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Non-alcoholic Fatty Liver Disease (NAFLD) - An Emerging Public Health Problem

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Abstract

NAFLD is an emerging problem in Asia, with raising prevalence and strong impact on the health care system. More and more people will suffer from not only the liver impairment of NAFLD but also the associated metabolic diseases e.g. DM and hypertension. The incidence of DM, hypertension, coronary heart diseases (CHD) and stroke will increase together with the prevalence of NAFLD and the health service expenditure will rise in coming decades. However the prevalence of and the metabolic diseases associated with NAFLD are not well studied in Asian populations. The objective of this project is to systematically review the articles related to NAFLD.

Keywords: Non-alcoholic fatty liver disease; Triglycerides; Intra peritoneal fat; Metabolic diseases

Introduction

Non-alcoholic fatty liver disease (NAFLD) represents a spectrum of medical conditions in which there is increased infiltration of fat, predominantly triglycerides, inside hepatocytes. NAFLD is defined when there is macro vesicular steatosis inside liver cells exceeding 5% of liver weight, in the absence of significant ethanol consumption or other specific causes of liver diseases [1].

Although NAFLD may occur in people with normal body weight, it is strongly associated with obesity. The prevalence among obese people (body mass index more than 30 kg/m^2) in the United States has been reported as 80-90% [2]. Body mass index (BMI) of more than 35 kg/m^2 and an intraperitoneal fat area of more than 158 cm^2 are strong predictors of NAFLD [3-5]. Besides of obesity, hyperlipidemia and type 2 diabetes mellitus (DM) is associated with NAFLD [2].

Increased fat accumulation in liver or fatty liver disease can also be secondary to a number of causes, including excessive alcohol consumption, drugs (especially chemotherapeutic agents e.g. methotrexate, tamoxifen), hepatic toxins (e.g. arsenic, carbon tetrachloride), chronic viral hepatitis (e.g. hepatitis B and hepatitis C viral infection) and congenital storage diseases (e.g. Wilson disease, hemochromatosis) [6,7].

NAFLD may progress through three different stages, from hepatic steatosis to steatohepatitis and finally to cirrhosis [8,9]. Hepatic steatosis represents simple increase in accumulation of fat in liver, without evidence of inflammation or liver damage. Inflammation and liver damage is however present in steatohepatitis. Both hepatic steatosis and steatohepatitis are potentially reversible with timely intervention. Cirrhosis represents irreversible liver damage with fibrosis. NAFLD-related cirrhosis 6 may also result in liver cancer or hepatocellular carcinoma, although it is less common than in cirrhosis secondary to excessive alcohol consumption and chronic viral hepatitis.

Fatty liver disease and alcohol consumption

Excessive ethanol intake is one of the most important causes of fatty liver disease. Although there is strong and consistent evidence on ethanol induced liver damage, there is still a lack of general consensus on what should be the meaning of "excessive alcohol consumption" [10]. In the Dionysos cohort [11], it was reported that 30 g of alcohol intake per day was the threshold of alcohol induced liver damage. However, other clinical studies suggested that the individual susceptibility to ethanol induced liver toxicity was highly variable in a given population [12]. It is now generally postulated that the relationship between alcohol consumption and liver damage is probably multi-factorial. Besides of amount of ethanol intake per day, other factors such as drinking patterns, drinking habits, genetic factors and gender also determine Individual vulnerability to ethanol induced hepatic toxicity [12]. Hepatic steatosis can be induced by drinking 20-30 g of ethanol per day [13], which is now generally regarded as the upper limit in NAFLD research.

Epidemiology of non-alcoholic fatty liver disease in Western countries

NAFLD is a common problem in Western countries. It is one of the most common causes of chronic liver disease in both children and adults in the United States. The current Western diet with high saturated fat and fructose is believed to be the culprit. It had been reported that the prevalence of NAFLD was as large as 25-35% in the general population of United States [2,14]. In another study involving 31 million Americans, NAFLD has been reported to affect 31% of men and 16% of women [15]. Although the true prevalence of NAFLD in children of the United States is unknown, it has been estimated to range from 2-10% and the prevalence may even be as high as 80% in obese children [16]. Other countries report similarly high prevalence rates.

