for increased liver-related morbidity and mortality but have increased risk of cardiovascular disease and diabetes mellitus on long-term follow-up. Various treatment modalities have been evaluated, targeting the various pathophysiological pathways of development of NASH. Although most interventions have been successful in decreasing steatosis, only few have convincingly been able to reduce necro-inflammation or fibrosis which is the hallmark of NASH and progressive liver damage. While lifestyle interventions and control of metabolic risk factors are sufficient treatment for SS, patients with NASH require further pharmacological therapy. Treatment of NASH related cirrhosis and HCC are similar to that for other etiologies. This article describes in detail the clinical aspects of diagnosis and treatment of NAFLD.

Diagnosis

Most patients are detected to have fatty liver or raised liver enzymes incidentally during evaluation of dyspepsia or work-up for other illness. Anthropometry usually is significant for overweight, obesity, or central obesity. Mild hepatomegaly may be seen in half the patients.[12,13]

Minimum work up in all patients

The minimum evaluation of a patient with NAFLD requires i) demonstration of hepatic steatosis, ii) rule out other causes of hepatic steatosis, iii) rule out other causes of raised transaminases if present iv) assessing the severity the liver disease by differentiating SS from NASH and by assessing the degree of fibrosis.

Demonstration of hepatic steatosis

While by definition hepatic steatosis is diagnosed on liver biopsy as macrovesicular steatosis occupying at least 5% of the hepatocytes, for all practical purposes the diagnosis is made on imaging. Ultrasound (US) is the most commonly employed imaging tool with a sensitivity and specificity of 85% and 94% with an area under receiver operating curve (AUROC) of 0.93 for steatosis >30%.[14] Sensitivity is lower for steatosis of 5-30% and also in patients with morbid obesity due to poor acoustic window. Grading of steatosis is done by visual impression based on increased liver echogenicity compared with that of kidney and spleen, blurring of intrahepatic vascular structures and deep attenuation of ultrasound signal.[15] While computed tomography (CT) and magnetic resonance imaging (MRI) remove the observer dependency associated with US they do not add to the diagnostic capability of US and are not routinely required.[16] While magnetic resonance spectroscopy and controlled attenuation parameter transient elastography are more sensitive and can accurately quantify hepatic steatosis none of the imaging modalities are useful for differentiating SS from NASH.

Rule out other causes of hepatic steatosis and raised transaminases

Other causes of hepatic steatosis include alcohol; drugs like

estrogens, glucocorticoids, methotrexate, amiodarone, tetracycline and tamoxifen; hepatitis C virus (HCV) and human immunodeficiency virus infection; metabolic causes like Wilson disease, hemochromatosis, abetalipoproteinemia, glycogen storage diseases, galactosemia and alpha 1-antitrypsin deficiency; celiac disease; total parenteral nutrition; malnutrition; bowel disorders like extensive small bowel resection, inflammatory bowel disease and jejuno-ileal bypass. A detailed history of these secondary causes, especially significant alcohol consumption (defined as ongoing or recent alcohol consumption more than 21 drinks on average per week in men and more than 14 drinks on average per week in women) and drug exposure should be taken, and HBsAg and anti-HCV testing should be done in all patients. Further work-up including autoimmune hepatitis markers, anti-tTG and serum ceruloplasmin need to be performed only in patients with raised liver enzymes depending on the age of the patient. Iron overload is uncommon in Indian patients with NAFLD as are the HFE gene mutations.[17,18]

Since majority of patients with NAFLD have evidence of insulin resistance, its determination in non-diabetic patients using clamp studies, homeostasis model assessment (HOMA) method or insulin tolerance (ITT) test may be of only academic interest. However, all patients should be evaluated for presence of metabolic syndrome and its individual components. Metabolic syndrome was present in 50% of patients with NAFLD in our Institute.[12,13] Other centres from India have reported prevalence of metabolic syndrome to range from 21-68% in patients with NAFLD with at least one metabolic risk factor being present in almost all patients.[19,20]Metabolic syndrome predicts for severe disease with an odds ratio of 3.2 and 3.5 for NASH and severe fibrosis respectively independent of age, BMI and gender.[21] Hence, presence of metabolic syndrome may be considered an indication for liver biopsy in a patient withNAFLD.

