

Non-alcoholic Fatty Liver Disease (NAFLD) in South Asia

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Abstract

Background

Non-alcoholic Fatty Liver Disease (NAFLD) is highly prevalent in the developed world. The prevalence has been increasing over the past few decades in parallel with an increase in the metabolic syndrome. South Asia hosts some of the most populated cities in the world and recent studies suggest the prevalence of NAFLD in some of these areas to be comparable to the western world. Earlier diagnosis should prompt life style modifications and the use of appropriate medications to prevent progression to hepatic fibrosis

Methods

All published articles in the MEDLINE database on NAFLD in South Asia were included. The important findings were summarized and critically analysed.

Results

NAFLD in South Asia is associated with obesity and insulin resistance. 'Lean NAFLD' is a new entity that describes low body mass index (BMI) individuals who develop NAFLD. Diagnosis of NAFLD is mainly using ultrasound scanning and Thromboelastography. The proven modalities of treatment include life style modifications and pharmacological agents.

Conclusion

NAFLD is an emerging problem in South Asia. Our review summarizes the key findings of studies on NAFLD from South Asia and discusses the important healthcare care delivery implications of these findings. Further studies on clinical manifestations, pathogenesis and disease progression of NAFLD in South Asia are needed to better manage this condition.

Key words – NAFLD; NASH; Liver Disease; Asia; South Asia; India; Pakistan; Sri Lanka.

I. INTRODUCTION

In recent years, Non-alcoholic Fatty Liver Disease (NAFLD) has gained widespread interest within the scientific community. (1)(2) NAFLD is considered the gastrointestinal component within the spectrum of disorders grouped as the Metabolic Syndrome. NAFLD could range from simple steatosis to non-alcoholic steatohepatitis (NASH) (3). The key points on NAFLD are given in Table 1. It is considered one of the commonest causes of cirrhosis worldwide and is the commonest cause of liver disease in the west.(4)

South Asia consists of eight countries: India, Sri Lanka, Pakistan, Afghanistan, Bangladesh, Nepal, Bhutan and Maldives. According to the 2014 World Bank statistics, twenty two percent of the world's population (that is 1.72 billion) live in South Asia. The region makes up more than 40% of the developing world. With declining fertility rates and increased longevity, population ageing is an important characteristic of this region. Aging tends to increase the risk of non-communicable diseases and countries in this region are poorly equipped to face such a challenge. A proper understanding of the epidemiology, risk factors, region-specific management issues and outcomes of NAFLD in

South Asia are urgently needed. Although there have been comprehensive reviews on NAFLD from the west, detailed accounts from South Asia are sparse. We have reviewed and critically analyzed the published literature on NAFLD in

South Asia and discussed the importance of these findings in reducing the burden of disease in this region.

Table 1: Key facts about NAFLD

Key Facts on NAFLD • Prevalence of NAFLD is increasing worldwide. • Several scoring systems available to stratify the risk. NAFLD fibrosis score (NFS) is one such validated scoring system.(76) • Cytokeratin-18 fragment (CK-18), adipocyte fatty acid binding protein (AFABP) and fibroblast growth factor 21 (FGF21 are biomarkers with high sensitivity and specificity for diagnosing NAFLD (77) • Criteria for diagnosis on USS are (1) parenchymal brightness with increasing discrepancy of echogenicity between the liver and kidney parenchyma (hepatorenal index) (2) deep-beam attenuation and (3) vascular blurring (loss of echoes from the walls of the portal veins). The presence of any two are sufficient for making a diagnosis (78) • Lean NAFLD has been increasingly recognized in the recent years.
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II. SEARCH STRATEGY

A search of the online Medline® database (Medical Literature Analysis and Retrieval System) was performed with a combination of MeSH® (Medical Subject Headings) terms; ‘NAFLD’ and ‘NASH’. The search limits were; language (‘English’), Species (‘Humans’). The conjunction of the above results was narrowed down by adding the name of each country in the region (India, Pakistan, Bangladesh, Sri Lanka, Nepal, Bhutan and Maldives). Since India had a large number of studies, only studies with more than 300 subjects were included in the tables. (Table 2:

