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Epidemiology and Natural History of Nonalcoholic Fatty Liver Disease

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Abstract

Nonalcoholic Fatty Liver Disease (NAFLD) is being increasingly recognized as a common liver disorder associated with one or more manifestations of metabolic syndrome. Liver morphology comprises a wide spectrum ranging from accumulation of fat within hepatocytes (steatosis) to associated inflammation and fibrosis (steatohepatitis); some cases progress to cirrhosis, liver failure or liver cancer. Prevalence rates of NAFLD have been variously reported depending on age, gender, BMI and presence of associated diseases especially Type 2 diabetes mellitus (T2DM). Geographic epidemiology of NAFLD cuts across developing and developed world. NAFLD is a slowly progressive disease. The course of illness is variable, and is determined largely by the presence or absence of necro-inflammatory changes and fibrosis. The presence of such changes indicates likely progression to cirrhosis, liver failure and hepatic carcinoma thus portending adverse prognosis both with respect of morbidity and life expectancy.

Introduction

Nonalcholic fatty liver disease (NAFLD), a condition in which excess fat accumulates in the liver in subjects who do not consume alcohol, was first recognised in obese patients half a century ago (1), but remained laregely ignored. The clinical importance of 'Fatty liver' noted during ultrasound examination of the abdomen, was not evident for the next three decades and was passed off as a normal variant. In 1980, Ludwig *et al.*, described the characteristic histopathological changes

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noted in NAFLD and coined the term 'nonalcoholic steatohepatitis' [NASH] (2). This drew attention to this hitherto unexplored entity and intense research on its epidemiology, natural history and treatment modalities followed.

Nonalcoholic liver disease is being increasingly recognized as a common liver disorder that represents the hepatic manifestations of the metabolic syndrome, a variable aggregate of clinical manifestations such as central obesity, type 2 diabetes mellitus, hypertension and hyperlipidemia with insulin resistance as its core pathogenetic mechanism. The liver morphology comprises a spectrum ranging from mere accumulation of fat within hepatocytes (steatosis) to associated inflammation and fibrosis (steatohepatitis); some cases progress to cirrhosis, liver failure or liver cancer.

In the present article we shall review the epidemiology of NAFLD with special attention to reports from India, and summarize the results of important longitudinal studies that have defined the natural history of this condition.

Epidemiology of NAFLD

Prevalence of NAFLD

For epidemiologic surveys, two approaches have been used: the demonstration of "fatty liver" on ultrasound examination or biochemical estimation of liver specific aminotransferase enzymes in serum samples obtained from large sections of the population. Both these approaches are useful only when patients with significant alcohol consumption (more than 20 g/day) (3) or other causes of "transaminitis" such as chronic infections with hepatotropic viruses, have been excluded. Further, ultrasound examination fails to diagnose non-alcoholic steatohepatitis (NASH), the progressive variety of the disease, for which liver biopsy, although impractical for field studies, remains the gold standard. Elevated liver enzymes in serum samples, on the other hand, is a surrogate marker of NAFLD as it could occur in other liver conditions as well.

Using data from the third National Health and Nutrition Examination Survey (NHANES III) in USA, Ruhl *et al* examined the frequency of abnormal levels of alanine aminotransferase (ALT) enzyme in serum samples (defined as an ALT> 43 U/L for men or women) . By eliminating individuals who had other potential causes of elevated ALT, such as moderate to high alcohol consumption, hepatitis B or C, elevated transferrin saturation or a history of diabetes mellitus, the authors used the elevated ALT as a surrogate for nonalcoholic fatty liver disease (NAFLD) and found that 2.8% of the population to be affected (4). Recently, population surveys have suggested that the upper limits of normal ALT should be revised to <30 U/L for men and <19 U/L for women (5). Using lower normal cut-off values for ALT, Ruhl and Everhart found elevated

levels in 12.4% of men and 13.9% of women, estimates significantly higher than their original 2.8%. These estimates may also be falsely low because diabetics, who are prone to NAFLD were excluded from the study.

Using ultrasound examination, frequency of NAFLD has been determined in the general population based on findings of fatty liver, and after exclusion of significant alcohol intake. The prevalence of NAFLD has been estimated 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).

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	2574	14	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

The increasing prevalence of NAFLD in the population reflects the growing pandemic of obesity and type 2 Diabetes Mellitus. 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 2 disorders explains the high frequency of their co-existence in the same individual.

NAFLD can affect children as well. With the current world wide epidemic of pediatric obesity, pediatric NAFLD 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 3 times the prevalence noted in a survey conducted in 1965 (19).

