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Non-Alcoholic Fatty Liver Disease : The Global Epidemic

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Abstract

Non- alcoholic fatty liver disease (NAFLD) comprises a spectrum of liver disease which encompasses steatosis, steatohepatitis and cirrhosis. Over the past 2 decades, NAFLD is being increasingly recognized as a manifestation of insulin resistance and metabolic syndrome.

The prevalence of NAFLD in community based studies varies from 2.8% (based on unexplained raised serum transaminases in USA) to 23% (based on USG evaluation of "fatty liver" in Italy). Contrary to earlier notion that NAFLD is a disease of affluent countries, data from developing countries, including India show similar high prevalence of 18 % (India) to 20% (China).

Natural history of NAFLD, as elucidated from serial liver biopsy studies, suggest slow progression in upto one third. While patients with steatosis have <1% risk of liver related mortality, 9-25% of those with NASH die due to end stage liver disease within 10 years.

Since NAFLD is considered as hepatic manifestation of metabolic syndrome, treatment of NAFLD entails correcting components of the same (Obesity, hypertension, diabetes mellitus, hypertriglyceridemia).

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Lifestyle modification, including restricted dietary intake of high energy foods, and aerobic exercises to achieve ideal body weight are the key components of treatment of NAFLD. Results from controlled trials have shown improvement in liver enzymes, insulin resistance and quality of life with lifestyle modification. Long-term sustainability of weight reduction by lifestyle modification needs constant patient motivation. Promising pharmacological options include insulin sensitizers and anti-obesity drugs.

With rising prevalence of obesity, diabetes, hypertension, NAFLD is emerging as a global epidemic with far reaching implications. "Prevention is better than cure". Promoting healthy lifestyle holds the key to check this growing global epidemic.

Keywords: non-alcoholic fatty liver disease, steatosis, steatohepatitis, cirrhosis

Introduction

Nonalcholic fatty liver disease (NAFLD) is a condition in which excess fat accumulates in the liver in subjects who do not consume significants amounts of alcolhol. This condition was described about 5 decades ago in obese individuls, but remained largely ignored till recent times, when it is being recognized as a emerging global epidemic. It is also becoming apparent that this condition is not always innocuous, and that the disease may progress in a small but significant proportion of subjects to liver cirrhosis and liver failure (1,2).

NAFLD is best described as the hepatic manifestation of the metabolic syndrome; most subjects have or develop one or more of the following features: central obesity, type 2 diabetes mellitus, hypertension and hyperlipidemia, and have insulin resistance as their core pathogenetic mechanism. The liver morphology comprises a spectrum ranging from mere accumulation of fat within hepatocytes (steatosis) to associated inflammation and fibrosis (steato-hepatitis); some cases progress to cirrhosis, liver failure or liver cancer.

How common is NAFLD?

How are community surveys conducted?

With the prerequisite of low (less than 20 g/day) or no consumption of

alcohol, two approaches have been used to identify subjects with NAFLD in the community; those with elevated levels of aminotransferase enzymes in the serum (3) or bright echoes on a routine ultrasound examination of the liver (4). Although puritans insist that a liver biopsy is the most definitive method to diagnose the condition, especially its progressive variety called non-alcoholic steatohepatitis (NASH), this invasive test is not practicable in community surveys. Nevertheless, the non-invasive tests of assessing liver functions or detecting excess fat in the liver, although surrogate, serve to provide useful data on the prevalence of NAFLD in the community.

What is the prevalence of NAFLD in the community?

Around 2.8 % of the American population was found to have abnormally elevated ALT values (>43IU/L) which could be ascribed to NAFLD (4). Recently, however, studies have suggested that the cut-off values for ALT should be brought down to 30 IU/L for men and 19 IU/L for women (5). With these lower cut-offs, 12.4% of men and 13.9 % of women are suspected to have NAFLD in the community.

Using ultrasound examination, frequency of NAFLD has been found to be 15-30% in various countries from across the globe. Some of the important epidemiologic population surveys (6-14) are listed in Table 1. The high prevalence of NAFLD is not limited to developed countries alone. Fan *et al* evaluated prevalence of fatty liver based on USG abdomen among adults in Shanghai, China. Of 3175 patients examined, 20.8% had fatty liver (7).

What are its common associations?

The increasing prevalence of NAFLD in the population reflects the growing pandemic of obesity and type 2 Diabetes Mellitus (15-17). The risk of NAFLD has been estimated to be 6 times higher in obese individuals compared with those with normal body weight. In a study from Japan, the prevalence of NAFLD was 3.5 % in non-obese and 20% in those who were obese (18).

