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REVIEW

How common is non-alcoholic fatty liver disease in the Asia–Pacific region and are there local differences?

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Abstract

Risk factors for development of non-alcoholic steatohepatitis include obesity, especially central adiposity, glucose intolerance or type 2 diabetes mellitus (T2DM), and dyslipidemia. Non-alcoholic fatty liver disease (NAFLD) is now considered a manifestation of metabolic syndrome. During the last two decades, NAFLD has become the most common chronic liver disease in North America and Europe, but until recently was thought to be uncommon (perhaps due to the lack of study) in Asia. Fatty liver can be identified on imaging modalities (ultrasonography, computed tomography scans, and magnetic resonance imaging) with high sensitivity, but steatohepatitis and fibrosis cannot be distinguished. Thus, an inherent drawback in studying the epidemiology of NAFLD is the lack of definitive laboratory tests, no uniform definition—with different studies using cut-off values of alcohol consumption from <20 g/week to 210 g/week, and case selections where biopsy was used for definition. In studies outside the region, the prevalence of NAFLD varies from 16% to 42% by imaging, and 15–39% of liver biopsies. The major risk factors for NAFLD, central obesity, T2DM, dyslipidemia, and metabolic syndrome, are now widely prevalent and are increasing geometrically in the Asia–Pacific region. It is therefore not surprising that NAFLD is common in this region. Estimates of current prevalence range from 5% to 30%, depending on the population studied. Central obesity, diabetes, and metabolic syndrome are the major risk factors. To date, however, data on the natural history and impact of NAFLD causing serious significant chronic liver disease are lacking and there is a need for prospective, cooperative studies.

Introduction

The terminologies and guidelines for the assessment of non-alcoholic fatty liver disease (NAFLD) have been discussed in this issue of the Journal by Farrell *et al*.[1] The term 'non-alcoholic steatohepatitis' (NASH) was developed by Ludwig in 1979 to describe an 'alcoholic-like liver disease that develops in people who do not drink alcohol'.[2,3] The cases described initially were based on histological findings among those totally abstinent from alcohol, and the pathological spectrum ranged from simple steatosis to steatohepatitis and cirrhosis. For this reason, the more encompassing term 'NAFLD' is now preferred.[2,3] The risk factors for the development of NASH were identified as those related to metabolic disorders, obesity, type 2 diabetes mellitus (T2DM), and dyslipidemia. By the late 1990s, NASH was conceptualized as part of metabolic syndrome.[2–5] NAFLD is becoming a major public health problem due to the rising prevalence of obesity and T2DM worldwide.[6] NAFLD/NASH are now considered to be common causes of chronic liver disease, an increasing indication for liver transplantation and a possible cause of hepatocellular carcinoma (HCC).[2]

Fatty liver can be identified on imaging modalities like ultrasonography, computed tomography (CT), and magnetic resonance imaging with a reasonably high sensitivity (~80% for 30% steatosis).[7–9] Because steatohepatitis and fibrosis cannot be judged on imaging modalities, histology remains the gold standard for the pathological diagnosis of NAFLD/NASH.[2,10] Although NAFLD has been reported worldwide, it is difficult to determine the true prevalence because of problems in interpreting data from various studies due to referral bias, population heterogeneity, study design, imaging modalities used, and use of liver biopsies. In general population studies using ultrasound, the prevalence ranges from 16% to 23%.[2,11] However, a recent study using magnetic resonance spectroscopy estimated that one in three American adults had

steatosis. The definition of hepatic steatosis in this study was hepatic triglyceride of more than 5.5% on magnetic resonance spectroscopic evaluation.[12] Data from the third National Health and Nutrition Examination survey have been analyzed using two different definitions of presumed NAFLD based on serum alanine aminotransferase (ALT) values and the exclusion of other liver diseases.[13,14] The prevalence varied from 5% to 24%, while another study estimated the overall prevalence of NAFLD to be 13%.[15] Because of the varying sensitivity and specificity of ALT,[13–16] ultrasonography, CT scans, magnetic resonance spectroscopy, and liver biopsy, there is wide variation in the estimates of NAFLD prevalence between studies.[11] The drawbacks of requiring liver biopsy for the definitive diagnosis of NAFLD in research studies and in clinical practice and the challenges of defining safe levels of alcohol intake are addressed in the first review by the Asia–Pacific Working Party for the study of NAFLD (APWP–NAFLD).[1,17]

