Chapter 4

Nonalcoholic Fatty Liver Disease: The Future Frontier of Hepatology for South Asia

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Additional information is available at the end of the chapter

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Abstract

This review is to know the magnitude of nonalcoholic fatty liver disease **(**NAFLD) among general population and risk group populations of the South Asian countries. A thorough search of evidence-based literature was conducted using the PubMed database with key words. Databases searched from inception to February 2017. Systematic search of the literature was conducted for studies pertaining. Prevalence of NAFLD in South Asia varies from 13 to 34%. The Highest rate is in Bangladesh (34.34%) and lowest in Pakistan (13.5%). Prevalence of NAFLD is 15–80% among obese people, 25–60% with dyslipidemia and 33–55% in pre diabetics and diabetics. Nonalcoholic steatohepatitis (NASH) is present in about 50% of the NAFLD cases that can lead to fibrosis, cirrhosis or even hepatocellular carcinoma (HCC). NAFLD is not the disease for only obese people, but it is also common in nonobese in this region. About 11.11% hepatocellular carcinoma developed from NASH. Incidence rate of diabetes and coronary artery disease is high among NAFLD patients. NAFLD is becoming a future challenge for South Asia region. Prevalence and severity has been remarkably increasing for last few years. The health system should get ready to confront burden of NAFLD in future for South Asia.

Keywords: nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, South Asia

1. Introduction

Nonalcoholic fatty liver disease (NAFLD) is a characterized by excessive accumulation of fat (defined as the presence of lipid in >5% of hepatocytes or a lipid content >5% of liver weight) [1] in the liver, who consume little (<20 g of alcohol/d) or no alcohol [1, 2]. It is the most common cause of chronic liver injury [3]. Worldwide millions of people are affected

by the NAFLD and it is prophesied to be the following universal epidemic [4]. Universally its prevalence rate is 25.24 with highest in the Middle East and South America and lowest in Africa [5]. The NAFLD with necroinflammation, defined as nonalcoholic steatohepatitis (NASH) [2]. According to Younossi ZM, universally overall mortality for NAFLD is 1.05; and incidence of hepatocellular carcinoma (HCC) and liver-specific mortality among NAFLD is 0.44 and 0.77 per 1000 person-years respectively. About 30% NAFLD progress to NASH, it can be lead to fibrosis, cirrhosis or even hepatocellular carcinoma [6]. HCC is one of the most common cancers worldwide and its burden is highest in the South-East Asia [7]. Countries with higher economic status tend to present a higher prevalence of NAFLD [8]. But it is not uncommon in low economic countries like countries of South Asia. The prevalence of NAFLD has increased remarkably over the years in South Asia and South-East Asia affecting 5–34% of general population [9, 10]. Metabolic syndrome common in people from South Asia is an important risk factor for NAFLD and Bangladeshi ethnicity is an important independent risk factor for NAFLD [3]. It is commonly described as hepatic manifestation of metabolic syndrome and insulin resistance. Though prevalence of NAFLD markedly increased in obese population, presence of NAFLD is further more challenging to diagnose and manage in lean population. In this study we aimed to know the prevalence NAFLD among general population and risk group populations of the South Asian countries. We also explored the prevalence of NASH and its associated conditions.

2. Materials and methods

We performed a systematic PubMed/MEDLINE literature search with the following key words: "Non-alcoholic Fatty Liver Disease/epidemiology"[Mesh], "Non-alcoholic steatohepatitis" [Text word] AND "Liver Transplantation/etiology"[Mesh], "Obesity"[Mesh], "Diabetes Mellitus"[Mesh], "Global," "Afghanistan," "Pakistan," "India," "Sri Lanka," "Maldives," "Nepal," "Bangladesh," and "Bhutan." Databases searched from inception to February 2017. Exclusions included data on alcohol consumption or other liver diseases. Relevant full article, abstract, review, mini review, editorial and conference proceeding are included in this review.