Assessment of severity of the liver disease by differentiating SS from NASH and by assessing the degree of fibrosis.

Differentiating SS form NASH

Liver function tests are either normal or show mildly elevated transaminases and are not helpful in differentiating between SS and NASH. The gold standard for diagnosis of NASH and degree of fibrosis is liver biopsy. Characteristic features of NASH include presence of lobular neutrophilic inflammation, Mallory bodies, ballooning degeneration, lipogranuloma, and pericellular fibrosis predominantly in the perivenular regions in the background of hepatic steatosis.[22] Various descriptive systems have been described to diagnose and stage NASH histopathologically such as the Matteoni[23] and Brunt[24] systems.Matteoni et al divided patients into four classes histologically, class I as simple steatosis, class II as steatosis plus lobular inflammation, class III as class II plus ballooning and class IV had either Mallory hyaline or fibrosis. Patients with class III or IV were classified as having NASH.[23] The NAFLD activity score (NAS) is a quantitative system that scores steatosis from 0-3, lobular inflammation from 0-3, and ballooning from 0-2. The total score ranges from 0 to 8 with score 0-2 representing no NASH, 3-4 borderline NASH and $\geq$5 NASH.[25] NAS score in paired liver biopsies is more helpful in looking at the therapeutic response to various modalities rather than making the histological diagnosis of NASH.

Indian data suggest that histological changes at initial liver biopsy in patients presenting with raised transaminases are relatively mild with histological NASH seen in only half the patients and cirrhosis in none.[12,13,20]

However, as liver biopsy is invasive, painful and has risk of complications various non-invasive tests are under evaluation.As mentioned earlier, liver enzymes do not correlate well with necoinflammatory activity in NAFLD and cannot be used to diagnose NASH.[26]Total and caspase cleaved CK-18 are the best evaluated biomarkers with AUROCs ranging from 0.81 to 0.92 for the diagnosis of NASH in clinical trials.[27]Various scoring systems and algorithms employ combinations of clinical and biochemical parameters like age, gender, height, weight, body mass index (BMI), race, liver function tests, lipid profile, presence of diabetes and hypertension with biomarkers like CK-18, alpha2-macroglobulin, apolipoprotein A1, haptoglobin, and adiponectin to diagnose NASH.[27] However, serum biomarkers are infrequently available, are costly, and lack standardization and many of the algorithms are proprietary and have not been validated. As such they are not used clinically at present. One study of 64 patients reported 100% accuracy of contrast enhanced US using Levovist in differentiating NASH from SS.[28] This modality needs further evaluation in larger studies.

Assessing degree of fibrosis

While liver biopsy is the gold standard for staging degree of fibrosis, various non-invasive panels such as AST/platelet ratio

index (APRI), FIB4, BARD, Fibrometer NAFLD, NAFLD fibrosis score (NFS), Fibrotest, and enhance liver fibrosis (ELF) test have been studied in patients with NAFLD. The NFS is calculated using age, hyperglycaemia, BMI, platelet count, albumin, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ratio. Using a low cut-off of -1.455 to rule out and a high cut-off of 0.676 to diagnose advanced fibrosis, the AUROC for NFS was 0.85 in a meta-analysis. However, 20%-58% patients fall in the intermediate group between these two cut-offs and need either liver biopsy or Fibroscan for further evaluation.[27]Elastography techniques such as transient elastopgraphy (Fibroscan), acoustic radiation forced impulse imaging (ARFI) and magnetic resonance spectroscopy (MRS) have been also been evaluated. Of these, Fibroscan has been validated in NAFLD in multiple studies, is simple to perform and hence useful clinically.[27]Using cut-offs of 7.0 KPa and 8.7KP respectively, Fibroscan has an AUROC of 0.84 and 0.94 for significant and advanced fibrosis respectively. However, using the standard medium probe, Fibroscan may not be possible in many obese individual with success rate only 75% for patients with BMI>30 Kg/m^2.[27]

Who needs a liver biopsy?