NAFLD is now considered to be a common manifestation or even predictor of metabolic syndrome.[2–5,18–20] Based on hepatic imaging and/or quantification of hepatic triglyceride content, the prevalence of fatty liver disease in Western countries is now estimated to be between 24% and 42%, depending on gender and ethnicity.[2,11,21] Of these cases, about 10–15% or 3–7% of the population (higher in studies from liver clinics) have NASH.[11] NAFLD is seen in ~70% of obese and ~35% of lean patients.[2,11]

Until recently, NAFLD has been assumed to be uncommon in the Asia–Pacific region because it was considered a disorder of affluence, and in this region the burden of viral hepatitis is huge.[22,23] However, the major risk factors for NAFLD, like glucose intolerance and T2DM, obesity, dyslipidemia, and metabolic syndrome, are now widely prevalent in the Asia–Pacific region and are increasing in geometric proportions.[6,19] The corollary is that NAFLD should be common in the Asia–Pacific region and this has been suggested in recent surveys and reviews.[18,19,22–24] In 1984, Nomura *et al*. reported that the prevalence of fatty liver based on ultrasounds in 2574 Japanese workers and their families undergoing annual health checks was 14%.[25] Similarly, in 1991, Oshibuchi *et al*. reported the prevalence of steatosis to be 15%.[26] In 1995, Ikai *et al*. reported the prevalence of fatty liver to be 22%.[27] All these studies failed to exclude alcohol intake, but in a subsequent well-designed study from Japan that excluded cases of excessive alcohol intake, patients were evaluated by liver enzymes, viral markers, and ultrasound. It was shown that the prevalence of NAFLD was 24%.[28] More recent studies have documented even higher rates of NAFLD in Japan, as well as more than double the prevalence over the last 15 years or so.[18,29–32]

The purpose of Working Party 2 of the APWP–NAFLD was to determine the epidemiology of NAFLD across this region. In order to provide insights into pathogenic factors, we particularly evaluated data between countries and zones on the prevalence of NAFLD in the general population. In the third review of this series, this epidemiology is considered in a different light, namely the settings and risk factors for NAFLD and its severity.[29] In the present study, we sought to corroborate the general importance of NAFLD in contributing to the burden of chronic liver disease by surveying members of the Working Party on this point, as well as on the likely role of NAFLD in individual countries or regional economic zones as a possible or probable cause of cryptogenic cirrhosis. Finally, the prevalence of NAFLD in high-risk population subgroups, like those with T2DM and/or obesity was considered in relation to the prevalence of these metabolic risk factors in the general population.

Table 1 Prevalence of non-alcoholic fatty liver disease (NAFLD) among the adult population of Asia–Pacific countries

Country	Individuals with NAFLD (%)
Japan	9–30%
China	5–24%
Korea	~18%
India	5–28%
Indonesia	~30%
Malaysia	17%
Singapore	5%

Details are contained in references.

Methods

Wherever possible, data from reports published in full papers have been cited. However, additional results from abstracts or work presented at major meetings have been considered where these data are not in the public domain, particularly for smaller countries. Finally, in light of the paucity of stronger data for issues, such as cryptogenic cirrhosis, the anecdotal perceptions of experienced clinicians are taken into consideration. In addition to complementing the picture of risk factors and settings for NAFLD in Asia (Working Party 3 report),[29] it is hoped that the present preliminary impressions (level 4 evidence) will form the basis for starting collaborative prospective studies.

Results

Prevalence of NAFLD in countries of the Asia–Pacific region

Based on surveys using ultrasonography, the prevalence of NAFLD in the general population across Asia varies from 5% to 40%.[18,19,24–46] In these studies, the various population subgroups surveyed include white collar workers, manual workers, employees of industrial plants, people undergoing annual health checks, and those engaged in community service. The available data are presented in Table 1 and general comments for each country are annotated below.

Japan

The prevalence of NAFLD in the general population was reported to be 9–14% in 1988.[25] Over the last two decades, there has been a dramatic increase in obesity and T2DM due to lifestyle changes, as indicated by the parallel rise in car sales and other criteria of affluence and inactivity. The rising incidence of obesity in Japanese adults has been paralleled by a dramatic increase in NAFLD. Thus, the prevalence of elevated ALT has increased from less than 10% in 1984 to 25% in 2001.[32] The main cause of elevated ALT in Japan was thought to be NAFLD. The prevalence of NAFLD was shown to be increasing according to body mass index (BMI), fasting blood glucose, serum cholesterol, and serum triglycerides. The prevalence of NAFLD ranges from 10% in lean patients (i.e.