3. Global epidemiology

Nonalcoholic fatty liver disease (NAFLD) is the commonest liver disease with global prevalence of approximately 25.24% of the general population [5]. Nonalcoholic steatohepatitis (NASH) and NAFLD are not only a Western disease. NAFLD and NASH have increasingly been diagnosed in all regions of Asia [11]. A study using the National Health and Nutrition Examination Survey (NHANES) found a 30% prevalence of NAFLD in the United States between 2011 and 2012 [12]. NAFLD is the most common cause of chronic liver disease in Western countries. It affects about 1 billion individuals worldwide [13]. Increasing prevalence of NASH is closely associated with prevalence diabetes and obesity, which may defined as epidemic worldwide. At least 1.46 billion obese adult is persisting in the world. Approximately 6 million individuals in the USA are in the risk of developing NASH and about 0.6 million

Region	Population studied	Prevalence of NAFLD in these populations (%)
USA	Pediatric population	13–14
	General population	27–34
Europe	Pediatric population	2.6–10
	General population	20–30
Middle East	General population	20–30
Far East	General population	15
South Asia	General population	5–30

Table 1. Estimated prevalence of NAFLD and NASH among different areas of the word.

to develop NASH-related cirrhosis [14]. **Table 1** shows estimated prevalence of NAFLD and NASH. Reports on the prevalence of NAFLD and NASH vary substantially due to varying definitions, differences in the populations studied, and the diagnostic methods used [14].

4. Delineation of South Asia and its population diversity

According to the United Nations geographic region ordering, South Asia comprised with Afghanistan, Bangladesh, Bhutan, India, Maldives, Nepal, Pakistan, and Sri Lanka (**Figure 1**). Topographically, it is dominated by the Indian Plate; the terms "Indian subcontinent" and "South Asia" are sometimes used interchangeably [15]. South Asia is the most populated region in the world [16]. Socially it is very mixed, consisting of many language groups and religions, and social practices in one region that are vastly different from those in another [17].

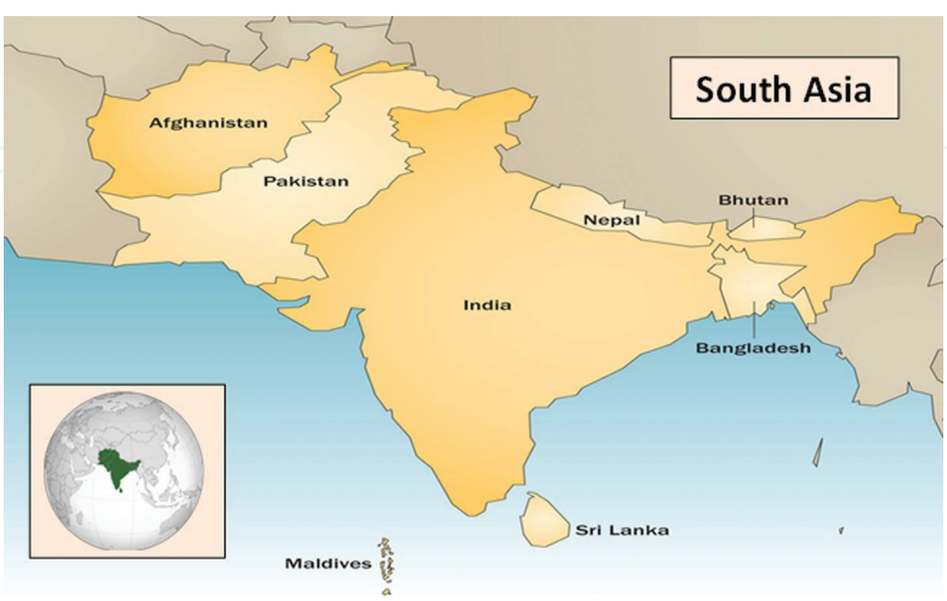

Figure 1. Geographical position and area of South Asia [16].

5. Prevalence of NAFLD among South Asian people

Recent socioeconomic changes have resulted in an emerging epidemic of non-communicable diseases such as type 2 diabetes and nonalcoholic fatty liver disease. The prevalence of nonalcoholic fatty liver disease in Asian Pacific countries now approximates and even overrides levels encountered in Western countries in some studies [18]. NAFLD is the emerging challenge for public health issue in Asia [19]. This has a potential burden not only on liver disease but also on metabolic syndrome related morbidity: obesity, diabetes, and atherosclerotic cardiovascular disease [19]. Largest population of the world inhabiting in Asia are passing through an economic growth and shift of focus from a dominant physical activity to knowledge, capital and physical inactivity. An increasing GDP is paralleled by a rising body mass index (BMI) in an almost linear fashion [19]. Countries with higher economic status tend to present a higher prevalence of NAFLD [8]. It is believed to provide a distinctive epidemiologic perspective to global situation of NAFLD. Especially for South Asia, according to increasing with their economy the prevalence of NAFLD is increasing day by day.