NAFLD prevalence in a Canadian autopsy study was 29% [5]. In Europe, NAFLD prevalence ranged from 16% in Italy [17] to 24% in Sweden [18-20]. In the Dionysos cohort [11] of apparently healthy subjects aged 12 to 65 years living in Northern Italy, the prevalence of NAFLD after excluding alcoholism, hepatitis B and C infection was 55%. It was more common in obese (91%) than in overweight (67%) and normal weight subjects (24.5%) ($p<0.0001$). The mean prevalence

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of fatty liver in Western Countries is generally accepted to range from 20-60%. It is more common in men than in women, with a ratio of 3: 1.

Inclusion and exclusion criteria

The inclusion and exclusion criteria set a priori were used to select relevant papers from those retrieved. The inclusion criteria were: a) estimated prevalence of NAFLD and/ or b) determined the metabolic risk of NAFLD in Asian countries, c) quantified the adjusted odds ratio of NAFLD risk factors (such as obesity, DM, hypertension, hyperlipidemia), d) original studies and e) human studies. The exclusion criteria were:

a) review articles/ protocols/ guidelines/ abstracts/ unpublished results/ conference presentations, b) biochemistry/ gene/ genotype/ cellular/ histology studies, c) studies only focusing on the abnormal population group such as those with smoking, DM, liver disease and obesity, d) studies which recruited the subjects with other causes of fatty liver or concurrent liver diseases, such as excessive alcohol consumption/ viral hepatitis (hepatitis B virus and hepatitis C virus) and e) studies which included non-Asian subjects. There was no limitation or restriction on the age, gender, residency and occupations of the subjects of the studies.

Citation assessments

Based on International guidelines such as STROBE (Strengthening the Reporting of Observational studies in Epidemiology) following ten studies were analyzed [21]. Study design, sample size, representative sample size, selection bias, reliability and validity formed the bases for selecting studies that are related to the review in question and the characteristics of the studies are cited in Table 1.

Definitions of obesity, abdominal obesity, insulin resistance and metabolic syndrome

Obesity is generally defined as BMI more than 25 kg/m^2 while abdominal/ central obesity is usually defined as waist circumference more than 90 cm in men or more than 80 cm in women, following the International Diabetes Institute/ Western Pacific World Health Organization/ International Obesity Task Force [22]. Insulin resistance is estimated by homeostasis assessment (HOMA): fasting insulin (mIU/ml) × fasting glucose (mmol/l)/22.50. Individual whose HOMA

