

Nonalcoholic Fatty Liver Disease: A New Frontier for Hepatology in Bangladesh and a Call for Action to Combat

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Summary:

Nonalcoholic Fatty Liver Disease (NAFLD) is the condition where fat accumulates in liver without significant ingestion of alcohol. NAFLD has become one of the most common liver conditions throughout the world. At the dawn of the history of NAFLD it was thought that NAFLD is disease of obese individual but lean patients are increasingly detected to have NAFLD. It seems that insulin resistance is central to the pathogenesis of NAFLD. In addition, oxidative stress and cytokines are important contributing factors, resulting in steatosis and progressive liver damage in genetically susceptible individuals. NAFLD varies considerably by ethnic group and Bangladeshi ethnicity is an independent risk factor for NAFLD. Prevalence of NAFLD in general population of Bangladesh is 4 - 18.4 %, which jumps up to 49.8% in diabetic patients. With the changes in socioeconomic condition and life style, aetiology

of chronic liver disease is drifting from infectious to noninfectious diseases and the contribution of NAFLD is progressively increasing. Hepatitis B and hepatitis C have been the leading causes of mortality and morbidity from chronic liver disease in Bangladesh. But with increase in awareness and mass vaccination against HBV, prevalence of both the diseases has been decreasing in the country. The most alarming feature is that there is a high prevalence of NASH among the NAFLD patients. NAFLD is emerging as the largest contributor of chronic liver disease in Bangladesh. This warrants the attention of health policy makers and clinicians to explore this frontier and combat it from right now.

Key words: Fatty liver, Bangladesh, Prevalence, Cirrhosis, Non-communicable disease.

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Introduction:

Nonalcoholic fatty liver disease (NAFLD) is a condition characterized by excessive accumulation of lipid

(defined as the presence of lipid in > 5% of hepatocytes or a lipid content > 5% liver weight)¹ in the liver in individuals, who consume little (< 20 g of alcohol/d) or no alcohol.¹⁻² It is the most common cause of chronic liver injury.³ When NAFLD is accompanied with liver cell injury and inflammation it is called nonalcoholic steatohepatitis (NASH).² About 30% NAFLD progress to NASH, if untreated it can lead to fibrosis, cirrhosis or even hepatocellular carcinoma (HCC).⁴ Indeed, NAFLD is now recognized to be the aetiology in many cases previously labelled as cryptogenic cirrhosis.⁵ HCC is one of the most common cancers worldwide and its burden is the highest in South-East Asia.⁶ In the Asia-Pacific region the prevalence of NAFLD has increased remarkably over the years affecting up to 30% of the general population.⁷ Prevalence of NAFLD in adult population both in developing and developed Asian countries has been increasing, the figures vary from 9 to 30% in Japan, 5 to 24% in China, 5 to 28% in India, 18% in Korea, 30% in Malaysia and 5% in Singapore.⁸ Metabolic syndrome, common in people from South Asia, is an important risk factor for NAFLD

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with Bangladeshi ethnicity being an important independent risk factor.³ NAFLD has become an important public health problem because of its high prevalence, potential to progress to severe liver disease and association with serious cardio-metabolic abnormalities including type-2 diabetes mellitus (T2DM), metabolic syndrome and coronary heart disease. Of particular concern, and with significant implications for future disease burden, is the increasing prevalence of NAFLD in children and young adults. Studies have reported a 3% prevalence of NAFLD in the general paediatric population, rising to 53% in obese children.^{9, 10} With the increasing prevalence of obesity, diabetes, and metabolic syndrome in the general population, NAFLD has become the most common cause of chronic liver disease in the western countries as well as lower BMI areas such as in regions of Asia. Thus the nature and extent of the problem of NAFLD in the context of Bangladesh needs to be addressed seriously.