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 to 30% [9, 10]. Recently a hospital based study in Pakistan had shown a frequency of approximately 14%. In India, it varies from 5 to 28% in general population, especially those who are undergoing health check-ups. Indians have increased propensity for visceral fat accumulation which may present from birth [9]. Prevalence of NAFLD in general population of Bangladesh has been estimated to vary from 4 to 34.34% [20, 21], which exceeds previous reports and it jumps up to 49.8% in diabetic patients [22, 23]. And in Sri Lanka the prevalence rate was found 32.6 in an urban based study [24]. So it is seen that, among South Asian countries the highest magnitude of NAFLD is in Bangladesh and lowest is in Pakistan (**Figure 2**).

Country	Population and place	Sample size (*n*)	Prevalence of NAFL
India	Selected population Mumbai	1168	16.6%
	General population West Bengal (rural)	1911	167 (8.7%)
	General population Chennai (urban)	541	173 (32%)
Bangladesh	General population Nation wide	2621	900 (34.34%)
	Selected Population Camilla (rural)	665	219 (33%)
Sri Lanka	General population (urban)	2985	974 (32.6%)
Pakistan	Tertiary care hospital, Karachi	952	129 (13.5%)

Table 2. Prevalence of NAFLD among the Indian, Sri Lanka and Pakistani people.

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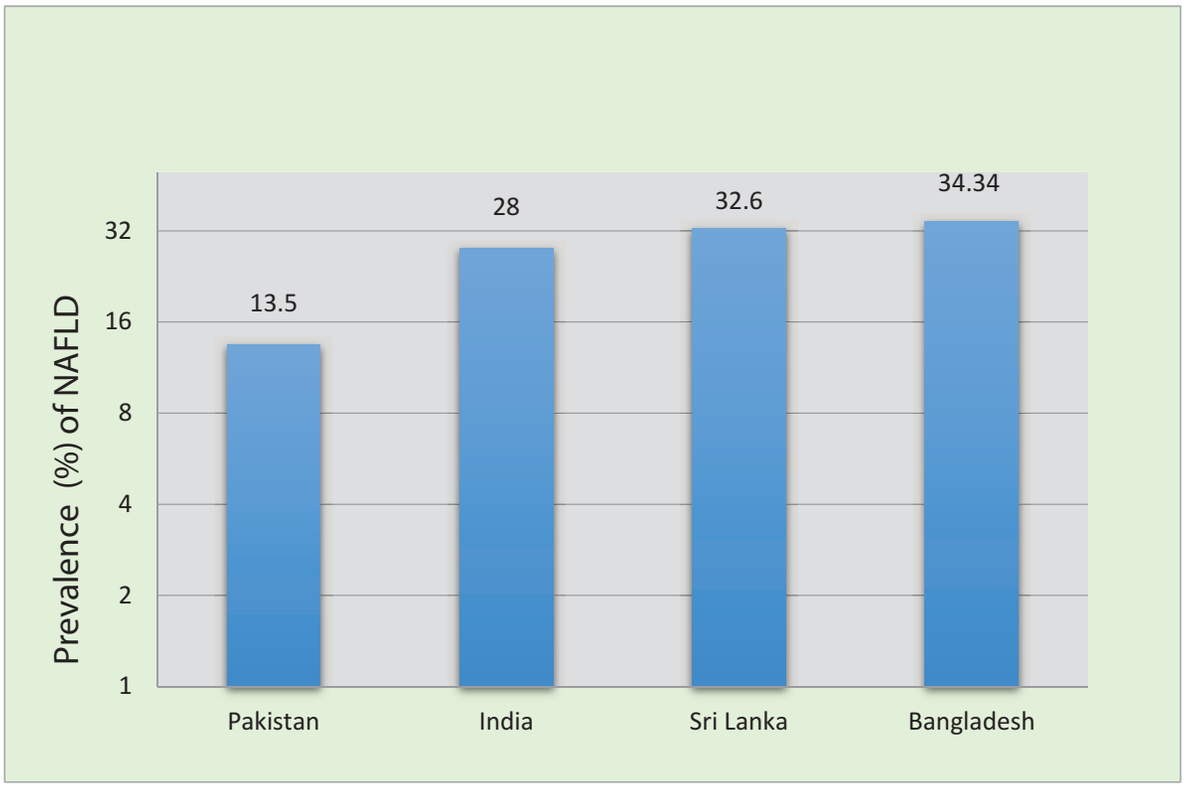

Figure 2. Prevalence of NAFLD in different countries of South Asia.

