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Research Article

Nepal Perspectives on Routine Clinical Practices for Management of NAFLD

Sudhamshu KC[1]*, Prasad VGM[2], Shreshta A[3], Pathak R[4], Lama T[3], Jaisi B[1,5], Karki N[6], Khadka S[7], Kashyap AK[8], Sharma D[1,9]

[1]National Academy of Medical Sciences, Nepal; [2]Dr. MGR Medical University, India; [3]Alka Hospital Liver Center, Nepal; [4]Institute of Medicine, TUTH, Nepal; [5]Star hospital, Nepal; [6]NORVIC International Hospital, Nepal; [7]BIR Hospital, Nepal; [8]Grande International Hospital, Nepal; [9]Everest Hospital, Nepal

ABSTRACT

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. In this paper we present the commentary of a group of experts from Nepal regarding the routine clinical management of NAFLD in Nepal from their clinical experiences.

Keywords: NASH; Non-alcoholic Fatty Liver Disease (NAFLD); Lean NAFLD; Nepal

INTRODUCTION

Non-Alcoholic Fatty Liver Disease (NAFLD) is present when more than 5% of the liver cells (hepatocytes) contain fat in the form of triglyceride droplets. NAFLD covers a wide histopathological range of disease subtypes from simple steatosis with no or only very mild inflammation over steatosis with concomitant more aggressive necro-inflammation to fibrosis and ultimately liver cirrhosis and finally hepatocellular carcinoma (HCC). Non-alcoholic steatohepatitis (NASH) is a more severe form of NAFLD and is characterized by lobular inflammation and hepatocyte ballooning which is presumed to progress into cirrhosis in quarter of the affected person [1].

The growth of NAFLD as an epidemic is related to increasing prevalence of obesity and sedentary life-style. The traditional risk factors for NAFLD include age, sex, central obesity leading to insulin resistance and development of metabolic syndrome. Furthermore genetic predisposition is also presumed to have a role given the differences noted amongst different ethnic groups [2,3].

NAFLD was believed to be a disease of the developed world, primarily related to sedentary life-style. However, a growing body of literature has highlighted NAFLD as a global epidemic. Studies have suggested a wide amount of diversity in prevalence based on country of interest. The average prevalence in Europe is 20–30% and in China appears to be 5–24%. In India, the prevalence is estimated to be between 16–32%. This is believed to be due to the increasing industrialization of these nations, along with changes in lifestyle and diet. Although, NAFLD is associated with high body mass index (BMI) in west world, it can also affect seemingly non-obese Asians. This has revealed a new concept of lean NAFLD [4-7].

Nepal is a geologically diverse country with multiple ethnicities located in south Asian region sandwiched between India and China. It covers 147181 km of land area inhibiting 29.3 million of population. Recently immigration of rural population to urban areas in search of better livelihood has exposed them to vulnerability of different non-communicable disease resulting from urban lifestyle and diet. This has sparked an interest in medical community to assess the condition and management of these diseases. This commentary tries to depict the NAFLD situation from Nepal perspective assessed by Key opinion leaders (KOLs) using their expertise in this therapeutic area and experiences at clinical setup.

EPIDEMIOLOGY

Until now, there has been no attempt made to study the prevalence of NAFLD in general population of Nepal. A study by Mittal et al. at Pokhara, Nepal reported that the prevalence of NAFLD was 17% [8].

***Correspondence to:** Sudhamshu KC, National Academy of Medical Sciences, Nepal, Tel: 9313533877; E-mail: rg18@spirant.org

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Risk factors associated with development of NAFLD

The risk factors for NAFLD in Nepal appear to be similar to those in the Western world with some subtle differences. There is a strong association between NAFLD and the components of the Metabolic Syndrome (MS): Obesity, Diabetes Dellitus and Dyslipidemia. Certain reports also describe the association of dietary habits with development of NAFLD such as non-vegetarian diet, fried food, spicy food and tea. Studies also have revealed the high prevalence of all metabolic syndrome components in NAFLD patients. South Asians usually have higher percentage of visceral body fat, abdominal obesity, insulin resistance, hyperinsulinemia, and low muscle mass compared to other ethnic populations therefore they are more prone to suffer from NAFLD and MS. Finally there are also non-modifiable risk factors associated with south Asian NAFLD that are related to genetic and epigenetic variations, such as in single nucleotide polymorphisms (SNPs). Interestingly, multiple studies from South Asia also reveal the early-onset of NAFLD with average age in the 40s and a male predominance in this region [9-12].