BMI less than 23 kg/m^2) to 80% in patients with a BMI of more than 30. Similar associations between an increase in fasting blood glucose and hyperlipidemia have also been shown. Obesity, increased fasting blood glucose, T2DM, and hyperlipidemia have been evaluated for the prevalence of fatty liver disease.[25–28,30–32] If none of the three risk factors were present, fatty liver was found on ultrasound examination in 25% of patients, while if one risk factor was present, the prevalence of fatty liver rose to 43%,[30–32] and for two risk factors, fatty liver was found in 72% of patients. Jimba *et al*. reported that the prevalence of fatty liver on ultrasonography among healthy adults from Saitama Prefecture was 30%.[31] BMI, total cholesterol and fasting blood glucose were independent predictors of fatty liver disease.

China

As discussed in more detail in the Working Party 3 report,[29] the prevalence of NAFLD in the general population of China varies from 5% to 24%,[19,33–36] being higher in urban areas than rural ones (J-G Fan, 2006, personal communication). Fatty liver disease was detected on ultrasound examination in 18% of white collar workers in Beijing and in 11% of laborers. Similar figures were reported from Shanghai.[33–35] The lowest prevalence of NAFLD observed was 5% in laborers from Dagin and 1.2% in Shichuan monks (J-G Fan, 2006, personal communication). A prevalence study of NAFLD among administrative officers in Shanghai highlighted the risk factors and the protective factors for fatty liver.[33] The former were identified as central obesity, dyslipidemia, T2DM, arterial hypertension, elevated ALT, heavy consumption of alcohol, and sleep apnoea syndrome. Protective factors were exercise, mild alcohol consumption, and working under moderate stress.[33] Viral hepatitis was not associated with fatty liver disease.[33] NAFLD has increased rapidly in China in the last decade due to the pandemic of diabetes and obesity.[6,19,29] Further, the majority of those with fatty liver have metabolic disorders.[29,33–36]

Hong Kong

The prevalence of NAFLD in an outpatient-based study in Hong Kong was 16%.[44] Compared to healthy controls, T2DM is the most important factor associated with NAFLD.[45] Patients with T2DM and higher BMI tend to have more advanced liver disease.[45]

Taiwan

Prevalence studies in the adult general population and among those undergoing a master health check-up have shown a prevalence of NAFLD ranging from 11.5% to 41%.[41,42] Risk factors identified include male gender, older age, BMI, diabetes, dyslipidemia, and hyperuricemia.[41,42]

Korea

The prevalence of NAFLD in the general population of Korea has been reported as being at 18%.[24,37] As with other Asian countries, the prevalence of obesity and T2DM is increasing in Korea. The increasing incidence of NAFLD has been attributed to the Westernization of diet, excessive food intake, lifestyle changes, lack of exercise, and increasing longevity. Insulin resistance and metabolic syndrome are very common in Koreans.[24,37]

India

The community prevalence of NAFLD in India varies from 5% to 28%.[38–40,46] These data are based on people undergoing master health check-ups, ultrasonography for non-liver-related causes, healthy relatives of hospitalized patients, and railway employees and their families. Diabetes and central obesity are common predisposing factors,[16,38–40] while insulin resistance is detectable almost universally. Asian Indians have increased predisposition to visceral fat accumulation, a feature that may be present from birth.[47,48] It is therefore noteworthy that Indians in other Asian countries have a higher prevalence of T2DM and fatty liver as compared to native or other ethnic (e.g. Chinese) populations,[49–51] as well as increased rates of hyperinsulinemia and insulin resistance.[51,52] In the last 15 years, there has been a 75% rise in the incidence of diabetes in India.[52] Two studies from north India have suggested that NAFLD in India may be milder than that in the west, but these studies included very few biopsy-proven cases.[38,53] Amarapurkar and Patel have reported that biopsy-proven patients reveal significant liver disease; some patients require liver transplantation and a few develop HCC.[16]

Indonesia

The prevalence of NAFLD in an urban population of Indonesia has been estimated in one study (presented only in abstract form) as approximately 30%.[43] Obesity was the strongest associated risk factor.

Malaysia

The prevalence of NAFLD in an urban population in Malaysia has been observed to be 17% (SC Goh, *et al*., 2006, unpublished observation). Diabetes is the major risk factor. In a detailed histological study, 4.3% of liver biopsies showed NAFLD and about 75% of patients had milder forms of NASH.[50] Eight of 70 patients (11%) had cirrhosis, even though this was not clinically overt. Central obesity was detected in 77% of patients. More than half (59%) the patients had impaired glucose tolerance or T2DM, while 97% had insulin resistance as measured by the homeostatic model of assessment.