From the study of Alazawi et al. the prevalence of recorded NAFLD varied considerably by ethnic group. This study identified that Bangladeshi ethnicity as an independent risk factor for NAFLD. Diagnosed NAFLD was significantly more prevalent among people of Bangladesh ethnicity (1.8% of the adult population) than other ethnic group, including other South Asian groups. Among Bangladeshis, there are higher rates of type 2 diabetes and cardiovascular disease that may have a genetic basis. Transaminase were measured on 218,032 patients, of whom 31,627 had elevated serum transaminases. In a multivariate analysis, independent risk factors for NAFLD included Bangladeshi ethnicity, diabetes, raised BMI, hypertension, and hypercholesterolaemia. As expected, the prevalence of NAFLD was significantly lower in the African and Caribbean ethnic groups [19]. Female are predominant sufferers of NAFLD in Bangladesh [25]. So the prevalence of NAFLD in South Asia has been increased from previous reports and now it ranges from 14 to 34.34% in general population. In systematic searching in PubMed/MEDLINE database, we found research articles on epidemiology of NAFLD of India, Bangladesh, Sri Lanka and Pakistan. But we did not get any article relevant to the epidemiology of NAFLD of Afghanistan, Maldives, Nepal and Bhutan.

6. Prevalence of NASH and its progression

The active form of NAFLD is non-alcoholic steatohepatitis (NASH), which is characterized by hepatocyte injury with liver inflammation, and progression of fibrosis [26]. And it has

emerged as one of the most important causes of liver failure and hepatocellular carcinoma. Up to 20% of cases NASH may progress to cirrhosis [27]. According to Alam et al. "Patients with NASH are at risk for progressive liver disease (which can progress to cirrhosis, hepatocellular carcinoma, and death from chronic liver disease), as well as cardiovascular mortality and type-2 diabetes" [25].

NASH is present in 42.4–53.1% cases of Bangladeshi NAFLD patients [25]. Diabetic is the principle cause to develop NASH. A study in Indian Diabetic Mellitus (DM) patient; it reported that severe NASH is present among 9.35% Indian DM patients [28]. Ultrasound based Indian study showed the prevalence of NAFLD to be 16.6%, while a study based on liver biopsy showed the presence of NASH was 53% [29, 30]. And in Sri Lanka a liver biopsy based study were performed on 296 patients and 100 (35.1%) were diagnosed as having NASH [31]. In another Asian study proven NASH at presentation was found in 32.6% patients of NAFLD [32].

Study from the West found that disease progression from NAFLD to NASH is 44% patients [33]. Multiple factors like obesity, insulin resistance, genetic factor, immune response and lipotoxicity are involved in the progression of NAFLD to NASH [34]. In patients with cirrhotic NASH, HCC and liver failure are the main causes of morbidity and mortality. A prospective Japanese study elucidated the progression from NASH to HCC is 11.3% [35]. The prevalence of NASH (9.35–59%) among NAFLD patients is much higher in South Asian countries than that of Western countries. Severity of NAFLD in the form of NASH is also highest in Bangladesh among the South Asian countries as evidenced by recent studies from tertiary level hospitals of the country.

7. Depiction of the magnitude among different risk group

According to Alam, one fourth of the Bangladeshi NAFLD patients are nonobese; among them 53.1% cases present NASH. Male are largely dominating in nonobese group, where female are in obese group [36]. High BMI, central obesity, triglyceridemia and age are important risk factors for Bangladeshi people, and risk factors contributed about 29% risk for the occurrence of NASH [37]. After adjusting the risk factors (BMI and TG) female gender is the independent risk for Bangladeshi [38]. Although insulin resistance (IR) is strongly associated with NAFLD, But IR is not the sole predictor in the pathogenesis of NAFLD [38–40].

