SYSTEMATIC REVIEWS

Non-alcohol fatty liver disease in Asia: Prevention and planning

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Abstract

AIM: To review all of epidemiological aspects of non-alcoholic fatty liver disease (NAFLD) and also prevent this disease is examined.

METHODS: We conducted a systematic review according to the PRISMA guidelines. All searches for writing this review is based on the papers was found in PubMed (MEDLINE), Cochrane database and Scopus in August and September 2014 for topic of NAFLD in Asia and the way of prevention of this disease, with no language limitations. All relevant articles were accessed in full text and all relevant materials was evaluated and reviewed.

RESULTS: NAFLD is the most common liver disorder in worldwide, with an estimated with 20%-30% prevalence in Western countries and 2%-4% worldwide. The prevalence of NAFLD in Asia, depending on location (urban *vs* rural), gender, ethnicity, and age is variable between 15%-20%. According to the many studies in the world, the relationship between NAFLD, obesity, diabetes mellitus, and metabolic syndrome (MS) is quiet obvious. Prevalence of NAFLD in Asian countries seems to be lower than the Western countries but, it has increased recently due to the rise of obesity, type 2 diabetes and MS in this region. One of the main reasons for the increase in obesity, diabetes and MS in Asia is a lifestyle change and industrialization. Today, NAFLD is recognized as a major chronic liver disease in Asia. Therefore, prevention of this disease in Asian countries is very important and the best strategy for prevention and control of NAFLD is lifestyle modifications. Lifestyle modification programs are typically designed to change bad eating habits and increase physical activity that is associated with clinically significant improvements in obesity, type 2 diabetes and MS.

CONCLUSION: Prevention of NAFLD is very important

in Asian countries particularly in Arab countries because of high prevalence of obesity, diabetes and MS.

Key words: Non-alcoholic fatty liver disease; Metabolic risk factors; Asian countries; Prevention

Core tip: Today non-alcoholic fatty liver disease (NAFLD) is one of the main concerns of the medical world. NAFLD is identified as a main risk factor for chronic liver disease across the world. NAFLD is clearly linked with obesity, type 2 diabetes and metabolic syndrome (MS). The prevalence of NAFLD is lower in Asian countries than Western countries but, it has increased dramatically in recent years because of increasing rate of obesity, type 2 diabetes and MS in this region. The high prevalence of obesity with diabetes, and MS would increase the risk of NAFLD in recent years. So, prevention of these factors is the key strategy to reduce the incidence of NAFLD.

INTRODUCTION

Nowadays, non-alcoholic fatty liver disease (NAFLD) is a major health concern worldwide which is characterized by abnormal fat accumulation in liver cells[1,2]. The development process of NAFLD can be started from simple steatosis (NAFLD) to non-alcoholic steatohepatitis (NASH) and finally leads to cirrhosis and hepatocellular carcinoma in absence excessive alcohol intake[3,4]. NAFLD is one of the main cause of chronic liver disease in industrializes countries[5,6]. According to the American Association for the Study of Liver Disease Guidelines[7], liver biopsy is the gold standard for the diagnosis of NAFLD, nevertheless ultrasonography is more commonly used particularly in developing countries, because of increased health risks and high expenditures associated with liver biopsies[2]. So, the prevalence of NAFLD varies according to the method used to diagnosis and study population[7-9]. In generally, the prevalence of NAFLD ranges is from 6.3% to 33% worldwide, and prevalence of NASH is from 3% to 5% in general population[7,10]. Despite the low prevalence of NAFLD in Asian countries (12%-24%)[11], than in Western countries (> 20%)[12], it is identified as a main risk factor for chronic liver disorder in all over world[13]. In Asian countries, the prevalence of NAFLD varies in different countries, and is related to the age, gender, locality and ethnicity[11]. NAFLD prevalence increases with age[6], and also men (40-49 years) tend to get NAFLD earlier than women (over 50 years)[11,14].