Patients with type 2 DM frequently have NAFLD. Its prevalence in this group has been reported to be as high as 50 %, and is around 2-3 times higher than in non-diabetics. Insulin resistance is central to both these disorders. The common pathogenetic mechanism of these two disorders explains the high frequency of their co-existence in the same individual.

Does it affect children?

NAFLD can affect children as well. With the current world wide epidemic of pediatric obesity, pediatric NAFLD

Table 1: Epidemiology of NAFLD

Author (year)	Study	Diagnostic method	Country	No. of individuals screened	Prevalence of NAFLD (%)	Prevalence of NASH (%)
Bedogni (2005)	Population-based	Ultrasonography	Italy	598	23	ND
Fan (2005)	Population-based	Ultrasonography	China	3175	15	ND
Nomura (1988)	Population-based	Ultrasonography	Japan	2571	11	ND
Ruhl (2003)	Population-based	Aminotransferases	USA	5724	2.8	ND
El-Hassan (1992)	Outpatient	Ultrasonography, CT	Saudi Arabia	1425	10	ND
Araujo (1998)	Outpatient	Ultrasonography	Brazil	217	33.5	ND
Lee (1989)	Hospital series	Liver biopsy	USA	543	ND	9
Nonomura (1992)	Hospital series	Liver biopsy	Japan	561	ND	1
Byron (1996)	Hospital series	Liver biopsy	USA	1226	ND	11
Daniel (1999)	Hospital series	Liver biopsy	USA	81	51	32

is increasingly being diagnosed. This increase is also associated with increasing prevalence of type 2 DM and hypertension in children, reflecting an increase of insulin resistance and metabolic syndrome. A recent survey found 31 % of American school children to be overweight and 16 % to be obese; these figures are three times the prevalence noted in a survey conducted in 1996 (19).

Does it occur in developing nations too?

The earlier notion that obesity, metabolic syndrome and NAFLD are

diseases of the developed "Western" world is being challenged by recent reports demonstrating similar trends in developing countries.(Fig.1) A survey of the Indonesian population (9) reported a 30 % prevalence of NAFLD, a figure higher than even that from USA (24%) or Japan (15%). Another recent study

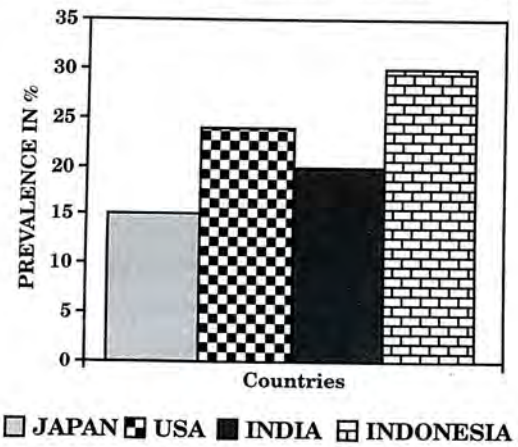

Figure 1 : Prevalence of NAFLD in general population

from Shanghai found 24% of the Chinese subjects to have the disorder (7). The increasing and widespread availability of high calorie "junk" food and sedentary lifestyles cutting across cities all over the world, is probably contributing to NAFLD becoming so ubiquitous.

How common is this entity in India?

Several reports from India suggest that NAFLD is quite common in this country as well (20-24). Epidemiological data on the prevalence of NAFLD in the general population in India though scarce, report figures of 16.6 and 24.5%. The survey of residents of railway colonies in Mumbai by Deepak Amarapurkar found 18.9% of those above 20 years to have bright echoes on ultrasound examination, suggestive of NAFLD. The prevalence was more in males (24.6%) than in females (13.6%) and was more often seen in those with central obesity or diabetes (22). In another ultrasonographic survey from the coastal areas of eastern India, 24.5% of "healthy" relatives of patients visiting the hospital were found to have NAFLD. This study also confirmed a higher frequency in males, and in those who were overweight (21).