In India the prevalence of NAFLD is 15–80% among obese people, 25–60% in patients with dyslipidemia and 33–55% in pre-diabetics and diabetics' Indian people [41]. Most of the non-diabetic NAFLD patients are overweight/obese with higher insulin resistance, dyslipidemia, and subclinical inflammation [42]. Among 65.7% Morbidly Obese South Indian Patients has NAFLD. Among them 33.6% were of NASH, 31.3% shows fibrosis and 14.1% shows advanced fibrosis [43]. The polymorphism T-455C in APOC3 gene and elevated serum triglycerides are associated with Indian NAFLD patients [44]. In another series, 56.5% T2DM patients have NAFLD, and the prevalence is higher in females (60%) than males T2DM patients [45]. NAFLD is the commonest liver disease in Indian psoriatic patients also [46]. Coronary artery disease (CAD) is more prevalent in the NAFLD compared to non-NAFLD; It is a surrogate

and fairly reliable marker of risk for CAD among type 2 diabetic patients [47]. According to Duseja NAFLD is the commonest cause of unexplained elevation of SGPT and cryptogenic cirrhosis and hepatocellular carcinoma in Indian patients. Insulin resistance and full blown metabolic syndrome are highly prevalent in Indian patients with NAFLD [48]; 51.4% of patients of NAFLD have metabolic syndrome [49]. And it is really threatening news that 3% of 5–12 years Indian children have NAFLD [50].

In Sri Lanka Incidence rate of diabetes are 64.2 per 1000 person-years among NAFLD persons [51]. NAFLD is an independent predictor of developing diabetes mellitus [51]. Increased age and presence of NAFLD conferred a higher mortality risk from ACS as predicted by GRACE score [52].

As like developed countries obesity, insulin resistance, diabetes, dyslipidemia are the major risk factors for development of NAFLD. But the paradox is that it could develop in nonobese population also and one fourth of NAFLD of South Asia is from nonobese people.

8. Global and South Asian publication trend on NAFLD

According to Zhang et al. study, with the globally increasing prevalence, nonalcoholic fatty liver disease (NAFLD) becomes the predominant cause of chronic liver disease. The global scientific research articles relevant to NAFLD revealed 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 3**). Bibliometric results suggest that the obviously rapid growth of the

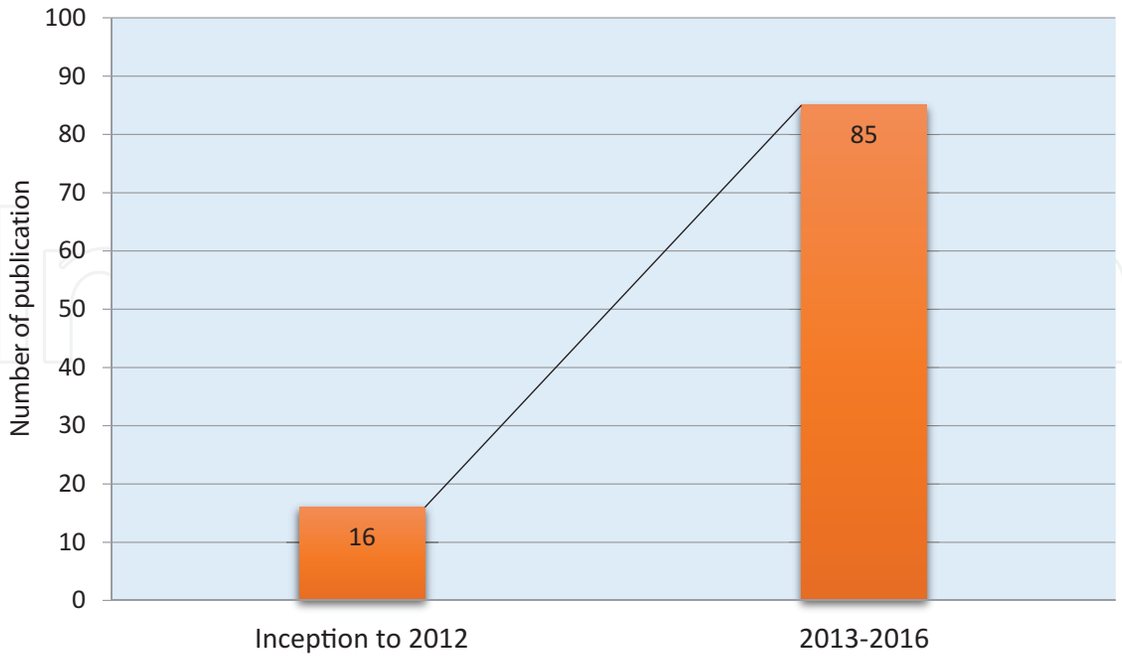

Figure 3. Trend of number of publication on NAFLD of South Asia (published in PubMed).