A study was conducted in which subjects attended liver clinics for evaluation of NAFLD to record different characteristics as shown in Table 1.

Extent to which individual MS components were present in the NAFLD patient is shown in Figure. 1.

Our observation is in tune with the result of the recently reported study by Paudel et al. from Nepal. They reported that metabolic syndrome was present in 222 (57.66%) participants, whereas at least a single component of metabolic syndrome was present in 352 (91.4%) participants.All five components of metabolic syndrome were present in 41 (10.64%) participants in comparison to our observation in 9 (7.96%) patients [13].

Table 1: Different characteristics of NAFLD patient.

S.No.	Characteristics	Value
1	Total number of subjects enrolled	113
2	Mean age	44.5 ± 11.3 years
3	Hypertension	24 (21.2%)
4	Diabetes	10 (8.8%)
5	Overweight (BMICat)	43 (38%)
6	Obese	55 (49%)
7	≥ 3 components of metabolic syndrome	83 (73.45%)

Effect of NAFLD on cirrhosis or hepatocellular carcinoma (HCC)

Non-alcoholic fatty liver disease (NAFLD) is a broad term and it confines simple deposition of adipose tissue in the liver to more progressive steatosis with related hepatitis, fibrosis, cirrhosis and in some cases hepatocellular carcinoma (HCC). NAFLD associated cirrhosis was earlier considered to have a higher risk for the development of HCC and the recent evidence showed that up to 50% of NAFLD-associated HCC patients did not have cirrhosis. Patients diagnosed with alcohol induced fatty liver disease had a high risk of developing cirrhosis and premature death [14-16].

Non-alcoholic steatohepatitis (NASH) a subtype of NAFLD has potentially progressive way leading to liver fibrosis, cirrhosis, hepatocellular carcinoma (HCC) and liver transplantation. As the progression of NASH occurs, there is a development of hepatic fibrosis thus the liver becomes stiff and functionally impaired, which can lead to cirrhosis, HCC, decompensated cirrhosis, death or liver transplantation. There is an increase in the rate of liver fibrosis progression which may lead to cirrhosis, HCC or death because of the presence of metabolic syndrome especially obesity and insulin resistance. There is an almost 7 fold increase in risk of HCC compared to people without liver disease with NAFLD fibrosis stages F3 and F4. Although most patients with HCC have underlying cirrhosis there is evidence that before fibrosis has develop a small proportion of cases of NAFLD can progress directly to HCC. NAFLD patients without cirrhosis with no or mild fibrosis are at some risk of developing HCC due to insulin resistance, hyperinsulinemia, increased TNF signaling, and alterations in cellular lipid metabolism [17].

NAFLD in Nepal: Genotype & phenotype

Patatin like phospholipase domain-containing protein 3 (PnPLA3) is one of the first genes shown to be associated with NAFLD in a genome-wide association study. The association has since been confirmed in several Asian studies. A single variant in PnPLA3 (rs738409 C/G) replacing cytosine with guanine creates the genetic variant I148M. This genetic variant has consistently been found more frequently in Hispanics and with the lowest rates in African Americans and might partly explain why African Americans to some degree seems to be protected from NAFLD development. Keeping this in mind we also conducted the genotype study in 381 NAFLD patients. The analysis showed in fact there is genotypic heterogeneity present in NAFLD patients in Nepal (Figure 2) [18,19].