(5)(6)(7)(8)(9)(10)(11)(12)(13)(14)(15)(16)(17)(18)) However, findings from the smaller studies were analyzed and included within the discussion. Table 3 ((19)(20)(21)(22)(23)(24)(25)(1)(26)(27)(28) summarizes the studies done in Sri Lanka. Table 4 ((29)(30)(31)(32)(33)(34)(35)(36)(37)(38)(39)(40)(41)(42) summarizes the studies from Pakistan, Bangladesh and Nepal. We accessed full text articles of the included studies. Although a formal systematic analysis was not done due to large variations in study designs, the available data were summarized and presented in the tables categorized by country.

Table 2 Studies in India

Year	Authors	Area	No of subjects	M:F	Prevalence	Comments
2007	Amarapurkar et al	Mumbai	1168	NA	16.60%	Risk factors for NAFLD include, age >40, male gender, central obesity, high BMI >25, elevated fasting blood sugar and raised AST and ALT
2009	Mohan et al	Chennai	541	282:259	32%	Prevalence increases with increasing severity of glucose intolerance and in the metabolic syndrome
2010	Sandhya et al	Chennai	120	67:53	NA	Hypoglutathionemia and hypoadiponectinemia was associated with NAFLD and/or T2DM
2010	Das et al	West Bengal	437	391:46	8.70%	Risk factors for NAFLD : abdominal obesity, dysglycemia and higher income
2012	Anbalagan	Chennai	409	NG	24.70%	Indian diabetes risk score (IDRS) can be a screening tool
2013	Kumar et al	New Delhi	307	NA	NA	In NAFLD patients, liver stiffness measurements correlated with fibrosis and increased progressively with increasing fibrosis
2013	Bhatt et al	North India	335	NA	NA	The Pro12Ala and C161T alleles of PPAR γ predispose North Indians to develop NAFLD.
2013	Singh et al	Lucknow	632	484:148	NA	Incidentally detected NAFLD (IDNAFLD) patients are predominantly middle aged males, most of whom are not lean

2013	Kalra et al	101 cities	924	569 : 355	44.1% in western India to 72.4% in northern states	middle aged males, most of whom are not lean.
2014	Puppala et al	Western regions	150	92:58	NA	T-455C APOC3 gene polymorphism and elevated serum triglycerides are associated with NAFLD.
2014	Vendhan et al	Chennai	541	259:282	NA	32% NAFLD subjects have an association with CAD.
2014	Dutta et al	Calcutta	2119	NA	NA	Increased serum fetuin-A levels have an adverse impact on glycaemic outcomes in pre-diabetes.
2015	Choudhary et al	Haryana	331 donors (147 males)	147:184	167 donors (50.4%)	Histological NAFL is present in half of apparently normal donors
2015	Anurag et al	Maharashtra	302	135:167	28.10%	Increased BMI, metabolic syndrome, increased fasting blood glucose, and serum triglycerides are potentially strong indicators of NAFLD.

NG: Not given

NA: not available

Table 3 Studies in Sri Lanka

Year	Authors	Number of subjects	M:F	Prevalence	Comments
2005	De Hewavisenth et al	296	NA	NA	Risk factors for NAFLD include DM, obesity, hyperlipidaemia, a family history of risk factors and a high dietary fat intake

2007	De Silva et al	62	50:12	NA	NAFLD leads to cirrhosis
2008	Randrajith et al	Five	4:1	32.60%	NAFLD leads to hepatic fibrosis even in children
2009	Dassanayake et al	2985	NA	NA	Obesity, acanthosis nigricans, insulin resistance, elevated diastolic BP, fasting plasma glucose, plasma triglycerides, and ALT twice the upper limit of the reference range or more were independently associated with NAFLD.
2011	Pinidiyapathirage et al	403	191:212	18%	Male sex, high BMI, high waist circumference, high diastolic blood pressure and high plasma glucose levels were significant predictors of NAFLD.
2013	Kasturiratne et al	2984	NG	NA	blood pressure and high plasma glucose levels were significant predictors of NAFLD.
2014	Silva et al	34	25:9	NA	44.8% had suspicion of NAFLD
2015	Kasturiratne, et al	3002	1343:1659	NA	Elevated BMI and elevated Total body fat were independently associated with NAFLD
2015	Jayasinghe et al	508	245:263	NA	Elevated BMI and elevated Total body fat were independently associated with NAFLD
2015	Niriella et al	2155	911:1244	Annual Incidence was 6.6%	Increased waist circumference, BMI > 23 kg/m ² , and raised plasma triglycerides were predictive of

NAFLD.