According to the other studies especially in South-East region of Asia[15-18], more men than women had NAFLD. For diagnosis of NASH, liver biopsy is required and it's costly especially in low-income countries so the establish the prevalence of NASH is difficult. More than 30% of obese patients may have NASH and 12%-25% have fibrosis[2,19,20]. In predictors and diagnosis of NASH and fibrosis, diabetes and insulin resistance are the two main factors than body mass index (BMI)[21,22].

MATERIALS AND METHODS

We conducted a systematic review according to the PRISMA guidelines. All searches for writing this review is based on the papers was found in PubMed (MEDLINE), Cochrane database and Scopus in August and September 2014 for topic of NAFLD in Asia and the way of prevention of this disease, with no language limitations. All relevant articles were accessed in full text and all relevant materials was evaluated and reviewed. We extracted data on epidemiology of NAFLD, Burden and prevalence of NAFLD, risk factors characteristics association NAFLD, and prevention of NAFLD. We analyzed the data and reported the results in the tables and text.

RESULTS

Based on systematic reviews, defines NAFLD as a compound disorder delineated by a set of metabolic syndrome (MS) risk factors, usually related to obesity, diabetes, hypertension and dyslipidemia[3,11,23,24]. Insulin resistance is the main factor in NAFLD pathogenesis, because of association between NAFLD and MS[11]. The presence of obesity and type 2 diabetes mellitus (T2DM) significantly increases the risk of NAFLD[11]. Available data from previous studies indicate that the prevalence of NAFLD likely increases 65%-70%[2,25-27] in T2DM populations and greater than 75% and 90% in obese people[28,29] and morbidly obese patients[30,31], respectively. In addition, NAFLD can be increase the risk of cardiovascular events in obese and diabetic people[2,32].

Obesity
Obesity has doubled worldwide since 1980. In Asia also, based on several national health surveys[33-36] prevalence of overweight and obese subjects has increased in the past few decades, but it varies between countries[37] [Table 1: Provides the 2010 World Health Organization (WHO); Global status report on non-communicable disease statistics for overweigh and obesity prevalence in Asian countries, Data adjusted for 2008 for comparability]. The prevalence of obesity in eastern Asia (*e.g.,* China, Japan, South Korea and Taiwan), Southern Asia (*e.g.,* Bangladesh, India, Pakistan and Sri Lanka), and South-Eastern Asia (*e.g.,* Malaysia, Philippines, Singapore, Thailand and Vietnam) is quite low compared with developed countries such as the United States[38-40]. The

Table 1 Prevalence of overweight and obesity in Asian countries, estimates for 2008 (%)

Country	Overweight[1]			Obesity[2]		
	Males	Females	Total	Males	Females	Total
Kuwait	78.4	79.5	78.8	37.5	49.8	42.0
Saudi Arabia	69.1	68.8	69.0	28.6	39.1	33.3
Qatar	73.1	70.2	72.3	31.3	38.1	33.2
Egypt	60.4	75.3	67.9	21.4	44.5	33.1
Bahrain	70.9	70.3	70.6	29.5	38.0	32.9
UAE	71.3	71.2	71.3	30.0	39.0	32.7
Turkey	59.7	64.1	61.9	21.7	34.0	27.8
Lebanon	66.1	57.9	61.8	25.8	29.0	27.4
Iraq	59.5	65.1	62.3	20.6	33.4	27.0
Oman	56.9	54.2	55.8	18.9	23.8	20.9
Iran	46.0	56.8	51.4	12.4	26.5	19.4
Malaysia	42.1	46.3	44.2	10.4	17.6	14.0
Thailand	26.5	37.4	32.2	5.0	12.2	8.8
South Korea	34.3	29.2	31.8	7.2	8.3	7.7
Singapore	33.9	26.4	30.2	7.0	7.1	7.1
Philippines	24.6	28.4	26.5	4.6	8.0	6.3
China	25.5	25.4	25.4	4.7	6.7	5.7
Pakistan	19.1	27.1	23.0	3.3	7.8	5.5
Japan	30.1	19.2	24.4	5.8	4.4	5.0
India	9.9	12.2	11.0	1.3	2.4	1.9
Vietnam	9.5	10.9	10.2	1.2	2.1	1.7
Bangladesh	7.4	7.8	7.6	0.9	1.3	1.1

