Emergence of Non-Alcoholic Fatty Liver Disease (NAFLD)
Rakesh K Tandon

There has been a remarkable change in the profile of chronic liver disease in India during the last four decades. Whereas viral aetiology predominated in the seventies and eighties, alcoholic liver disease did so in the nineties and thereafter viral aetiology predominated in the seventies and eighties, alcoholic liver disease did so in the nineties and thereafter.

In India, the prevalence of NAFLD in the general population varies from 10% to 30%, the lowest figures being from rural areas of West Bengal and the highest from urban population of Chennai. In people with metabolic syndrome however, the prevalence is much higher; 15-80% among obese people, 25-60% in patients with dyslipidemia and 33-55% in pre diabetics and diabetics.

Individuals of Asian-Indian ancestry are at enhanced risk of developing NAFLD as compared with those of Eastern Asian, Caucasian, black, and Hispanic descent. This is because of a higher prevalence of insulin resistance in them. This increased susceptibility is attributed to two polymorphisms (rs2854116 and rs2854117) in the apolipoprotein C3 (ApoC3) gene. This polymorphism leads to a roughly 50% higher plasma concentration of ApoC3, and postprandial hypertriglyceridaemia. As a result, the carriers of these polymorphisms can take up increased amounts of lipid from the chylomicron remnant, leading to NAFLD and hepatic insulin resistance.

The multicentre study of NAFLD in diabetic population of India, published in this issue of the journal, is a laudatory effort in establishing the prevalence of NAFLD in diabetes. A total of 924 patients of type-II diabetes were enrolled from 189 centres in 101 cities in India. Of them, 572 (56.5%) patients were found to have NAFLD. More females (60%) than males (54.3%) had NAFLD and a steady increase in prevalence of NAFLD was noted with increasing age of the subjects. It is also notable that subjects with additional components of metabolic syndrome had higher prevalence of NAFLD than others, the increased risk being 14%, 17% and 38% in those with obesity, hypertension and dyslipidemia, respectively. These observations reiterate the close association of NAFLD with metabolic syndrome and hence also its possible role in the development of cardiovascular disease (CVD). A long-term mortality study of a cohort of NAFLD patients has shown that cardiovascular complications constitute the most common cause of death in them. Common pathogenetic processes are under play in NAFLD and CVD. Increased insulin resistance and atherogenic dyslipidemia along with pro-atherogenic factors like C-reactive protein released from the liver may lead to progression of CVD. Cardiot artery intima—media thickness (IMT), an accepted marker of subclinical atherosclerosis, has been shown to be significantly increased in patients with NAFLD as compared with age, sex, and BMI matched healthy controls. Furthermore, this increase was much more in those with NASH than in those with simple steatosis. The pathological fat accumulation combined with an increase amount of inflammation in NAFLD sets in motion a cascade of pathologica processes that accelerate progression of atherosclerosis.

It is therefore important to treat pre-emptively all factors associated with metabolic syndrome.

Most patients with early or potential NAFLD are detected accidentally or through executive check up – fatty liver on ultrasound examination or raised AST and/or ALT. In either case, a set of investigations need to be done to establish the diagnosis NAFLD vs other diseases with such findings. They include alcoholic liver diseases, chronic hepatitis B, chronic hepatitis C, hypothyroidism, autoimmune liver diseases, Wilson’s diseases and hemochromatosis. Alcoholic steatohepatitis constitutes an important and common differential diagnosis. It is identified by a history of alcohol consumption and an AST/ALT ratio >2 (in contrast to AST/ALT ratio < 1 in NASH). Consumption of alcohol more than 20 G/day becomes suspect and hence used as an exclusion criterion for labelling the subject as NAFLD as was done in the study under discussion. In this study, the authors used NHANES III criteria to mark AST and ALT levels as raised. Those criteria may not however, be strictly applicable to Indian patients as indicated by occasional reports from different parts of India. Notwithstanding this limitation, the finding of ALT higher than AST in the diabetic subjects with NAFLD is in consonance with earlier reports.