NAFLD is commonly seen in type 2 diabetics. Around half of diabetics screened by ultrasound were found to have fatty liver (20). In a hospital based study from Chandigarh aimed at describing the clinicopathological spectrum of NAFLD, 100 NAFLD patients with increased liver enzymes were prospectively evaluated for clinical presentation and components of metabolic syndrome. Risk factors for the grade and stage of the disease on histology were studied in 38 biopsy-proven patients. Twenty percent of

patients were overweight, 68% had obesity, and 78% had central obesity. Abnormal cholesterol, HDL, and triglycerides were present in 36%, 66%, and 53% of patients, respectively. Twelve percent of patients had diabetes mellitus and 16% patients had various associated diseases. All 22 (100%) patients studied by ITT and all but one (98%) studied by HOMA-IR were found to have reduced insulin sensitivity and 50% were found to have metabolic syndrome by the modified ATP III criteria. Twenty patients of 38 (53%) had histological evidence of NASH (class 3=6, class 4=14). The other 18 (47%) qualified for class I (n=1) or class II (n=17) NAFLD. Four (10.5%) patients had bridging fibrosis and none had evidence of cirrhosis liver.(23)

In a similar hospital based study from Delhi, the clinical and biochemical profile at initial presentation of patients with histologically proven NASH was evaluated. Fifty-one patients with NAFLD formed the study population. Their median age and BMI were 34(17-58) years and 26.7(21.3-32.5) kg/m(2) respectively and 90.1% were males. The majority of the patients had mild inflammation, either grade 1 (63%) or grade 2 (31%) and only (6%) patients had severe (grade 3) inflammation. Twenty-three (45%), 19 (37%), 8(16%) and 1(2%) patient had stage 0, 1, 2 and 3 fibrosis respectively on index biopsy and none had cirrhosis. On multivariate logistic regression analysis, hypertriglyceridemia >150 mg% was the only factor independently associated with presence of high grade of inflammation (OR = 1.6; 95% CI: 1.3-22.7, P = 0.02), while none was associated with advanced fibrosis. Triglyceride levels correlated positively with inflammatory grade (r = 0.412; P = 0.003). A closer look at this study however shows that the mean age of subjects was (34 y) around 3 years less than the study from Chandigarh (37 y), thereby explaining the milder histological changes and lower association with other components of the metabolic syndrome (24).

In 65 patients of NASH (mean age 38 years) studied in Lucknow, 72.8% were found to have high BMI; however 98.3% had increased waist-hip ratios indicating that central obesity was a more sensitive indicator of NAFLD in Indian subject. This study also highlighted the limitations of applying the NCEP ATP III criteria in Indian patients for the diagnosis of metabolic syndrome; the Indian criteria with lower anthropometric cut-offs for diagnosing central obesity showed a better correlation with NAFLD (25).

The recent rapid increase in prevalence of obesity amongst Indian children is causing concern. In a survey of Indian urban school children, Marwaha (26) found 19% to be overweight and 5-6% to be obese. Hypertension and early onset of type 2 DM are being increasingly seen in Indian children. Fast food, sedentary habits, lack of sports and outdoor activities are common in Indian cities where these trends are being observed. With India already acquiring the dubious label of becoming the "Diabetic Capital" of the world, these trends in unhealthy life style are likely to result in a burgeoning epidemic of NAFLD and metabolic syndrome in the population

Is NAFLD a cause of cryptogenic hepatitis?

On the basis of liver biopsies, features of NASH could be identified in 65-9% of cases of 'cryptogenic' hepatitis. All large surveys (27-29) of cirrhotics from across the globe have found a proportion of 15-30% in whom no etiologic cause for their chronic liver damage could be identified; many of these patients are diabetics or provide a history of having been obese. It is conjectured that these patients have liver cirrhosis due to long standing and progressive NASH.

What is the natural history of NAFLD?

The natural history of NAFLD can be gauged by longitudinal follow up of a large number of subjects with this disorder. As the rate at which this disease progresses is slow, requiring a very long period of follow up to assess outcome, studies on the natural history of NAFLD are difficult to perform. They are based on two approaches

1. serial biopsy studies
2. cohort studies with clinical end points

There are significant limitations in each of these. While serial biopsies are limited by selection bias in patients undergoing repeat liver biopsies, cohort studies have limited follow up. Despite these limitations, the studies have provided data on which some inferences can be drawn. There have been no studies from India on the natural history of NAFLD; hence the few studies available from other countries are reviewed here.

NAFLD is a slowly progressive disease. Serial liver biopsy studies (30,38,40) have shown that around half of the subjects with NAFLD seem to remain stable at the same stage for 5 - 13 years, 15-20% in fact show some improvement while only 30-40 % progress from one stage to another as shown in (Table 2).

Table 2 : Fibrosis progression in liver biopsy based follow up in NAFLD.