[1]Overweight: The percentage of the population aged 20 or older having a body mass index (BMI) $\geq$ 25 kg/m^2; [2]Obesity: The percentage of the population aged 20 or older having a BMI $\geq$ 30 kg/m^2. Adapted from World Health Organization, non-communicable diseases report[41]. UAE: United Arab Emirates.

highest rate of obesity in these regions of Asia are in Malaysia and Thailand, where 14% and 8.8% of adults are reported to be obese, respectively[41]. The lowest obesity rates in these regions are in the less developed parts of Asia: 1.1% in Bangladesh, 1.7% in Vietnam and 1.9% in India[36,41]. In contrast to these regions of Asia, in West Asian countries (Middle East countries; *e.g.,* Iran, Iraq, Bahrain, Egypt, Kuwait, Saudi Arabia, Oman and Qatar) prevalence of obesity is very high and almost is equal with the Western developed countries. So that in countries such as Kuwait (42%), Saudi Arabia (33.3%), Qatar (33.2%) and Egypt (33.1%), the prevalence of obesity is higher than United States (33%)[41]. Except in Japan, Rates of obesity among women are twice that of men in all Asian countries.

NAFLD prevalence is much higher estimates in obese people[42]. Population-based survey from Iran reported that obesity and MS are the most predictive factors of NAFLD[43]. In addition, in the other Population-based study conducted China, the relationship between NAFLD and obesity have been reported so that, among 661 patients with fatty liver, 611 (92%) patients were obese[44]. The high prevalence of obesity in the West of Asia also increases the risk of NAFLD[11].

Diabetes mellitus
Diabetes mellitus is present as one of the biggest public health problems of the recent century[45]. The International diabetes federation (IDF)[46] estimated the global burden diabetes was 382 million (comparative prevalence: 8.3%) in 2013 and it would be likely more than double to 592 million (comparative prevalence:

8.8%) by 2035. Approximately 175 million people worldwide living with diabetes are unaware of their disease[46]. According to the 6th edition of the Diabetes Atlas in 2013[46], Saudi Arabia (24%), Kuwait (23.1%) and Qatar (2.9%) are among the world's top ten countries with the highest prevalence of diabetes in 20-79 years population are in the Middle-East countries. And also from the ten countries with the highest number of diabetic people (20-79 years), five countries are located in Asia that which includes; China, India, Indonesia, Egypt and Japan. T2DM consist 85% to 95% in high-income countries and even higher percentage in low and middle income countries[47]. It is one of the major health problems in the world, and also is known as an important risk factor for NAFLD[48,49]. T2DM prevalence is increasing in the world[50] and also in Asian countries the prevalence rate of it has increased during the past three decades[51]. Increasing the T2DM in Asian countries for the following reasons is different from the countries because of the short time spread, and that can be seen in a younger age group and people with much lower BMI[37]. Many ethnic studies on Asian population pointed out, that they have more abdominal obesity and visceral fat (3%-5%) than other ethnic groups[52-54]. Improper accumulation of fat in abdominal and visceral adiposity can cause to increase hepatic insulin resistance and T2DM, which can cause an abnormal accumulation of fat in the liver[55,56]. This rapidly-growing prevalence of T2DM among the Asian countries is related to the rapid economic developments, aging, urbanization, changes in nutrition, and increases in sedentary lifestyles, and also increases with increasing prevalence of obesity and