Only those patients whom have a high risk of having NASH or advanced fibrosis should be subject to liver biopsy as the management and prognosis of this subgroup is different from those with simple steatosis. Patients who have metabolic syndrome, age > 45 years, high NFS, Fibroscan or CK 18 values, high APRI or AST/ALT ratio > 1 may be suitable candidates for liver biopsy.[29]Another indication is to evaluate competing causes of hepatic steatosis and deranged liver enzymes in patients with suspected NAFLD.Also, all patients enrolled in therapeutic trials of NAFLD should undergo paired liver biopsies before and after the intervention for assessment of efficacy.

Diagnosis of NASH as cause of cirrhosis and HCC

Liver biopsy is not often useful to establish NASH as the etiology of cirrhosis since liver fat decreases with the development of advanced fibrosis. After eliminating all other etiologies, NASH should be considered as cause of cirrhosis/ HCC in the presence of two or more components of metabolic syndrome. As patients may lose weight after development of cirrhosis and HCC, a past history of premorbid obesity/ overweight should be taken. Cirrhosis related diabetes mellitus should be differentiated from long-standing type 2 diabetes mellitus when including it as a component of MS.

Treatment

Lifestyle modifications

Life style modifications are the cornerstone of management of NAFLD and include nutritional counselling, dietary restriction, exercise and weight loss. A small study of 31 biopsy proven subjects with NAFLD randomized patients to intensive lifestyle counselling including dietary advice, exercise, and weight loss or standard advice. There was significant improvement on NAFLD Activity Score (NAS) in 72% patients in intensive group compared to 30% in patients receiving standard advice. Mean weight loss was 9.3% in intensive group versus 0.2% in standard therapy group. This study also found that 7% weight loss was needed for significant histological improvement, a target achieved by only 39% patients. However, there was no improvement in fibrosis in either group.[30] Another studyfound 8.5% weight loss in intensive counselling group with significant improvement in steatosis on magnetic resonance spectroscopy (MRS) compared to only 0.05% in standard advice group.[31]

Role of exercise

By improving insulin resistance, regular exercise by itself can improve liver enzymes, visceral fat and intrahepatic triglycerides, even without significant weight loss.[32]Increasing physical activity by > 60 minutes per week and maintaining at 150 minutes per week improves liver enzymes and metabolic parameters independent of weight loss.[32] Aerobic exercise, 3-4 times per week with loss of 400 Kcal per session was effective in one analysis.[33] Whether there is a ceiling effect after which level further exercise does not result in incremental benefit in NAFLD is not known.

Studies from India have confirmed the key role of exercise and lifestyle modification in NAFLD.[12] Significant improvements in liver enzymes, insulin resistance and liver histology was seenonly in patients compliant to a lifestyle modification program in 2 studies from Lucknow.[34,35]

Type of diet

Most studies have reported on caloric restriction rather than a specific diet type. Studies have variable prescribed calories

based on ideal body weight (25-30Kcal/Kg/day) or based on caloric reduction (~ 500Kcal/day)[36,37] or set specific caloric goals (1000-1500Kcal/day).[38] There is no specific advantage of carbohydrate restriction (<50g/day) versus regular diet (>150g of carbohydrate/day) but of the same caloric value with comparable weight loss and intrahepatic triglyceride reduction in both groups.[39] Hence, it is difficult to advocate one dietary prescription for all patients. Diet should be tailored according to the patients' excess weight and dietary habits. Rapid weight loss by extremely hypocaloric diets should be avoided as these can worsen liver functions.[40]Weight reduction should be targeted at 10% of the body weight over 6–8 months.