Pathogenesis of NAFLD and diagnosis:

The pathogenesis of NAFLD is still not fully elucidated. It seems that insulin resistance (IR) related to obesity is central to the pathogenesis of NAFLD (Figure – 1). In addition, oxidative stress and cytokines are important contributing factors, together resulting in steatosis and progressive liver damage in genetically susceptible

individuals. Key histological components of NASH are steatosis, hepatocellular ballooning, and lobular inflammation. The degree of fibrosis on liver biopsy (stage) is predictive of the prognosis. Current evidences are in favor of the “multiple-hit hypothesis,” for the pathogenesis of NAFLD where the first insult, or hit, to the liver occurs from insulin resistance.¹¹ This causes increased levels of fatty acids that result in fatty infiltration of the liver, or steatosis. These hits continue and the increasing fatty acids eventually cause apoptosis, or cell death, of hepatocytes. The identities of the multiple “hits” are probably different in each patient and largely undefined at present.¹² Sedentary life style, metabolic syndrome, diabetes mellitus, and dyslipidemia are risk factors of NAFLD in non-obese persons.^{6, 13} Diabetes is also one of the main culprits in the progression to NASH,¹⁴ and liver biopsy is recommended in NAFLD patients who have diabetes and elevated GGT.¹⁴ Although elevated liver enzymes are consequences of NAFLD,¹³ male sex, raised ALT, high LDL cholesterol, and insulin resistance are significant and independent factors associated with the presence of NAFLD in T2DM subjects.¹⁵ Furthermore, South Asian populations may be more genetically susceptible via the inheritance of polymorphisms in apolipoprotein-3 that increase IR and cause NAFLD (Figure - 2).¹⁶

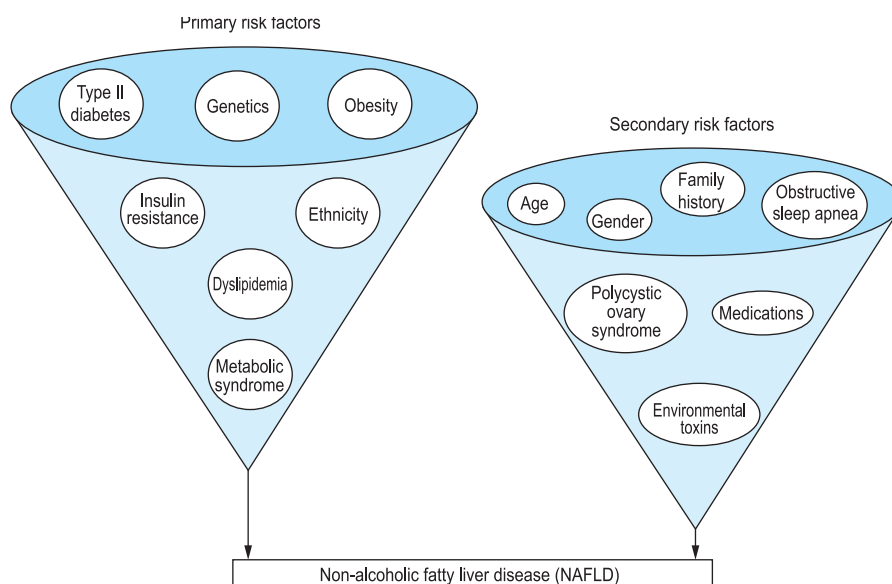


Fig.-1: Risk factors for NAFLD.

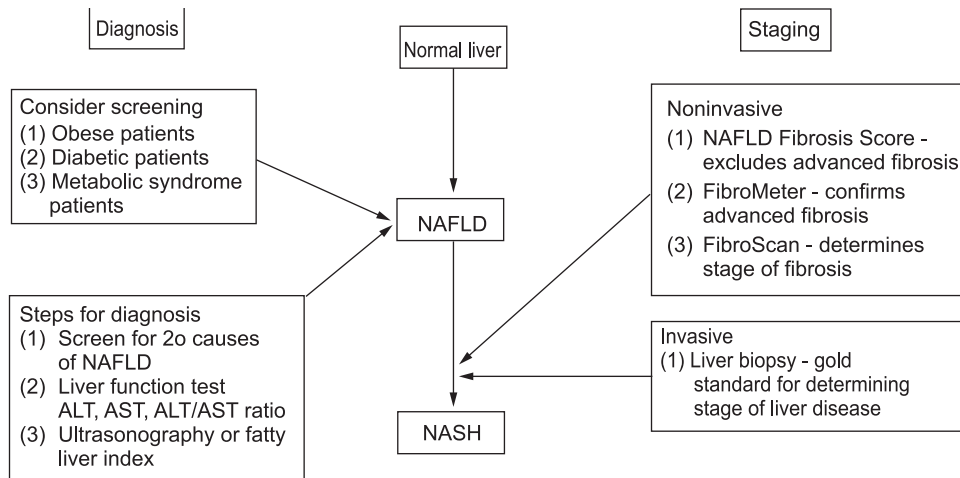


Fig.-2: Showing diagnosis steps and staging of NAFLD. 12

Burden of NAFLD:

It is increasingly apparent that NASH and NAFLD are not Western diseases. There is evolution of Western-style life among the Asian population and NASH has increasingly been diagnosed in several regions in Asia (Table- 1).¹⁷ A study using the National Health and Nutrition Examination Survey (NHANES) found a 30% rate of NAFLD in the United States between 2011 and 2012.¹⁸ NAFLD affects about 1 billion individuals worldwide and is the most common cause of chronic liver disease in Western countries.¹⁹ NASH is an increasingly common chronic liver disease with worldwide distribution that is closely associated with

diabetes and obesity, which have both reached epidemic proportions (Figure -3). It is estimated that there are at least 1.46 billion obese adults worldwide. The Asia Pacific region is the most diverse and the most populous region in the world. Recent socioeconomic changes with increased affluence and changes in lifestyle have resulted in an emerging epidemic of non-communicable diseases such as T2DM and NAFLD. The prevalence of NAFLD in Asian Pacific countries now approximates that seen in Western countries,¹⁶ and is thus an emerging health-care priority in Asia. This has a potential impact not only for the emerging liver disease burden in this region but also as a broader public health issue in view of the

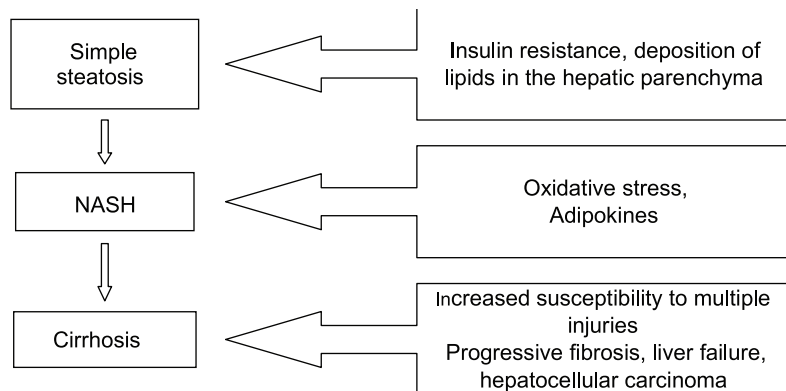


Fig.3: Progression of NAFLD

association of NAFLD with the other metabolic syndrome-linked noncommunicable diseases—obesity, diabetes, and atherosclerotic cardiovascular disease.¹⁵

Most of the available epidemiological studies in NAFLD from Asia are ultrasound based and hence detect prevalence of hepatic steatosis alone initially, correlating it with anthropometric, biochemical, and demographic features of the population (Table 2). The community prevalence of NAFLD in South Asia and South East Asia ranges from 5- 30%.²⁰ In India it varies from 5-28% in general population especially those who are undergoing healthy checkups.²⁰

According to Zhang et al study, with the globally increasing prevalence, NAFLD becomes the predominant cause of chronic liver disease.² The global scientific research of NAFLD are increasing drastically. To sum up, 6356 articles were published in 994 different journals during 1986–2013. Starting from the late 1980s, the publication on NAFLD grew slowly and entered into a highly developing period in the 21st century, especially in the last decade (Figure 4). Bibliometric results suggest that the obviously rapid growth of the articles in recent years appears to be associated with the accelerating incidence of NAFLD. In addition, epidemiology focusing on comparing different regions and population is attracting ever-growing attention.

Burden of NAFLD in Bangladesh:

Alazawi et al³ demonstrated that the prevalence of recorded NAFLD varies considerably by ethnic group and Bangladeshi ethnicity is an independent risk factor for NAFLD. Among Bangladeshis, there are high rates of T2DM and cardiovascular disease that may have a genetic basis. In that study in the UK, liver function tests were performed on 218,032 patients, of whom 31,627 had elevated serum transaminases. The prevalence of NAFLD was the most frequently recorded liver disease and was most common among Bangladeshi patients. In a multivariate analysis, independent risk factors for NAFLD included Bangladeshi ethnicity, diabetes, raised BMI, hypertension, and hypercholesterolaemia. Diagnosed NAFLD was significantly more prevalent among people of Bangladeshi ethnicity (1.8% of the adult population) than any other ethnic group, including other South Asian groups (Table 3 and Figure 5). The prevalence of NAFLD was significantly lower in the African and Caribbean ethnic groups.¹⁵