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

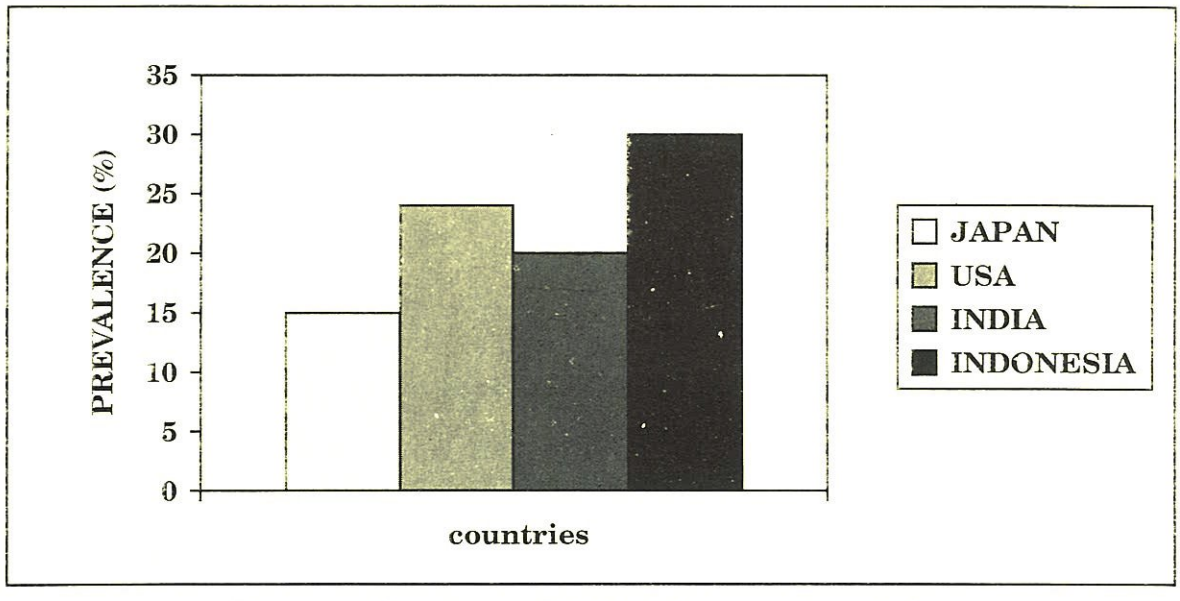

Figure 1: Prevalence of NAFLD in general population

Indonesian population (9) reported a 30 % prevalence of NAFLD, a figure higher than even that from USA (24%) or Japan (15%). Another recent study from Shanghai (7) found 24% of the Chinese subjects to have the disorder. 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.

Prevalence of NAFLD in India

Several reports from India suggest that NAFLD is quite common in this country as well. 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 Amarapurkar *et al* 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 1 (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

Prevalence of NAFLD in patients with cryptogenic hepatitis

On the basis of liver biopsies, features of NASH could be identified in 65-90% 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.

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 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 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).

Table 3 : Long term prognosis of NAFLD

Author (year)	Diagnosis[a]	*n*	Cirrhosis prevalence (%)[b]	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

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.

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.

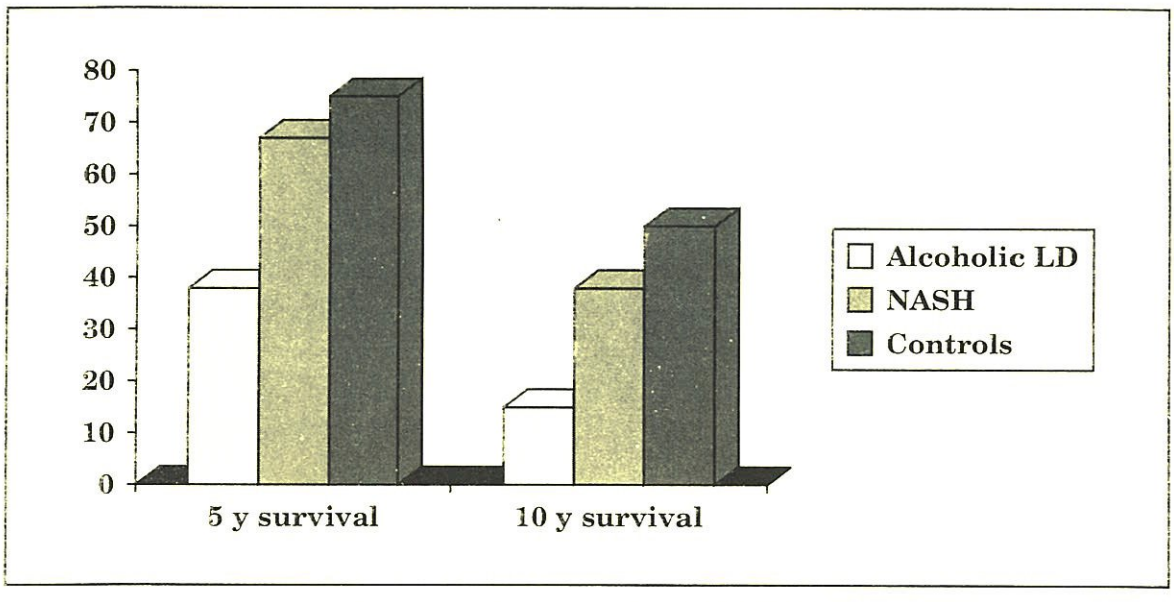

Figure 2: NAFLD: Life expectancy

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