Pharmaceutical agents for weight loss

The use of pharmaceutical agents to aid weight loss seems attractive due to poor compliance to lifestyle changes. Rimonabant, phentermine, and sibutramine are no longer used due to poor side effect profile. In a study, 6 months of orlistat did not show any advantage over placebo with regards to histological improvement or weight loss (8% versus 6%). Only 32% patients could achieve the 9% weight loss required to improve NAS despite orlistat.[41] Hence, pharmaceutical agents to promote weight loss are not recommended for the treatment of NAFLD.

Insulin-sensitising agents

Thiazolidinediones

Thiazolidinediones improve peripheral and hepatic insulin sensitivity, promote redistribution of fat from liver and muscle to adipose tissue and increase adiponectin levels. The PIVENS trial used 30 mg per day of pioglitazone for 96 weeks in histologically proven non- diabetic patients with NASH and showed improvement in steatosis, lobular inflammation and liver enzymes but not in fibrosis as compared to placebo.[42] A meta-analysis has also confirmed the benefits of thiazolidinediones in improving histology in NASH.[43]The maximum benefit with pioglitazone was achieved by one year of therapy and no incremental benefit was seen with further treatment in the FLIRT trial.[44]Withdrawal of pioglitazone leads to reversal of all beneficial effects including histology.[45]Hence, appropriate duration of therapy and long-term efficacy is controversial. Long term safety of pioglitazone is has been questioned in view of its potential side effects such as weight gain, osteoporosis, and congestive cardiac failure. The American Academy for the Study of Liver Diseases (AASLD) recommends pioglitazone for the treatment of biopsy proven NASH in non-diabetic patients.[29]

Metformin

Metformin decreases hepatic glucose production, increases glucose uptake by the skeletal muscle, decreases inflammation, suppresses lipogenesis, and increases free fatty acid oxidation and causes weight loss. However, two randomized controlled trials have failed to show any histological benefit.[46,47]A meta-analysis found beneficial effect of metformin on liver enzymes, but no effect of histology, including steatosis, inflammation or fibrosis.[43]We have found metformin to be useful in patients with NAFLD not responding to lifestyle modifications.[48]Various cohort and cross-sectional studies have found significant reduction in risk of HCC in diabetic patients using metformin, with 2 meta-analyses reporting relative risk of 0.24 and 0.69 respectively for HCC in patients exposed to metformin.[49,50]Hence, while metformin may not be useful for treatment of NASH per se, it is a good and safe anti-diabetic agent for use in patients with NAFLD due to its weight reducing and proposed anti-tumorogenic properties.

Anti-oxidants and anti-inflammatory drugs

Vitamin C, vitamin E, betaine, reduced glutathione, N-acetyl cysteine and pentoxifylline have been evaluated for the treatment of NAFLD. These studies are extremely heterogenous and overall a meta-analysis did not find any beneficial effect of various anti-oxidant and anti-inflammatory drugs on liver histology or enzymes.[43]Of these agents vitamin E and pentoxifylline have been best studied with significant positive findings in trials evaluating these drugs.

Vitamin E

Most studies of vitamin E in combination with drugs like vitamin C or ursodeoxycholic acid (UDCA) documented improvement in steatosis, inflammation and fibrosis and reduction in the progression of NASH. The PIVENS trial reportedsignificant improvement in liver enzymes and histologicalendpoints including steatosis and inflammation but not fibrosis with 96 weeks of vitamin E at a dose of 800mg per day. NAS improved

in 43% patients with 36% patients showing complete resolution of NASH.[42]The pediatric TONIC trial reported similar results.[51]While histology based studies on vitamin E are not available from India, a study from New Delhi found significantly better improvement in liver enzymes with vitamin E and lifestyle modification compared to lifestyle modification alone.[52]AASLD recommends vitamin E for the treatment of biopsy proven NASH in non-diabetic patients.[29]