Prevalence of NAFLD in general population of Bangladesh has been estimated to vary from 4 to 18.4 %, which jumps up to 49.8% in diabetic patients.^{21, 22} Rahman et al in their rural population based study revealed prevalence of 18.4% with a higher prevalence of 59.4% in diabetic patients. In this study binary logistic

Table-I

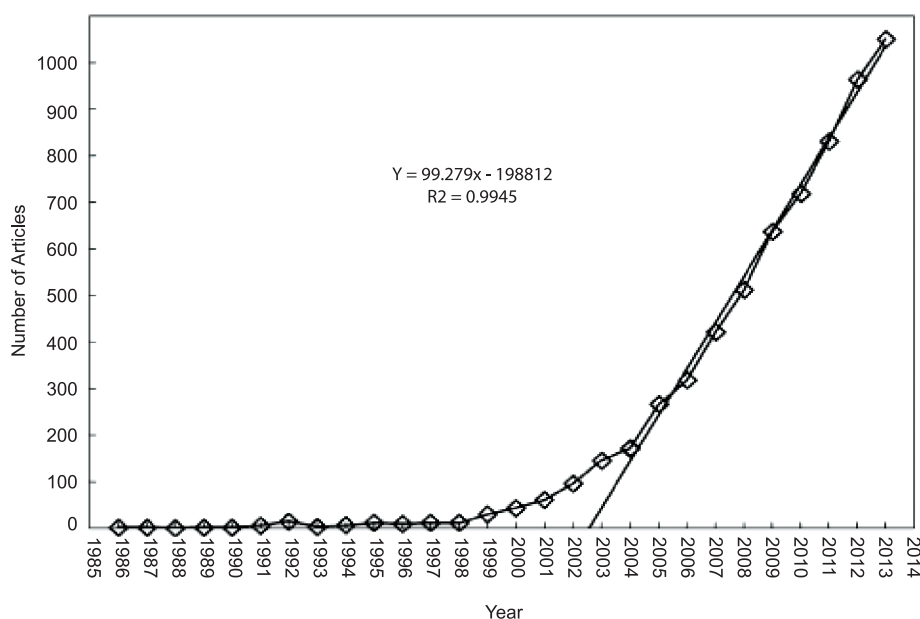
<i>Prevalence of NAFLD among different areas of the world.</i>		
Region	Population Studied	Prevalence of NAFLD in these populations (%)
USA	Pediatric population	13-14
	General population	27-34
	Morbid obesity	75-92
	European-Americans	33
	Hispanic-American	45
	African-American	24
Europe	Pediatric Population	2.6-10
	General Population	20-30
Western countries	Pediatric population	20-40
	Obesity or diabetes	75
	Morbid obesity	90-95
Worldwide	Obese population	40—90
Middle East	General population	20-30
Far East	General population	15
Pakistan	General population	18

Table-II*Showing prevalence of NAFLD among the Indian, Sri Lanka and Pakistani people*

Country and place	Population	Sample size (n)	Prevalence of NAFL
Mumbai, India	Selected population (railway colonies)	1168	16.6 %
West Bengal, India	General population (Rural)	1911	167 (8.7 %)
Chennai, India	General population (Urban)	541	173 (32 %)
Sri Lanka	General population (Urban)	2985	974 (32.6 %)
Karachi, Pakistan	Tertiary care hospital	952	129 (13.6 %)

Table-III*Showing Prevalence of NAFLD among different ethnic group living in UK.*

	Bangladeshi	Indian	Pakistani	White	African	Caribbean	Total
n	1678	325	245	1889	209	143	5250
Prevalence %	1.8	0.6	0.8	0.7	0.4	0.6	0.8

**Fig.-4:** *Publication trend of article on NAFLD from 1986 to 2013.*

regression analysis explored that diabetes, obesity (BMI>25), increased waist circumference and hypertriglyceridemia are independent risk factors for development of NAFLD.²² This is the 2nd commonest cause of hepatology out-patient consultation in the country after chronic hepatitis B.²³ These data are in concordance with prevalence of neighboring countries.²⁴⁻²⁵²⁶

Unique character of NAFLD in Bangladesh:

Though NAFLD appears to be a disease of the obese, in Bangladesh non-obese populations are also affected and the severity is also similar to that found in obese population.^{22, 27, 28} Though NAFLD is a male predominating disease in Europe and USA, it appears to affect Bangladeshi females more than males. Social

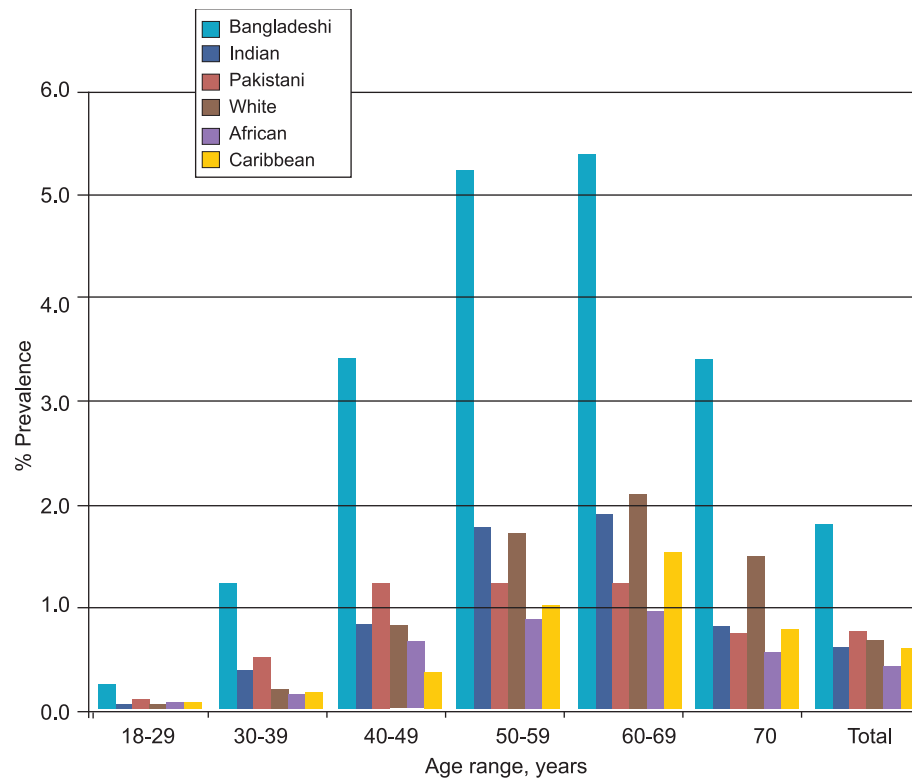


Fig.-5: Showing Prevalence of NAFLD among different ethnic group in different aged group people living in UK.

conservative attitude leading to sedentary life style of the female may be responsible for this.^{29, 30} Affluence is another reason for development of NAFLD.²² The child and adolescent populations of urban society with very little physical activity will constitute the future burden of NAFLD in the country in near future. ALT as well as GGT is good detector of NASH in Bangladeshi population with GGT having better sensitivity and specificity.¹⁴ Liver biopsy is the gold standard for assessing severity of NAFLD and that is safe in expert hand.³¹ Although IR has the central role in the pathogenesis of NAFLD, a subgroup of NAFLD of Bangladeshi population are not associated with IR, where genetic polymorphism and dietary habit may be responsible for it.³² The most alarming feature is that there is a high prevalence of NASH of about 40% among the NAFLD patients^{14, 25, 27} These NASH patients are the future patients of cirrhosis and hepatocellular carcinoma.

Changing landscape of liver disease of Bangladesh:

Hepatitis B and hepatitis C have been the leading causes of mortality and morbidity from chronic liver disease in Bangladesh. But with increase in awareness and mass vaccination against HBV, prevalence of both the diseases has been decreasing in the country. - With the changes in socioeconomic condition and life style, the predominant aetiology of chronic liver disease is drifting from infectious to noninfectious diseases and the contribution of NAFLD is progressively increasing.

Conclusion:

NAFLD is emerging as the largest contributor of chronic liver disease in Bangladesh. Both obese and nonobese populations are affected. Insulin resistance, genetic factors, dietary habit and sedentary life style - all may be responsible for this. This is the time to start “a stitch to save nine” for this new frontier of hepatology to combat the crisis. This warrants the attention of health

policy makers, stakeholders, service providers, clinicians and social worker to explore this frontier and combat it from right now.

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