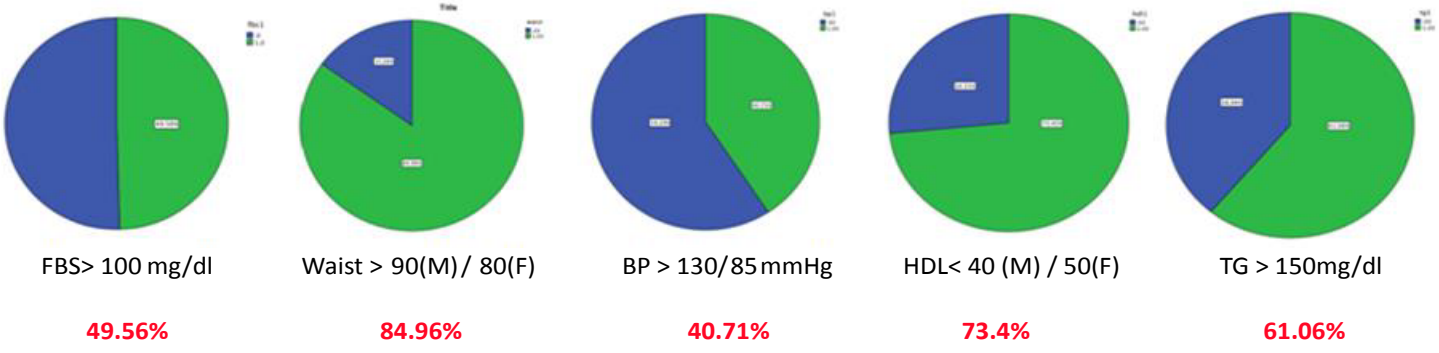

Figure 1: Prevalence of Metabolic Risk Factors present in NAFLD Patients. (FBS: Fasting Blood Glucose; BP: Blood Pressure; HDL: High Density Lipoprotein; TG: Triglycerides).

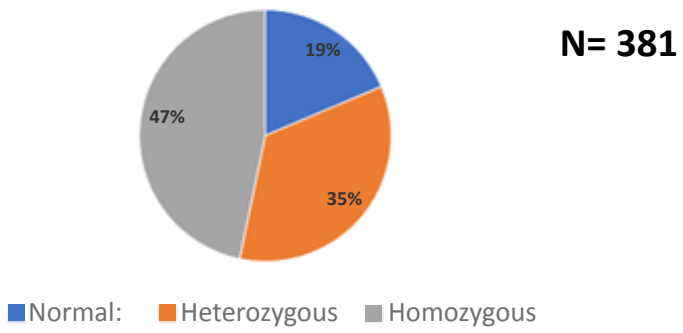

Figure 2: Genetic Polymorphism (PnPLA3 status in NAFLD in Nepal).

While NAFLD is strongly associated with obesity and metabolic syndrome, a proportion of NAFLD patients have relatively normal BMI especially in South Asian population. South Asian patients that present with NAFLD appear to have lower BMI and obesity rates. Despite this, the prevalence of NAFLD is significant on this sub-continent [20,21]. This phenomenon is hypothesized to be related to ethnic disparities in visceral fat distribution. This phenotype of NAFLD is usually described as "Lean NAFLD".

This has also led to concerns regarding the use of nomenclature broadly to define obesity, which may not be accurate in the South Asian population. In fact, the average BMI in South Asian patients is only about 26 and does not reflect the true risk of developing NAFLD. There is further implication, as even non-obese NAFLD has been shown to be an independent risk factor for coronary artery disease in this population. Hence, it is important for clinicians to be aware that Asians with lower BMI are also at increased risk of cardiovascular and metabolic diseases. Additionally, these patients develop insulin resistance despite having lower BMI as compared to western patients and subsequently are still high risk of developing NAFLD [22,23].