Pentoxifylline

Pentoxifylline inhibits a number of pro-inflammatory cytokines including TNF-á , increases hepatic glutathione levels, reduces free oxygen radicals, and has antifibrogenic effects. A meta-analysis found beneficial effect on ALT and inflammation but not fibrosis.[43] Subsequently, a study demonstrated reduction in fibrosis in conjunction with diet and exercise over a period of 12 months.[53]Major side effects included nausea and vomiting but dropouts were minimal.Studies from India have also reported improvement in liver enzymes, insulin resistance, and histological endpoints like steatosis, inflammation and fibrosis on paired liver biopsies.[54,55]Pentoxifylline is not approved for treatment of NASH as yet.

UDCA

UDCA is an anti-cholestatic and anti-inflammatory drug that has cytoprotective action by replacing hydrophobic bile acids with hydrophilic bile acids. Seventy four of 100 patients with NAFLD showed improvement on liver enzymes with lifestyle modification and UDCA with 64 of them having complete biochemical normalization in an uncontrolled study from our Institute.[12] A study from New Delhi found significant improvement in liver enzymes with UDCA and lifestyle modification which was comparable to that seen with lifestyle modification and vitamin E.[52]A meta-analysis found that while UDCA reduced liver enzymes there was no benefit on any histological endpoint.[43]Two subsequent studies using high dose UDCA (28-35 mg/kg/day) in biopsy proven patients with NASH[56,57] found improvement in ALT levels with onestudy reporting reduction in serum markers of fibrosis.[56] However, none of these studies had histological end points so a definite role of high dose UDCA in treatment of NASH remains to be proven.

Anti-lipidemic drugs

Results of studies using statins have been conflicting with regards to improvement in liver enzymes and histology. Statins were better than fibrates in improving liver enzymes and steatosis on ultrasound in one study.[58] A retrospective analysis of patients with NAFLD and dyslipidemia showed improvement in liver steatosis and slower fibrosis progression in patients treated with statins, despite having a higher baseline risk for progressive liver disease.[59] Statins are safe for use in NAFLD and do not lead to significantly increased hepatotoxicity.Statin use may be associated with a reduced risk of HCC in patients with diabetes.[60] Hence, although statins are not used primarily for the treatment of NAFLD in the absence of controlled prospective studies, they are safe for treatment of dyslipidemia in patients with NAFLD.

Probucol is a lipid lowering drug with additional anti-oxidant properties. A trial comparing 6 months treatment with 500mg/day of probucol with placebo found better improvement in mean ALT in probucol group with normalisation of liver enzymes in 50% patients compared to none in placebo group.[61]An uncontrolled trial reported histological improvement with 1 year treatment with probucol.[62] However, probucol is known to reduce high density lipoprotein cholesterol, potentially increasing cardiovascular risk.

Probiotics

Pre and probiotics have been tried in NAFLD to modulate gut bacteria in to reduce gut derived endotoxemia related liver inflammation. Uncontrolled studies with various formulations have shown reduction in weight, improvement in liver enzymes and reduced markers of lipid peroxidation.[63]

Do all patients with NAFLD need treatment?

Given the natural history of NAFLD, not all patients need pharmacotherapy. Patients with simple steatosis have a relatively benign liver disease and chief cause of death in these patients is related to non-hepatic malignancies and cardiovascular disease. Management of metabolic risk factors along with lifestyle modifications seems appropriate. Patients with NASH are at high risk of liver related complications and are appropriate candidates for pharmacotherapy. Currently

vitamin E and pioglitazone are the only approved pharmacotherapy for NASH and are recommended only for biopsy proven cases.[29]