2016	Niriella et al	678	NA	NA	Lean NAFLD(BMI<23) had low prevalence of hypertension and central obesity.
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Table 4 Studies in Pakistan, Bangladesh and Nepal

Pakistan					
Year	Authors	Subjects	M:F	Prevalence	Comments
2008	Luxmi et al	120	41:79	60.80%	The prevalence of NAFL is higher in type-2 diabetic patients
2011	Niaz et al	952	952	13.50%	Among individuals undergoing annual check up NAFLD prevalence is high.
2014	Abbas et al	806	492:314	15.30%	Even in Non obese individuals NAFLD should be looked into
2015	Haider et al	145	71:74	NA	Serum triglyceride and serum cholesterol are raised significantly in NAFLD.
Bangladesh					
2013	Majid et al	NA	NA	NA	BMI and triglyceride level correlated with NAS score.
2013	Alam et al	493	189:250	NA	GGT was the only biochemical marker of NASH.
2013	Dey et al	NA	NA	NA	The mean fasting blood glucose, ALT, total cholesterol and triglycerides were significantly higher in case group compared to control group

2014	Alam et al	NA	NA	NA	Nonobese was 25.6 % among NAFLD, and 53.1 % of nonobese NAFLD cases were NASH. NASH and fibrosis were similar in the obese and nonobese.
2015	Alam et al	493	189:250	NA	Presence of diabetes could predict NASH
2015	Hossain et al	110	63:47:00	NA	Elevated levels of GGT and insulin resistance are more likely to develop NAFLD
2016	Alam et al	30	7:23	NA	Telmisartan improved NAS and fibrosis score in NASH with insignificant adverse events.
2016	Akter et al	203	NA	26.60%.	High WHR and low HDL cholesterol were significantly associated with NAFLD
Nepal					
2011	Mittal et al	202	NG	NG	Non invasive tests have demonstrated a reasonable ability to identify significant fibrosis, cirrhosis in particular.
2011	Mittal et al	200	140:60	NA	In NAFLD patients, there was mild to moderate elevation in serum levels of AST, ALT or both.
2011	Mittal et al	653	NG	NA	Mild to moderate elevation in serum levels of AST, ALT seen in NAFLD
2013	Basnyat et al	NG	NG	NG	NAFLD is associated with obesity
2016	Parmar et al	102	39:63	NA	De Ritis ratio(can be used as a prognostic marker of liver disorder and can be considered as a noninvasive, cost-effective means of screening liver diseases.

III. PREVALENCE

There is a wide range (5 – 40%) in the population prevalence of NAFLD in South Asia. (5). Some of the reported prevalence values are: India (9-32%)(13), Pakistan (13.5%)(29), Bangladesh (26.60%)(7). Some countries in the Asia Pacific region also have similar rates: 20% in China, 27% in Hong Kong, and 15-45% in South Korea,

Japan and Taiwan (43). Longitudinal studies from China and Japan have shown an increasing prevalence in recent years (44) and it is likely the South Asian region would show a similar trend.

In the SPRINT study (13), the prevalence of NAFLD in India was 56.5% (North 72.4%, South 60.4%, East 55.2% and west 44.1% respectively). Quite surprisingly, the

NAFLD prevalence rates in urban areas were similar to those in rural areas. Prashanth et al(45) studied Type 2 Diabetes Mellitus (T2DM) patients and found a prevalence of NAFLD to be 87%, using histological methods. This prevalence figure was much higher than that reported in the SPRINT study (which diagnosed NAFLD on ultrasound criteria), and reiterates that histology is the definitive and more sensitive method for diagnosing NAFLD.