Role of PnPLA3 gene in next generation

PNPLA3 gene encodes a 481 amino acid protein and the biochemical analysis indicates that the PNPLA3 protein exerts lipase activity. It may also play a role in the hydrolysis of glycerolipids, with maximum enzymatic activity against triglycerides, diacylglyerol and monacylglycerol. The G allele of the PNPLA3 gene is a risk factor for cirrhosis and that the homozygous GG and GC genotype had a greater effect on this risk than the heterozygous CC genotype [24]. The rs738409 I148M variant of PNPLA3 gene, is strongly associated with NAFLD in different populations, and convincingly linked to enhance liver disease severity, such as fibrosis cirrhosis and even cancer, suggesting that rs738409 could be considered as an independent risk factor for liver dysfunction, beyond its metabolic background. Patients at risk for liver cirrhosis may benefit from PNPLA3 genotyping and, as a consequence, more intensive monitoring if the rs738409 C>G polymorphism is identified. Defining the specific PNPLA3 function in order to loosen the novel therapies for the treatment of NAFLD will be the important aspect of future research [25].

Diagnosis

Majority of NAFLD patients are asymptomatic with regard to liver specific symptoms until development of clinical manifestations related to NASH cirrhosis or HCC. Typically the suspicion of NAFLD arises due to an incidental finding of elevated liver enzymes (alanine aminotransferase (ALT) and aspartate aminotransferase (ASAT). However, abnormal liver biochemistry correlates poorly with NAFLD subtype and poses one of the biggest clinical dilemmas in NAFLD: the inability to distinguish NAFL from NASH/fibrosis where liver enzymes within normal biochemical range do NOT exclude a diagnosis of NASH. Even in the diabetic patient with NASH and advanced fibrosis liver blood tests may be normal. Hence, liver biochemistry remains insufficient as a screening tool for progressive disease [26,27].

Moderate and severe steatosis can be detected by Ultrasound (US) of the liver where high echogenicity (bright liver) points to presence of excess hepatic lipid accumulation [28]. Ultrasound scanning remains the most commonly used modality of NAFLD diagnosis in Nepal due to its ease of availability and cost effectiveness. However, operator variability is an important drawback. Magnetic resonance imaging (MRI) can quantify the triglycerides stores in liver, which may be useful in assessing the efficacy of therapeutic intervention. For assessment of disease severity, liver histology study is required, which can clearly differentiate NAFLD from NASH and liver fibrosis which is never possible by other available imaging modalities [29].

In Nepal, we conducted an observational study to characterize the extent of significant fibrosis in 40 NAFLD subjects using Shear wave elastography (Toshiba Aplio 500TM) and 13 valid readings were taken for each subject (IQR<30%). The result is shown in Figure 3.

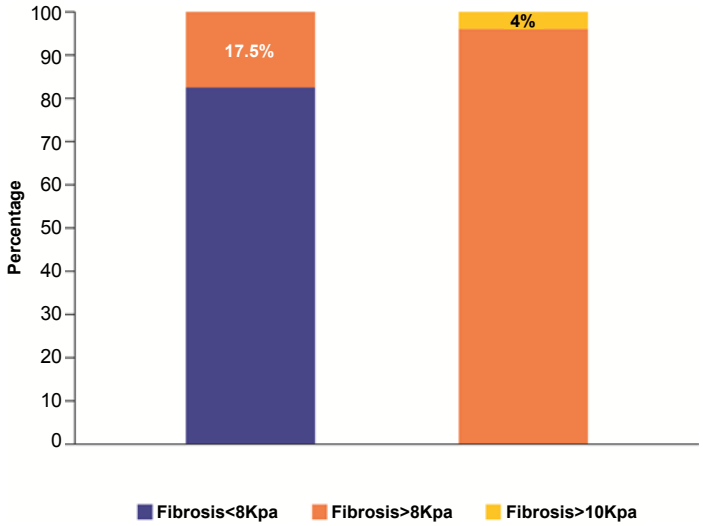

Figure 3: Significant Fibrosis in NAFLD Subjects in Nepal.