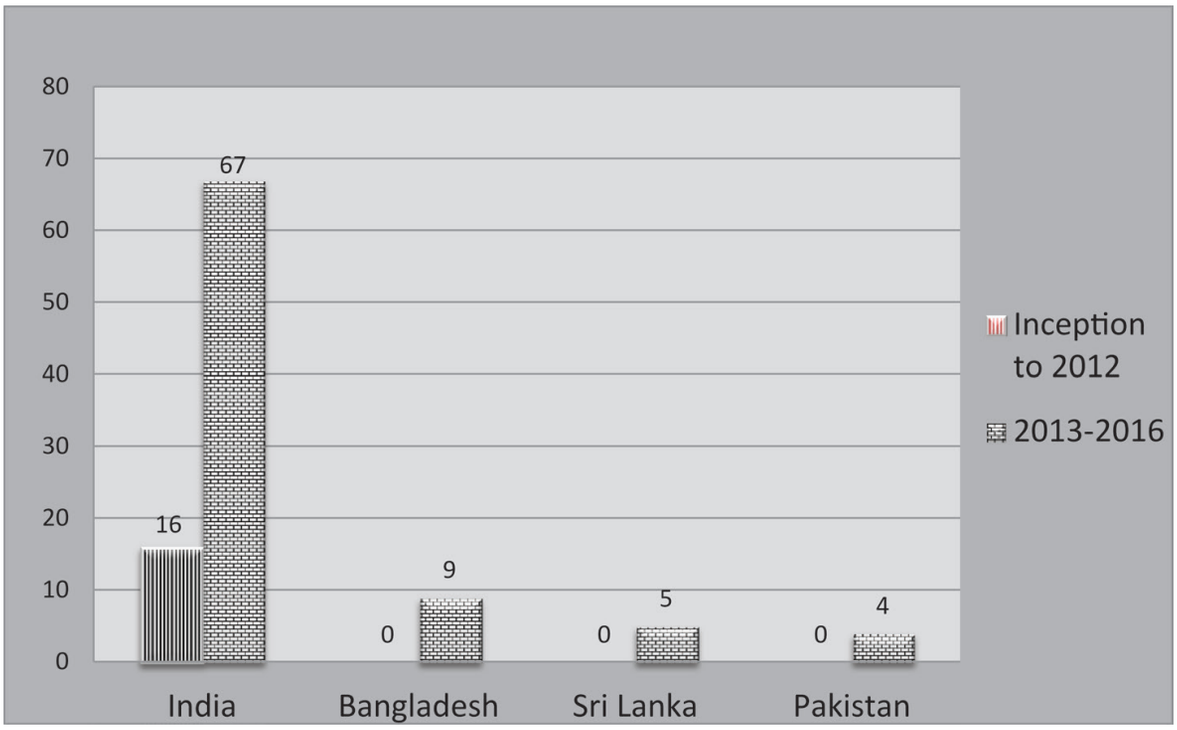

Figure 4. Article on NAFLD publication in South Asia Trend in PubMed from inception-2016.

articles in recent years appears to be associated with the accelerating incidence of NAFLD and its cofactors such as metabolic syndrome. In this study we found that, from inception to 2012 only 16 Indian research articles have been published in PubMed. Where from 2013 to 2016 total 85 research articles of India, Bangladesh, Sri Lanka and Pakistan has been published in PubMed (**Figure 4**). This phenomenon indicate that, how NAFLD is growing in South Asia.

9. Conclusion

The increase in NAFLD will continue to burden the health care system, especially because of its association with obesity, IR and metabolic syndrome. Along with globalization the prevalence of NAFLD is increasing alarmingly. The prevalence of NAFLD has been increasing remarkably for the last 12 years. Currently it is not only a disease of the Western countries but also becoming a major challenge for South Asia region. NAFLD is not the disease for only obese people, but it is also common in nonobese. And if the condition remains untreated it can turn into cirrhosis and hepatocellular carcinoma. It is really a great threat for us that, NAFLD is being seeing among our subcontinent's children also. The burden of NAFLD and its severity projects that obviously it will be the biggest frontier of Hepatology in South Asia in near future.

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