References	Sample size	Demographics	Study Design	Diagnosis of NAFLD	Prevalence of NAFLD	Significant metabolic risk factors and disease (adjusted OR and CI)
Alavian et al. [33]	996	Iran children Age-17-18 years	Cross sectional stratified multistage random sampling	US	7.10%	IR (4.4.CI=1.6-12.3).). hypertriglyceridemia (2.5 CI=1.3-4.8). Elevated TC (2.8 CI=1.5-5.1) elevated LDL-C(2.8 CI=1.5-5.3) Abdominal obesity, HT, high FPG and low HDL-C are NOT significant risk factors
Das et al. [24]	1911	Indian adults ≥ 18years of age living in rural areas	Cross sectional stratified random sampling (1 ,3 subsample i.e. every 3rd person was selected)	US and CT	8.70%	Obesity(4.3 CI=1.6-11.5)abdominal obesity(3.6 CI=1.7-7.2) high family income(2.4CI=1.2-5.0) elevated FBG(2.6 CI=1.5-4.6)
Dassanayake et al. [27]	2,985	Sri Lankan adults aged35-64 years living in urban areas	Cross sectional stratified random sampling by different age groups	US	32.60%	Obesity (3.75.CI=3.07-4.5), IR (2.16.CI=1.73-2.68) HT (1.53.CI=1.25-1.88) raised FBG (1.7.CI=1.39-2.08) Hyper triglyceridemia (1.33. CI=1.08-1.63)
Fu [29]	220	Taiwan adolescent students Aged 12-13 years	Cross sectional stratified random sampling	US	39.3% (16% in non-obese 50, 5% in over weight 63.5% in obese)	Obesity in (5.98), elevated Non HDL-C (3.8 per mg/dL)
Lee et al. [26]	13,768	Korean adults recruited from a health promotion center	Cross sectional	US	25%	Obesity (4.4-9.7) gender (0.6 women *vs* men)
Lee et al. [25]	589	Korea consecutive potential Liver donor, aged 21-41 years	Cross sectional	Liver biopsy	51.4	Age>30(2223,CI=1.175-4.207) obesity (5.320, CI=2.764-10.240). Hypertriglyceridemia (2.253, CI=1.140-4,450)
Li et al. [28]	8,925	Chinese adults Employee of a company attending annual checkup in 2005	Cross sectional	US	11.8% (11.6% in men and 12.1% in women)	Hyperuricaemia (1.29.CI=1.067-1.564) obesity (1.174.CI=1.120-1.231) age (1.088CI=1.080-1.096) abdominal obesity (1.09CI=1.071-1.110) Hyper triglyceridemia (1.48.CI=1.385-1.582). elevated HDL-C (0.525 CI=0.373-0.737) elevated LDL-C (1.450.CI=1.287-1.631) elevated FPG-(1.216. CI=1.131-1.308)
Mohan et al. [30]	541	Indian adults living in Urban area	Cross sectional stratified random sampling	US	325 (men 35.1% Women 29.1%)	Abdominal obesity (2.0CI=1.3-3.1), obesity (2.4CI=1.6-3.5), DM (3.4CI=2.2-5.3). IR (2.1CI=1.4-3.2) hypertriglyceridemia (1.8CI=1.2-2.7) hypercholesterolemia (1.8CI=1.2-2.6) elevated LDL-C (1.5.CI=1.0—2.3).low HDL- C (2.0.CI=1.4-3.0) MS (2.8.CI=1.9-4.2)
Shitata et al.	3,139	Japanese Male Workers of a company aged at or above 40 years	Observational cohort study	US	ND	DM (4.6.CI=3.0-6.9) (incidence of DM in NAFLD Patients 2,073 per 100,000 person years, incidence of DM in non-NAFLD group is 452 per 100,000 person-years
Zeber-Sagi et al.	326	Israel adults	Cross sectional, stratified random sampling	US	30% (38% in men and 21% in women	Male gender (2.8 CI=1.3-3.3) IR (5.8 CI=2.0-17.2) abdominal obesity (2.9 CI=1.3-6.4). hypertriglyceridemia (2.4, CI=1.3-4.5)

Table 1: Summary of the citations on the prevalence and the risk factors of NAFLD in Asia.

insulin resistance values above the third quartile for the non-diabetic population (i.e. >2.58) are classified to have insulin resistance (HOMA-IR) [23]. Metabolic syndrome, sometimes denoted as Syndrome X or dysmetabolic syndrome, is generally defined based on modified National Cholesterol Education Program and Adult Treatment Panel III (NCEP-ATPIII) guidelines [24] and International Diabetes Institute/Western Pacific World Health Organization/ International Obesity Task Force [22]. A subject is classified as having metabolic syndrome if three or more of the following criteria were fulfilled: 1) elevated triglycerides (>150 mg/dl), 2) low high-density lipoprotein (HDL)cholesterol (<40 mg/dl in men or <50 mg/dl in women), 3) high blood pressure(>130/85 mmHg), 4) elevated fasting blood glucose (>110 mg/dl) and 5) abdominal obesity (waist circumference>90 cm in men or >80 cm in women).

A number of studies in different countries documented that the prevalence of NAFLD in men was significantly higher than in women [25-45].