NAFLD in Nepalese diabetic population

Worldwide the prevalence of the metabolic syndrome (MS) is estimated to be 70% among those with type 2 diabetes mellitus (T2DM). T2DM and MS are associated with abnormal liver enzyme levels which can be the result of non-alcoholic fatty liver disease, cirrhosis, hepatocellular carcinoma or acute liver failure. A recently conducted study in Nepal reported that central obesity and MS following National Cholesterol Education Program Adult Treatment Panel III (NCEPATP III) criteria were independently associated with elevated ALT (58.9%) and AST (42.2%). This follows with conclusion that monitoring of metabolic components along with liver enzymes in T2DM may help with early detection and treatment of progressive liver disease. A similar study from Nepal reported a prevalence of 75% NAFLD in diabetic population. Additionally significant fibrosis (NAFLD Fibrosis Score) was found

in 18.52% of observed NAFLD patients in diabetic cohort [30,31].

Diabetes is an endemic disease in this part of the world. More the duration of diabetes and higher the BMI the severity of fatty liver is increased. Fatty liver is found to be seen even in patients with normal BMI. So diabetic patients with normal BMI should be routinely screened for fatty liver disease. The level of enzymes also does not correlate with severity of fibrosis. Even in patients with high fibrosis score have normal enzymes and patient with low fibrosis scores may have high enzymes.

Management

Treatment strategies for NAFLD have revolved following step:

(1) Identification and treatment of associated metabolic conditions such as diabetes and hyperlipidaemia.

(2) Improving insulin resistance by weight loss, exercise or pharmacotherapy.

(3) Using hepato-protective agents such as antioxidants to protect the liver from secondary insults.

Since NAFLD is a product of sedentary lifestyle, lifestyle intervention with a combination of diet and exercise is considered first-line treatment [32]. If the patient is over-weight, the American Gastroenterology Association recommends a 10% weight loss as an initial goal. The rationale for weight reduction is that it decreases ectopic fat distribution, decreases hepatic steatosis which leads to an improvement in hepatic and peripheral insulin resistance thereby facilitating a decrease in systemic and tissue inflammation and hereby reduces the risk of hepatic inflammation and fibrosis progression. Several studies have found weight reduction to normalize transaminases, reduce liver size and improve insulin resistance [33,34].

According to current European and American guidelines, vitamin E and pioglitazone may be considered in selected patients with NASH. Thioglitazone and Vitamin E reduces liver inflammation but has no effect on liver fibrosis [35]. Long-term safety of vitamin E is under dispute because of its complications like hemorrhagic stroke and others. Two different meta-analyses leaded to conflicting results when the all¬ cause mortality in NAFLD patients treated with the doses of >800 IU/d were analyzed. A Meta-analysis suggests a positive association between chronic exposure to pioglitazone and bladder cancer [36-38]. So, it should be taken into consideration while prescribing pioglitazone.

While a few agents have entered phase III development for NASH, Asian patients have been underrepresented in drug trials. Their response to pharmacological treatment is largely unknown. In particular, Nepal lacks any framed guideline or consensus from experts to treat the NAFLD subjects. With increasing prevalence of NAFLD it becomes necessary for stakeholders involved to frame treatment guideline for NAFLD.

CONCLUSION

A westernized diet and sedentary lifestyle have led to the emergence of obesity and NAFLD in Asia over the last decade. While HCC and end-stage liver disease secondary to NASH remains uncommon in Asia, these complications take decades to develop, and major changes in the epidemiology and natural history of NAFLD are expected. The lack of sufficient solid data greatly impacts the ability of diagnosing NAFLD correctly and differentiating it from NASH/fibrosis. This in turn impairs the selection of those patients who particularly are at risk of developing cirrhosis and severe cardio vascular disease. Also with the global rise in the disease there is a pressing need to clarify how we best diagnose, follow and treat NAFLD patients in both a clinical and socio-economical context.

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 especially Nepal 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. Understanding the factors driving NAFLD in Nepal should also impact on how those living in a different geographical location are best managed.

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All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work, and gave final approval for the version to be published.

DISCLOSURES

Conflict of interest

None In conclusion, our study showed that CO_2 may cause temporary endothelial dysfunction in lower extremity arteries, but clinical significance is not known.

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