Table 2 Prevalence of diabetes in Asian countries, estimates for 2013				
Country	Adult population (20-79) in 1000s	Diabetes cases (20-79) in 1000s	Diabetes national prevalence (%)	[1]Diabetes comparative prevalence (%)	Diabetes related deaths (20-79)
Saudi Arabia	18056.84	3650.89	20.22	23.87	22113
Kuwait	2293.74	407.53	17.77	23.09	1122
Qatar	1796.42	282.53	15.73	22.87	651
Bahrain	974.96	168.66	17.30	21.84	706
UAE	7443.81	745.94	10.02	18.98	1385
Egypt	48276.39	7510.60	15.56	16.80	86478
Lebanon	3295.49	478.96	14.53	14.99	6637
Oman	2493.25	199.78	8.01	14.24	1214
Malaysia	18919.44	1913.24	10.11	10.85	24049
Singapore	4058.27	498.19	12.28	10.42	4134
Iran	52145.45	4395.93	8.43	9.94	38002
Iraq	16473.21	1226.22	7.44	9.50	17643
India	760429.73	65076.36	8.56	9.09	1065053
China	1023050.42	98407.38	9.62	9.02	1271003
Yemen	11568.55	708.12	6.12	8.45	9892
Taiwan	17605.38	1721.06	9.78	8.30	-
Afghanistan	12619.61	794.70	6.30	8.27	18864
Pakistan	99369.82	6712.70	6.76	7.90	87354
South Korea	37365.67	3323.90	8.90	7.48	30836
Philippines	54210.53	3256.21	6.01	6.86	54535
Bangladesh	92271.61	5089.04	5.52	6.31	102139
Vietnam	61387.55	3299.11	5.37	5.81	54953
Thailand	49049.75	3150.67	6.42	5.67	66943
Japan	95304.38	7203.78	7.56	5.12	64680

[1]All comparisons between countries should be done using the comparative prevalence, which is adjusted to the world population. Adapted from International Diabetes Institute[46]. UAE: United Arab Emirates.

MS[57,58].

Middle East region, particularly Arab speaking countries have some of the highest rate of diabetes in the world[59]. The prevalence of T2DM has increased dramatically in this region over the last three decades because of industrial development. Most of countries in the Middle East such as Kuwait, Saudi Arabia, Qatar, Bahrain and the United Arab Emirates are the world's leaders in term of T2DM prevalence[60]. In both developed and developing countries diabetes is the main cause of NAFLD, and also the prevalence of NAFLD is higher in people with diabetes than in non-diabetic[61] (Table 2: Provides the 2013 IDF statistics for diabetes prevalence in Asian countries).

MS

MS is known as a collection of interrelated abnormalities that increase the risk of T2DM and NAFLD[62]. According to the available data, experimental and epidemiological studies describe the NAFLD as the hepatic manifestation of MS[63,64]. Today prevalence of MS is increasing and the main risk factors associated with MS are abdominal obesity, hypertension, dyslipdemia, insulin resistance and glycemia intolerance[24]. Different criteria have been introduced in recent years to detect MS. The first criteria definition of MS was published in 1998 by WHO, according to this definition impaired glucose tolerance, and impaired fasting glucose, T2DM or insulin resistance are known as essential components of the MS, along with at least two of the following parameters: hypertension (> 140/90 mmHg), obesity (BMI = 30

kg/m^2), hypertriglyceridemia ($\geqslant$ 150 mg/dL) or high density lipoprotein cholesterol (HDL-C) values (< 35 in males and < 40 in females) and microalbuminuria ($\geqslant$ 20 μg/min)[65-67]. On the other hand, in 2001, the National Cholesterol Education Program Adult Treatment Panel Ⅲ (NCEP-ATP Ⅲ) published a new set of criteria of MS that included waist circumference as define obesity ($\geqslant$ 102 cm in males and $\geqslant$ 88 cm in females), arterial hypertension ($\geqslant$ 130/85 mmHg), fasting glucose($\geqslant$ 110 mg/dL) and blood lipids as HDL-C values (< 40 mg/dL in males and < 50 mg/dL in females) and hypertriglyceridemia ($\geqslant$ 150 mg/dL)[68]. The NCEP-ATP Ⅲ definitions differed from WHO and European Group for the study of Insulin Resistance definitions in that insulin resistance is not necessary for diagnostic. In 2005, the IDF published other criteria to define the MS which proposed abdominal obesity as the essential components of the diagnosis of MS, abdominal obesity (Europe men: $\geqslant$ 94 cm, Europe women $\geqslant$ 80 cm and for Asian men: $\geqslant$ 90 cm, Asian women $\geqslant$ 80 cm), arterial hypertension ($\geqslant$ 130/85 mmHg), fasting glycaemia ($\geqslant$ 100 mg/dL), HDL-C values (< 40 mg/dL in males and < 50 mg/dL in females) and hypertriglyceridemia ($\geqslant$ 150 mg/dL)[69-72]. The American Heart Association/National Heart Lung and Blood Institute (AHA/NHLBI) published a new set of criteria of MS that abdominal obesity is not required as a risk factor. The definition provided by the AHA/NHLBI of abdominal obesity with IDF guidelines was quite different[70,73]. So, in recent years AHA/NHLBI and IDF offered a new definition of criteria that two side agreed that abdominal obesity is 1 of 5 criteria for identifying