In India, NAFLD was more prevalent (21%) in families with high income [25] and in China NAFLD prevalence was higher in urban (20.3%) than rural areas (11.1%) [35]. The prevalence of NAFLD in children also varied by country, with 39.8% prevalence in adolescent students aged 12-13 years in Taiwan [30], 7.1% in children aged from 7 to 16 years in Iran [34], and 1.3% among children aged 7 to 18 years in China [35]. Studies focusing on the Asian elderly were very scarce. NAFLD prevalence among Israeli elderly aged 81 to 90 years was 46.2% [43]. Both obesity and abdominal obesity were independent and significant risk factors of NAFLD, with reported adjusted odds ratios 1.17-7.21 and 1.09-3.6, respectively [25,28,29,31-33,37-40,44]. Consistent with the reported impact of obesity, the insulin resistance, elevated fasting blood glucose and type 2 DM were significant risk factors for NAFLD with adjusted odds ratio of 2.1-5.8, 1.42-2.6 and 1.7-4.6, respectively [25,28,29,31,33,36,38,40,42,45].

NAFLD was associated with dysfunction of lipid metabolism or dyslipidemia with odds ratios of 1.45 - 1.8 (elevated total cholesterol), 1.45 - 1.5 (elevated low-density lipoprotein cholesterol), 1.61 - 2.0 (low high-density lipoprotein cholesterol) and 1.33-3.51 (elevated triglyceride), respectively [28,29,31,33,37-40,45]. Others have suggested an association between NAFLD and elevated blood pressure (blood pressure higher than 130/85 mmHg) with adjusted odds ratio of 1.53 - 3.7 [28,45]. Other studies reported that metabolic syndrome adjusted odds ratio between 2.37 to 2.8 [31,33] and elevated blood uric acid level (>7 mg/dl in men and >6 mg/dl in women) adjusted odds ratios ranging from 1.29 to 2.3 [26,27,29,38,46] were associated with NAFLD.

In summary, NAFLD was associated with obesity, abdominal obesity, elevated fasting blood glucose, insulin resistance, DM, elevated total cholesterol, elevated low-density lipoprotein (LDL) cholesterol, low HDL cholesterol, elevated triglyceride, hypertension, hyperuricemia and metabolic syndrome in adults. As contrast to adults, only obesity, elevated total cholesterol, elevated LDL cholesterol, elevated triglyceride and insulin resistance were associated with NAFLD in children and adolescents [30,34] but not abdominal obesity, hypertension, elevated fasting blood glucose and low HDL cholesterol [34].

Non-alcoholic fatty liver disease: why is it important?

NAFLD represents wide spectrum of liver damage, varying from simple steatosis (increase in fat accumulation), to steatohepatitis (inflammation) and liver cirrhosis (irreversible fibrosis). The natural history of NAFLD globally is currently unclear. Although it is generally believed that most patients are asymptomatic, NAFLD can potentially progress into cirrhosis and even hepatocellular carcinoma. The true incidence of chronic hepatitis, cirrhosis and hepatocellular carcinoma related to NAFLD is still unclear and the data is lacking.

According to the Queen Mary Hospital – liver clinic records, 1.5% of patients with chronic liver disease were attributed to NAFLD [47]. Among cases of chronic hepatitis of unknown etiology, the prevalence of biopsy proven non-alcoholic steatohepatitis was reported to be 16% [48]. As suggested by research elsewhere, 10-11% of these patients may progress to liver cirrhosis [49]. Some of these patients may require liver transplantation due to severe liver function impairment or may develop liver cancer [50].

However, what is much more important and crucial is the salient but high risk of NAFLD patients to develop other metabolic diseases. Like in Caucasians, studies have shown that NAFLD in Asians is strongly associated with metabolic disorders including glucose intolerance, DM, hyperlipidemia (high cholesterol and high triglyceride) and hyperuricemia. These metabolic disorders are good predictors of NAFLD.

In India, 41% (seven) patients with NAFLD developed hypertension or DM during a 6 year-follow-up [51,52] and had higher risk of CHD which reflected the findings of overseas research [36,41,51,53]. Therefore, NAFLD is not just a liver disease. Patients with NAFLD are also at risk of developing other metabolic diseases (e.g. DM, hypercholesterolemia and hypertriglyceremia), perhaps much higher than the risk of liver cirrhosis and hepatocellular carcinoma.