The reported prevalence of NAFLD within an urban setting in the Western province of Sri Lanka was 32.6% (22). In rural Sri Lanka, the rate was significantly lower at 18%(23). The more sedentary life style of persons living in the urban areas may contribute to this difference. At present, the true country wide prevalence of NAFLD in Sri Lanka is not known. In Pakistan, 13.5% of the healthy males that were screened (29) and 15.3% of persons attending a hepatitis awareness program had NAFLD(30). We could not find any studies on the population prevalence of NAFLD in Nepal.

In most of the Indian studies (except the SPRINT study), more males were affected with NAFLD. In Sri Lanka too, Pinidiyapathirage et al found more males to be affected and suggested this may be due to undisclosed alcohol consumption and higher abdominal obesity in men. However, the largest study from Bangladesh, found more females to be affected (46) and the relatively sedentary lifestyles led by females in some Asian countries may account for this difference.

IV. ETIOLOGY, RISK FACTORS, NATURAL HISTORY AND PATHOGENESIS:

There is a strong association between NAFLD and the components of the Metabolic syndrome: obesity, diabetes mellitus and dyslipidemia.(48) There has been recent controversy on the anthropometric cut offs to be used in Asians when compared to Caucasians. Asian Indians have an increased predisposition to visceral fat accumulation.(48) As a result, at a lower Body Mass Index (BMI) Asians tend to get the metabolic syndrome. The World Health Organization suggested cut-off points for observed risk varies between 22 and 25 kg/m² in different Asian populations and the potential public health action point for BMI in Asians is 23.(49)

Several studies from India, have found South Asians to develop NAFLD at a lower adiposity than Caucasians (51). So called 'Lean NAFLD' is spurring much interest within the scientific community as those affected are younger and have less insulin resistance(53). However, studies have used

varying cut-off BMI's for defining lean NAFLD. For instance Bhat et al used the Asia-Pacific criteria cut-off: BMI < 23 kg/ m² and WC<90 cm in men,<80 cm in women(52), whereas in China, the cut-off was BMI< 24.

In Sri Lanka, dietary patterns have changed from a more traditional to a more western type in recent years. The prevalence of obesity is high and showing an increasing trend (54). For instance, a large cross sectional study done in four (Western, North Central, Southern and Uva) of the nine provinces in Sri Lanka showed the prevalence of obesity to be 20.3% in men and 36.5 % in women.

In 2005/06, Katulanda et al (57) found the prevalence of DM to be 10.3% in a nationally representative sample. Urban areas had a higher prevalence when compared to rural areas. In a community based study (one part of the Sri Lanka Diabetes and Cardiovascular Study - SLDCS) done in seven provinces of Sri Lanka, the estimated prevalence of metabolic syndrome in Sri Lanka was found to be 24.3%.(58) This rate is in par with the prevalence in the western world (range: 30-35%) (59) and the rest of Asia (range: 19-45%).(60)

Among adolescents in Sri Lanka, higher **BMI** and total body fat were independent predictors of NAFLD. (1) Dassanayake et al found obesity, acanthosis nigricans and insulin resistance to predict the development of NAFLD in adults.(22) In Bangladesh, diabetes was a predictor for the presence of NAFLD.(46), and in several Indian cities, insulin resistance was found to be common in patients with NAFLD.(61)

Increasing evidence supports a genetic susceptibility to development of NAFLD. The commonest Single Nucleotide Polymorphisms (SNPs) found to be associated in the European Genome Wide Association Studies (GWAS) studies on NAFLD are : GSTM1 and SOD2 A16V from the oxidative stress response pathway, TNF G-238A involved in inflammatory/immune responses and PNPLA3 I148M, which has a potential lipolytic role (62). Asian studies have found SNPs in PNPLA3 to have a strong association with NAFLD (63)(64) In India, association between SNPs in the PNPLA3, PARVB, SAMM50 and PZP genes and NAFLD was noted (65) and in Sri Lanka an association was found with SNPs in PNPLA3(25). The clinical implication of such genetic variations in day to day clinical practice is still to be ascertained.