Bariatric surgery and NAFLD

A meta-analysis of 15 studies on bariatric surgery found resolution of steatosis in 91.6%, NASH in 69.5% with improved in steatohepatitis and fibrosis seen in 81.3% and 65.5% patients respectively.[64] Presence of advanced fibrosis on baseline is a negative predictor for improvement in fibrosis.[65] Five years after bariatric surgery, the percentage of patients with steatosis decreased from 37.4% to 16%, NAS from 1.97 to 1, ballooning score from 0.2 to 0.1, while inflammation remained unchanged. However, there was slight increase in the level of fibrosis but 95.7% of patients had F0 or F1 fibrosis.[66] Bypass procedures that cause very rapid initial weight loss should be avoided. In the absence of randomized controlled trials and concerns about long term increase in fibrosis, bariatric surgery is as yet not recommended specifically for the treatment of NAFLD. However it can be performed in otherwise eligible obese individuals with NAFLD or NASH without established cirrhosis.However, a majority of Indian patients of NAFLD do not have very high BMI, with the mean being 29 Kg/m^2 and only about 16% having BMI >30 Kg/m^2.[12,13] Hence, most Indian patients of NAFLD may not be candidates for bariatric surgery.

Liver transplantation in NASH

Liver transplantation is the only definitive treatment for patients with NASH related decompensated cirrhosis or HCC due to NASH as none of the above mentioned therapies have been evaluated in these settings. Graft and patient survival after transplantation for NASH is similar to that of other etiologies. The risk of cardiovascular events and cardiovascular deaths is higher but the risk of liver related deaths is lower compared to transplantation for other etiologies.Development of recurrent fatty liver is almost universal after about 5 years post transplant as compared to only 25% in other transplant recipients, but recurrent NASH is infrequent (~ 10-20% at 2-5 years follow-up) and advanced fibrosis or cirrhosis even rarer (~4-10% at 5-10 years follow-up).Recurrent NAFLD is related to cumulative dose of steroids, use of calcineurin inhibitors and weight gain after transplant. Steroid sparing/free regimens with use of anti-metabolites like mycophenolate with low dose of tacrolimus is preferred and weight gain should be kept in control.[67] These patients also have higher frequency of post-transplant metabolic syndrome[68] and hence 6 monthly screening and adequate treatment for metabolic syndrome is recommended.[67] No specific therapy has been evaluated for treatment or prevention of recurrent or de novo NASH after transplantation but diet, weight reduction and exercise seem to be the best options along with control of metabolic syndrome.

Alcohol and NAFLD

There is some recent epidemiological data that light-to-moderate drinking may reduce the prevalence and severity of NAFLD. However, these studies are cross-sectional and have utilized surrogates of like aminotransferases and liver imaging rather than histology to assess disease severity. The cardiovascular and metabolic effects of light-to-moderate alcohol consumption are not clear in patients with NAFLD, most of who have metabolic syndrome. Hence, until further high quality data is available, alcohol consumption in any amount or type should not be advocated for patients with NAFLD.[29]

Multidisciplinary management of NAFLD

Morbidity and mortality of NAFLD is related not only to cirrhosis and HCC, but also due to associated diabetes mellitus and cardiovascular disease.Management of metabolic syndrome components like obesity, diabetes mellitus and hyperlipidemia are essential to the holistic management of NAFLD. Endocrinology consultation is helpful for implementationof lifestyle changes, achieving weight loss and control of hyperglycemia. Cardiologists' opinion may be sought for management of hypertension and dyslipidemia and is necessary for evaluation and management of associated ischemic heart disease.

Conclusions

From a clinical standpoint it is imperative to differentiate simple steatosis from NASH. Definite diagnosis of NASH is currently based on liver biopsy. Various non-invasive methods such are now available to diagnose NASH and significant fibrosis in NAFLD but liver biopsy remains the gold standard for assessing severity of NAFLD. Lifestyle modification in the form of diet, exercise and weight loss that targets the basic pathophysiology of NAFLD is the cornerstone for the

management of NAFLD. Of the many drugs evaluated for the treatment of NASH only Vitamin E and pioglitazone are currently approved. Management of NASH related cirrhosis and HCC including liver transplantation is similar to that for other etiologies. A multidisciplinary management including hepatologist, endocrinologist and cardiologist as required should be followed for optimum care of patients with NAFLD.

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