Table 3 American Heart Association/National Heart, Lung and Blood Institute metabolic syndrome diagnostic criteria

Measure	Categorical cut points
Elevated waist circumference[1]	Population and country specific definition
Elevated triglycerides	$\geq$ 150 mg/dL (1.7 mmol/L) or drug treatment for high triglycerides (*i.e.*, fibrates or nicotinic acid)
Low HDL-C[2]	< 40 mg/dL (1.0 mmol/L) in males
	< 50 mg/dL (1.3 mmol/L) in females
	Or drug treatment for low HDL-C (*i.e.*, fibrates or nicotinic acid)
Elevated blood pressure	Systolic $\geq$ 130 mmHg
	Diastolic $\geq$ 85 mmHg
	Or drug treatment for hypertension
Elevated fasting glucose	$\geq$ 100 mg/dL
	Or drug treatment for elevated glucose

[1]Waist circumference for abdominal obesity by different organization for each population or country specific: (1) Asian (WHO) $\geq$ 90 cm men or $\geq$ 80 cm women; (2) Japanese (Japanese obesity society) $\geq$ 85 cm men or $\geq$ 90 cm women; (3) China (Cooperative Task Force) $\geq$ 85 cm men or $\geq$ 80 cm women; (4) Mediterranean and Middle East (Arab) population (IDF) $\geq$ 94 cm men or $\geq$ 80 cm women; (5) United States (AHA/NHLBI) $\geq$ 102 cm men or $\geq$ 88 cm women; (6) South and Central American (WHO) $\geq$ 90 cm men or $\geq$ 80 cm women; (7) European (European Cardiovascular Societies) $\geq$ 102 cm men or $\geq$ 88 cm women; and (8) Sub-Saharan African (IDF) $\geq$ 94 cm men or $\geq$ 80 cm women; [2]High density lipoprotein cholesterol indicates high-density lipoprotein cholesterol. Adapted from Alberti *et al*[74]. AHA/NHLBI: American Heart Association/National Heart, Lung and Blood Institute; WHO: World Health Organization; IDF: International diabetes federation.

but is not essential for diagnosis[74] (Table 3: Provides the criteria for clinical diagnosis of the MS).

Prevalence of MS varies and depends on the criteria used in different definitions[75,76]. And it is increasing in different region like Asia[77] and developing countries[78], it has been reported 12.8% to 41.1% in different part of the world[79]. Prevalence of MS depends on criteria used is different for example the IDF guidelines with a lower abdominal obesity cut-off (90 cm for men, 80 cm for women) identify a greater prevalence of MS than the NCEP-ATP III[80-83]. In 2007, the prevalence of MS in the Iran was reported by IDF and ATPIII criteria 32.1% and 33.2% respectively[84]. According to 2005 version of IDF criteria, China[67], Taiwan[85,86], Hong Kong[87], and Thailand[88] had prevalence rates ranging between 10%-15% (in 2008). On the other hand, rates for Koreans[89], approximately one quarter, were higher than the Chinese and Thais. India[90] had significantly high prevalence rates compared to the rest of Asia. Unfortunately, no many studies have been done in the field of MS in Arab countries[81]. Because of increasing prevalence of obesity and diabetes in Middle-East countries particularly in Arab countries, increased risk of MS is high[91,92].