Long term follow-up studies have found a small percentage of persons with NAFLD to end up with cirrhosis. In 2007, cryptogenic cirrhosis was the second commonest

cause of cirrhosis in Sri Lanka (66) and 44% of them had diabetes. It is likely the majority of cryptogenic cirrhosis patients had NAFLD.

V. DIAGNOSIS:

Accurate diagnosis of NAFLD may involve both invasive and non-invasive methods. Ultrasound scanning (USS) remains the most commonly used modality. This is likely to be because it is easily available and cost effective, especially within a developing middle income country. However, operator variability is an important drawback. In a study from the Cleveland clinic, that used liver histology (at least 30% fat) as the gold standard, the sensitivity and specificity of liver USS for NAFLD was good (89% and 93% respectively), but less suitable for liver fibrosis (77% and 89% respectively)(67).

Magnetic resonance spectroscopy, liver enzymes, thromboelastography (TE) and liver biopsy are the other methods available. TE (also called Fibroscan) is accurate, reproducible and needs minimal training, but lacks accuracy in obese individuals(68). So far, almost all studies on NAFLD in Sri Lanka have used ultrasound scan criteria. At present, TE is only available in the private sector in Sri Lanka. Despite been easy to do, liver enzymes do not correlate with the severity of fibrosis.

Several scoring systems have been developed to assess NAFLD. In the CURES study, the Indian diabetes risk score (IDRS) derived from four parameters: age, abdominal obesity, family history of diabetes, and physical activity was independently associated with NAFLD. (9) Among 29 patients that underwent a liver biopsy, the AST/ALT ratio (AAR) correlated better than the AST-to-platelet ratio index (APRI) with liver fibrosis.(69). Parthik et al also found NAFLD Fibrosis score (NFS), APRI, and AAR to be highly sensitive.(70)

VI. TREATMENT

At present, the treatment options for NAFLD are still limited. Life style modifications including exercise (71) and diet are beneficial in preventing progression to liver fibrosis. If the **patient** is over-weight, the American Gastroenterology Association recommends a 10% weight loss as an initial goal. Several studies have found weight reduction to normalize transaminases, reduce liver size and improve insulin resistance.(41), (72) Thioglitazone and Vitamin E (73) reduces liver inflammation but has no effect on liver fibrosis. Metformin (an insulin sensitizer) has been used in several randomized controlled trials but its effects are not clear cut. In some studies liver biochemistry and

insulin resistance improved but not liver histology(74). Furthermore, most studies were small with limited follow-up (74). Studies in India have assessed the effect of metformin and lifestyle modifications on NAFLD. However, most were non-randomized and did not have a control group(75) There have been no NAFLD treatment studies from Sri Lanka.

VII. PRESENT AND FUTURE DEVELOPMENTS

NAFLD is an emerging public health problem in South Asia. Prevention should form the cornerstone of NAFLD management and at present, public health measures to reduce obesity and combat insulin resistance appears to be the most promising modalities. Some of the challenges faced by the South Asian region in relation to NAFLD includes: poor physician and public awareness, poor availability of cheap diagnostic methods and limited clinical trial data on the best treatment modalities for this region. Larger well powered studies on prevention and treatment modalities in NAFLD are urgently needed. Genetic susceptibility loci in different South Asian populations need to be further explored and the effective use of mass and social media for promoting healthy life style options should be expanded. Once NAFLD is diagnosed, other components of the metabolic syndrome should be screened for and treated according to accepted guidelines.

In some areas of South Asia, NAFLD occurs at or a higher frequency than in the developed world. The sheer number of people living in the South Asian region, makes the numbers of patients with NAFLD to be very large. Most of the countries are limited by financial, technological and manpower resources to combat this growing burden. One would need to better understand the intricacies of NAFLD in South Asia, if we are to successfully reduce the burden and improve outcomes of NAFLD in this region. Additionally, a sizeable proportion of South Asia immigrants live in the western countries. Understanding the factors driving NAFLD in South Asia should also impact on how those living in a different geographical location are best managed.

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