Liver biopsy is considered the gold standard for diagnosing NAFLD but is not practical and most patients shy away from getting it done. As a result, surrogate markers have been used to diagnose NAFLD. Ultrasound of the liver showing increased echogenicity or elevated liver enzymes (increased AST and ALT) are the most common markers as mentioned above. Proton Magnetic Resonance Spectroscopy has been shown to be superior to ultrasound for detecting lipid deposition but has limited availability.

Novel biomarkers have appeared in the recent past to help diagnose NAFLD. These are dependent on byproducts arising from the pathogenetic mechanisms accompanying inflammation, oxidative stress and fibrosis. A good concise review of the existing potentially useful markers has been given by Choudhuri in a recent monograph on NAFLD.

Elevated levels of tumour necrosis factor-alpha (TNF-α) and decreased adiponectin levels are markers for inflammation. They correlate well with inflammation and fibrosis in patients having NAFLD. Serum adiponectin levels may help distinguish simple steatosis from advanced stages of the disease. If adiponectin levels are combined with other non invasive markers such as HOMA insulin resistance level >3.0 and type IV collagen 7S >5.0 ng per ml, the sensitivity and specificity for predicting relevant diagnosis are substantially increased. Leukotriene (IL 6) has also been shown to distinguish differing disease states and independently correlate with fibrosis. Leptin levels correlate well with liver histology; increased levels in combination with HOMA distinguish differing disease states from simple steatosis to steatohepatitis.

It is important to assess the status of fibrosis in NAFLD patients. Type IV collagen 7S domain and hyaluronic acid (HA) are good markers of fibrosis and help identify patients with advanced fibrosis. In patients having NAFLD, the HA levels are useful for predicting severe fibrosis with a sensitivity of 85% and a specificity of 80%. Platelet count and serum laminin levels are also good independent predictors of fibrosis in NAFLD patients.

Thioredoxin, known to be induced under many oxidative stresses, is seen to be elevated among steatohepatitis patients as compared with patients with steatosis.

Since apoptosis plays an important role in the liver injury in patients with NAFLD, its byproducts are increased and may...
likely be good markers of steatohepatitis. One such marker is caspase-generated cytokeratin-18 (CK-18) fragment. It has been found to be considerably elevated among those with steatohepatitis than those with fatty liver or healthy subjects. This and several other markers such as plasma homocysteine levels and tissue polypeptide specific antigen are of potential use and deserve to be tested through well planned clinical trials.

Instead of using individual markers however, the recent approach has been to use a panel of markers to identify steatosis and fibrosis. The NAFLD liver fat score is one such panel marker. It comprises the following variables: presence of metabolic syndrome and type 2 diabetes mellitus, fasting serum insulin and serum AST values and the AST/ALT ratio. This scoring tool has a high negative (92.0%) and positive (72.0%) predictive value.

Another panel of NAFLD fibrosis score is a combination of 6 variables, viz age, hyperglycemia, BMI, platelet count, serum albumin and AST/AlT ratio. A fatty liver index, based on BMI, is also available that uses the BMI, waist circumference and serum triglyceride levels. An area under the curve of 0.84 detects liver steatosis in the general population with low prevalence of diabetes mellitus.

Fibrotest has been used to quantify fibrosis in NAFLD patients. It includes 2 macroglobulin, apolipoprotein A-1, haptoglobin, total bilirubin, gamma glutamyl transpeptidase and serum ALT. Another panel of NAFLD fibrosis score is a combination of 6 variables, viz age, hyperglycemia, BMI, platelet count, serum albumin and AST/ALT ratio. This scoring tool has a high negative (92.0%) and positive (72.0%) predictive value. Many other similar panels are available but none has passed through rigorous clinical testing.

Emergence of NAFLD poses a major health burden as its prevalence is steadily increasing. It behaves like any other chronic liver disease progressing on to cirrhosis (about 10% in 20 years) and hepatocellular carcinoma and its management is far from satisfactory. The present study highlights the additional risk of CVD it poses when accompanied by diabetes mellitus or other components of metabolic syndrome. An additional problem with NAFLD is that it remains asymptomatic till features of chronic liver disease appear. It is thus very important that family physicians as well as public should be educated to check for its presence in diabetics, obese people and persons with other features of metabolic syndrome. Preventive programs should be launched to encourage people to adopt healthy life style ie do regular exercise, take low calorie - high fibre diet, and avoid over indulgence in alcohol.

References