Non-alcoholic Fatty Liver Disease: An Emerging Public Health Problem in Asia

At present NAFLD is regarded as a liver manifestation of metabolic disorder, which more commonly affects those in affluent Western countries where the average prevalence is estimated up to 20-40%. Although a number of studies on the NAFLD of Asian countries have been published, there are some difference among these studies in terms of sample selections, population subgroup heterogeneities, study designs and diagnosis criteria. Most of these studies are city or hospital based. As a result, there is wide variation of the reported prevalence and the true nationwide prevalence of NAFLD in Asian countries is difficult to determine. However, the prevalence of NAFLD in Asia has been reported up to 51.5% [37], which is comparable to the Western countries.

Similar to results in Western world, obesity (especially central obesity), impaired glucose metabolism, DM, hyperlipidemia and metabolic syndrome are important risk factors and predictors of NAFLD in Asians. Because of the industrialization, affluence and Westernization of lifestyle, the prevalence of obesity, DM, hyperlipidemia and metabolic syndrome has rapidly increased in recent decades globally. Asia has followed suit, the prevalence of DM and obesity has risen exponentially (2- to 5- fold) over a period of 20 years in Asia-pacific region [54].

Therefore it is not surprising that the rapidly rising prevalence of obesity and DM has put a very large proportion of Asian populations at risk of developing NAFLD, and the prevalence of NAFLD is expected to increase in coming decades.

Visceral adipose mass is another important predictor of NAFLD, independent of BMI [55]. As Asians have higher proportion of visceral fat and lower proportion of lean body mass (sum of the weight of

bones, muscles and organs) compared with Caucasians of similar BMI [56], the prevalence of NAFLD in normal BMI in Asians is higher than that in Caucasians. Therefore, even though only a small percentage of Asians would be classified as obesity according to Western criteria, the prevalence of NAFLD is still high.

Non-alcoholic fatty liver disease in children and adolescents

NAFLD in children was first documented in 1983 in United States [57]. The first reported pediatric case of NAFLD induced cirrhosis was an 11-year-old Japanese child who had been obese since the age of 3 [58]. Compared with adults, there is sparse published research on the epidemiology of NAFLD in Asian children and adolescents [30,34,35,59,60]. As selection bias is a feature of many of these studies, the true prevalence of NAFLD in children and adolescents is unclear. However, there is strong evidence of association between obesity and NAFLD in children. Childhood NAFLD is also more common in boys, and in children of 10 to 15 years of age.

Implications of NAFLD to India

Like other urbanized countries, DM, CHD and stroke are important contributors to the burden of healthcare in Hong Kong. The prevalence of DM was estimated up to 9.8% in India [61]. A retrospective cohort observation study estimated that the mean annual total cost of Type 2 DM in a patient was about $ 13,457, of which the government paid 78.4% [62]. In 2004, DM contributed up to 6.4% of the Authority's public sector expenditures on health and 3.9% of the total India healthcare expenditure [62]. The cost markedly increased if the diagnosis was delayed and the complications were present. Therefore early detection and treatment of DM before the appearance of complications not only improves the prognosis of the patients but also save the budgets. However, it had been estimated that up to 31.9% of DM was undiagnosed in India [63,64].

Stroke and CHD are the leading causes of death in India [64]. The average management cost of CHD was estimated to be about $85,324 India per patient per year [65]. As NAFLD is strongly associated with metabolic disorders including hyperlipidemia, DM and hypertension – the risk factors for stroke and CHD, increasing NAFLD will increase the management cost of CHD and stroke.

However, the level of alertness of NAFLD remains low in India. A random telephone survey recruiting 521 India adults (aged>18 years), reported that up to 83% of the respondents had never heard of the term "NAFLD".

As a significant risk factor of stroke, CHD, DM and hypertension, public awareness of NAFLD should be improved. More health promotion programs and educations focusing on NAFLD by the Government should be provided. Guidelines on the management of patients with NAFLD should be designed and endorsed among the primary health care providers. People with NAFLD should be screened and regularly followed up for the associated metabolic diseases. Aggressive treatments of NALFD such as lifestyle modification and anti-obesity treatment should also be actively considered and provided (Figure 1).

Directions for Further Research

The true nationwide prevalence of NAFLD in most Asian countries still remains uncertain. Most NAFLD epidemiological studies were confined to a city, a company, a hospital or a clinic and may not represent the whole population of the country.