The major reason for the higher rate using in the new definition is because of focus on abdominal obesity, which is the most common component in Arab countries[81]. The increased prevalence of MS was shown in both genders, whereas the increased prevalence is higher in women in Arab populations[91,93]. And also the other components of the MS, diabetes is more common among the Arab population than other regions of the world and is estimated to have increased rapidly in the region[81,91]. Approximately 50% of patients with T2DM also suffer from MS, whereas the risk of NAFLD in these patients is higher more than the other persons[94].

DISCUSSION

Due to the increasing rate of NAFLD, prevention of this is one of the most important issues of the world. Prevention methods of NAFLD that is limited to the prevention of risk factors, because the pathogenesis of this disease is unknown. So prevention of the risk factors of NAFLD such as obesity, insulin resistance, T2DM and MS is the key strategy to reduce the incidence rate of NAFLD in the world[95]. Today, due to drastic changes in lifestyle and desire to in sedentary lifestyle, because of rapid economic and social changes in many countries, including Asian countries, prevalence of obesity, T2DM and MS are on the rise, which are important risk factors for NAFLD.

Hence, the key management of NAFLD is lifestyle modifications. Lifestyle modification programs are typically designed to change bad eating habits and increase physical activity that is associated with clinically significant improvements in obesity, T2DM and MS. Many studies indicate that lifestyle modification, including a reduction in intake of saturated fat and refined carbohydrates and sweetened beverages, may reduce aminotransferases and improve hepatic steatosis[96-99]. Earlier studies suggested that reduction of body weight by 10% can normalize liver test, but recent studies have shown that loss of at least 3%-5% of body weight can achieve improvement in hepatic steatosis[100,101]. Control and reduce the incidence of insulin resistance and MS is another important aspect of prevention and management of NAFLD[7,14]. Early detection, appropriate treatment, and also care programs with essential training can be an effective step in control and reduce the incidence of MS, insulin resistance and also cardiovascular disease and diabetes. Not only Lifestyle changes, weight loss and regular physical activity are essential first steps for the prevention and treated patients with NAFLD, but also the prevention of metabolic risk factors, such as diabetes, dyslipidemia, hypertension is also very important[4]. However, in addition to lifestyle changes for the treatment of patients with NAFLD, are there specific pharmacologic therapies such as insulin sensitizers (metformin and thiazolidinediones)[102-105], weight loss drugs (orlistat and sibutramine)[106], antioxidants (vitamin E)[107], and have also considered bariatric surgery for morbidly obese patients[4,108].

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COMMENTS

Background

Non-alcoholic fatty liver disease (NAFLD) is a major health concern worldwide which is characterized by abnormal fat accumulation in liver cells. Today, NAFLD is identified as a main cause of chronic liver disease in Asia. Due to the increasing rate of NAFLD, prevention of this is one of the most important issues of the world. Prevention methods of NAFLD that is limited to the prevention of risk factors, because the pathogenesis of this disease is unknown.

Research frontiers

The objective of this study was to review systematically all of aspects of NAFLD in Asia, provides updated epidemiological data on NAFLD and its etiology and also this study has examined the current and future possibilities of prevention of this disease in Asian countries.

Innovations and breakthroughs

Based on systematic reviews, NAFLD is tightly linked with obesity, type 2 diabetes mellitus (T2DM) and the presence of metabolic syndrome (MS). Because of increasing prevalence of obesity, T2DM and MS in Asian countries particularly in Arab countries, increased risk of NAFLD is high in this region. So, by increasing the prevalence and incidence of NAFLD in this region prevention of this disease is very important.

Applications

Prevention of NAFLD should be considered in the Asian countries, because it is increasingly recognized as a major chronic liver disease in these regions.

Terminology

NAFLD is characterized by abnormal fat accumulation in liver cells. The development process of NAFLD can be started from simple steatosis (NAFLD) to non-alcoholic steatohepatitis and finally leads to cirrhosis and hepatocellular carcinoma, in absence excessive alcohol intake.

Peer-review

This is a well-written and comprehensive review of the epidemiology of nonalcoholic fatty liver disease in Asia.

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