In an ongoing study, the results of routine ultrasounds performed as part of a medical check-up for insurance and executive screening purposes ($n = 729$) showed a prevalence of NAFLD at 15%, with a slight preponderance amongst men (SC Goh *et al*., 2006, unpublished observation). Impaired glucose tolerance (15%) or T2DM (15%) were found to be common, while hypercholesterolemia was present in almost three-quarters.

Singapore

Large community-based studies of NAFLD in Singapore are lacking, but the prevalence of NAFLD in the general population is estimated at being approximately 5% (W-C Cheng, 2006, personal communication). Cases of NASH are often noted in tertiary referral centers, and like other countries, obesity and metabolic syndrome are the most common associations.

Table 2 Prevalence of non-alcoholic fatty liver disease in high-risk populations within the Asia–Pacific region

Country	Diabetes (%)	Obesity (%)	Dyslipidemia (%)
Japan	40–50%	50–80%	42–58%
China	35%	70–80%	57%
Korea	35%	10–50%	26–35%
India	30–90%	15–20%	N/R
Indonesia	~52%	~47%	~56%

N/R, not reported. For original sources, see text.

Sri Lanka

In Sri Lanka, NAFLD accounts for approximately 35% of patients who undergo liver biopsy for raised ALT.[54] NAFLD has been reported in 18% of children attending an obesity clinic in Colombo.[55] NAFLD with advanced fibrosis (stages 3 and 4) has also been described in Sri Lankan children (HJ de Silva HJ, 2006, personal communication).

NAFLD in high-risk populations

The prevalence of T2DM is increasing globally and the Asia–Pacific region is at the forefront of the current pandemic.[6] The prevalence of NAFLD among diabetics is reported to be from 30% to 90% in Japan, China, Korea, India, and Indonesia.[31,34–37,43,55,56] In a prospective study of Indian patients with diabetes, histologically significant liver disease (fibrosis grade 3 or 4) was seen in 10% of patients with NAFLD.[57] The prevalence of NAFLD in obese people has been reported to be from 15% to 80%, with no apparent differences between countries.[2,31,36,37,43] The prevalence of NAFLD among patients with dyslipidemia ranges between 25% and 60% in reports from the Asia–Pacific region (Table 2).[33–37,41,57]

NAFLD in patients with chronic liver disease

There are few prospective studies that discuss the relative importance of NAFLD in contributing to the burden of chronic liver disease in the Asia–Pacific region.[23] Studies from Australia and New Zealand, China, Japan, India, Korea, and Sri Lanka have reported advanced liver disease in 1–20% of patients with NAFLD. The development of HCC and requirement of liver transplantation for NASH-related end-stage liver disease have been reported from these countries.[16,23] However, the magnitude of the problem, particularly compared with that of hepatitis B or C, has not yet been defined.

NAFLD as a cause of cryptogenic cirrhosis

There are scant studies on the importance of NAFLD/NASH as a cause of cryptogenic cirrhosis in the Asia–Pacific region. Two reports from India showed that diabetes was present in a significantly higher proportion of patients with cryptogenic cirrhosis compared to patients with other causes of cirrhosis.[56,57]

Conclusion and directions for further study

NAFLD seems to be a major public health concern in the Asia–Pacific region. In all countries where some estimation of NAFLD prevalence has been made, the magnitude of the problem is comparable to Western countries. However, there are many deficiencies in putting together the epidemiology of NAFLD in this region and in establishing the proportion of cases that are likely to be clinically significant. Future studies should attempt to improve the detailed knowledge of the prevalence of NAFLD and the metabolic risk factors with which it is so strongly associated. Regional (e.g. urban *vs* rural) and ethnic differences (as reported in North America and noted in the Working Party 3 report),[29] are of particular interest as they may provide clues to pathogenesis and individual risk factors for liver disease and metabolic complications. Further studies are also required to learn the impact of fatty liver on chronic liver disease in the Asia–Pacific region, either as the sole cause of cirrhosis and as comorbidity with liver disease attributable to hepatitis C, hepatitis B, alcohol, or drug toxicity.

The number of people suffering from T2DM appears to be rising exponentially in the Asia–Pacific region, with prevalence rates increasing from 2- to 5-fold over a period of 20 years.[6] As discussed in more detail in another review in the Journal,[29] Asians who develop diabetes have a less degree of obesity at a younger age than Caucasians, but suffer from a higher rate of complications and premature deaths. The similar increases in obesity and metabolic syndrome prevalence in Asia with increasing rates of NAFLD indicate that the overall prevalence of NAFLD is likely also to increase progressively in the next decade.

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