Therefore, it is difficult to interpret and compare these various results from different Asian countries. Countrywide cross-sectional studies with stratified random sampling would be much more representative and easier to compare.

There is strong evidence of the association between NAFLD and other metabolic disorders such as DM and hyperlipidemia, which are also the risk factors of CHD and stroke. The incidence of these metabolic disorders in NAFLD patients is however unclear. Furthermore early NAFLD (simple steatosis and steatohepatitis) is potentially reversible and can be treated by lifestyle modification and anti-obesity therapy.

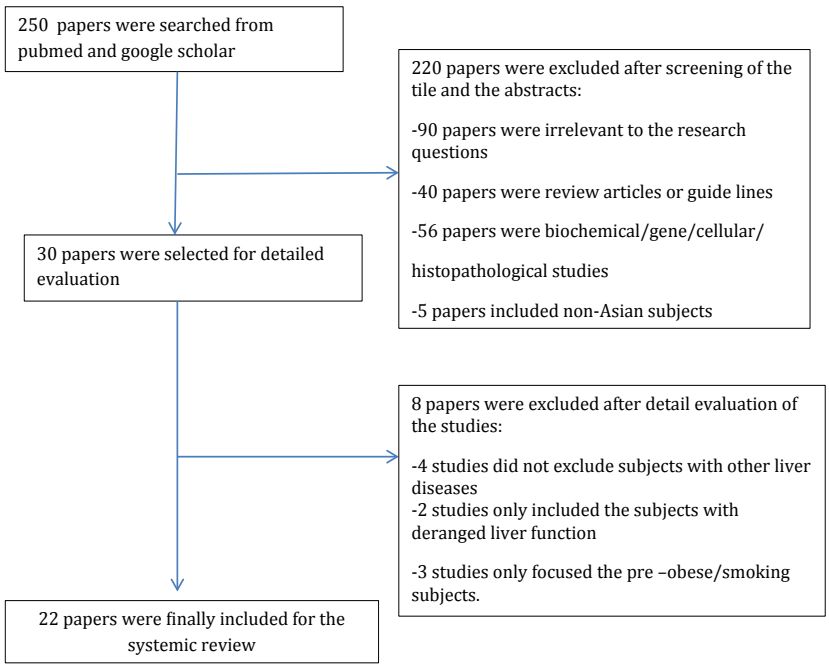

Figure 1: Inclusion and exclusion process of the systematic review.

However it is still uncertain whether the incidence of the metabolic diseases and thus the risk of cardiovascular diseases reduce after treatment of NAFLD. Prospective cohort studies would be necessary to answer these questions. The prevalence of childhood obesity and NAFLD is rising in Asia. Weight reduction is probably the only effective treatment for NAFLD in children so far, but it is still unknown how much weight should be lost to achieve the optimal outcome. .Furthermore, only few pharmacological treatments and anti-obesity drugs have been tested and investigated in children.

Limitations of this Systematic Review

As a result of industrialization, affluence, Westernization of lifestyle, lack of physical activity and over nutrition, the prevalence of NAFLD in Asian countries keeps rising and is comparable to the Western countries in recent decades. Similar to the results in Caucasian studies, obesity, glucose intolerance, DM, hyperlipidemia, hypertension and hyperuricemia are significant risk factors of NAFLD. Meanwhile, NAFLD is a strong predictor of metabolic diseases such as DM, hyperlipidemia and hypertension which are also the risk factors of cardiovascular diseases e.g. CHD and stroke. Only a small proportion of NAFLD patients may progress to liver cirrhosis and even hepatocellular carcinoma over a long period of time. However, more importantly, NAFLD patients may have much higher risks of developing diseases such as DM, hypertension, CHD and stroke.

Yet, the level of alertness of NAFLD remains low in India. As a significant risk factor of stroke, CHD, DM and hypertension, public awareness of NAFLD should be improved. More health promotion programs and educations focusing on NAFLD by the Government should be provided. Guidelines on the management of patients with NAFLD should be designed and endorsed among the primary health care providers. People with NAFLD should be screened and regularly followed up for the associated metabolic diseases. Aggressive treatments of NALFD such as lifestyle modification and anti-obesity treatment should also be actively considered and provided.

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