Author (year)	No. of patients	Average time interval (years) between biopsies (range)	Progressed *n* (%)	Stable *n* (%)	Improved *n* (%)
Harrison (2003)	22	5.7 (1.4-15.7)	7 (32)	11 (50)	4 (18)
Adams (2005)	103	3.2 (0.7-21.3)	38 (37)	35 (34)	30 (29)
Ekstedt (2006)	70	13.8 (10.3-16.3)	29 (41)	30 (43)	11 (16)

NAFLD comprises a histological spectrum; those with steatosis alone (without necro-inflammation or fibrosis) seem to run a very benign course. Less than 5% of these subjects showed progression to cirrhosis over more than15 years. This contrasts sharply with those who had NASH at initial evaluation; progression to cirrhosis was seen in twice the number (10%) and over half the time (8 years) in this group. Higher BMI, greater insulin resistance or the presence of type 2 diabetes constitute risk factors for a higher rate of fibrosis progression (31).

With the development of fibrosis and morphological features of cirrhosis over time, many of the classical changes of excess fat accumulation in the liver such as steatosis, or features of inflammation such as presence of inflammatory cells or ballooning of hepatocytes, disappear. In a grossly scarred cirrhotic liver, it is therefore difficult to establish what caused the damage. As a corollary, liver biopsy features other than fibrosis severity, may not be useful to predict the long-term prognosis in an individual patient with NAFLD.

Long term prognosis of patients with NAFLD studied by following cohorts till clinical end points occur, have shown slow disease progression over time; the prognosis however varies with the stage of NAFLD (Table 3). Patients with bland steatosis have <1% chance of dying due to their liver disease. On the other hand, those with aggressive steatohepatitis or cirrhotic stage NASH have a worse prognosis, as demonstrated in three recent studies; 9-26% of patients died within 4-10 years

Table 3 : Long term prognosis of NAFLD

Author (year)	Diagnosis	*n*	Cirrhosis prevalence (%)	No. of liver-related deaths (%)	No. of deaths overall (%)	Average follow-up (years)
Dam-Larsen (2004)	Bland steatosis	109	1	1 (0.9)	27 (24.8)	16.7
Matteoni (1999)	NAFLD	98	20	9 (9)	48 (49)	8.3
Adams (2005)	NAFLD	420	5	7 (1.7)	53 (12.6)	7.6
Ekstedt (2006)	NAFLD	129	7.8	2 (1.6)	26 (20.2)	13.7
Lee (1989)	NASH	39	16.3	1 (3)	10 (26)	3.8
Powell (1990)	NASH	42	7	1 (2)	2 (5)	4.5
Hui (2004)	Cirrhotic-stage NASH	23	100	5 (21)	6 (26)	5.0
Hashimoto (2005)	NASH with septal fibrosis or cirrhosis	89	48	6 (6.7)	8 (9)	3.7
Sanyal (2006)	Cirrhotic-stage NASH	152	100	22 (14.5)	29 (19.1)	10

of follow-up, with most causes of death being related to end-stage liver disease (34-37). Risk of progression to liver failure is increased five fold among obese NASH patients as compared to non obese patients.[5% Vs 1%] (39). When compared with other etiologies of chronic liver disease, NASH-cirrhosis has outcomes comparable with HCV cirrhosis (34).

Overall, a diagnosis of NAFLD is associated with a shorter survival than expected (Fig. 2). In a community based study at Minnesota, USA, NAFLD patients had significantly lower 10 year life expectancy than the healthy general population [77 Vs 88%, $p<0.05$] (38) Liver failure, variceal hemorrhage and HCC were important causes of mortality in this study population.

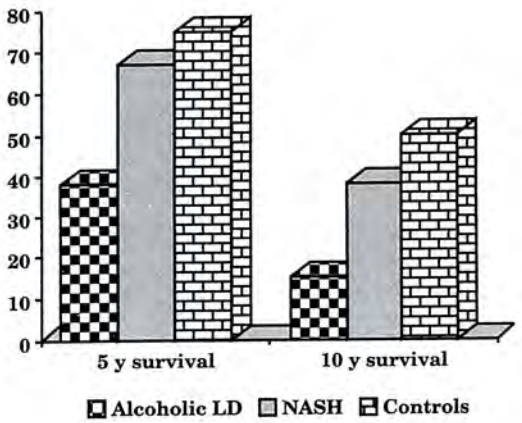

Fig 2: NAFLD: Life expectancy

Conclusion

Non-alcoholic fatty liver disease is a recently recognized entity characterized by accumulation of fat in the liver in non-alcoholic subjects. It is associated with insulin resistance and metabolic syndrome. A significant proportion of Indians are being affected by this disorder. A subgroup of patients runs a progressive course with damage to liver cells and development of cirrhosis.

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