

REVIEW

Non-alcoholic fatty liver disease in the Asia–Pacific region: Definitions and overview of proposed guidelines

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Abstract

Non-alcoholic fatty liver disease (NAFLD) is the most common liver disorder in Western industrialized countries, affecting 20–40% of the general population. Large population-based surveys in China, Japan, and Korea indicate that the prevalence of NAFLD is now 12% to 24% in population subgroups, depending on age, gender, ethnicity, and location (urban versus rural). There is strong evidence that the prevalence of NAFLD has increased recently in parallel with regional trends in obesity, type 2 diabetes, and metabolic syndrome; and that further increases are likely. The relationship between NAFLD, central obesity, diabetes, and metabolic syndrome is clearly evident in retrospective and prospective Asian studies, but the strength of association with these metabolic risk factors is only appreciated when regional definitions of anthropometry are used. Pathological definition of NAFLD, particularly its activity and the extent of liver fibrosis, requires histological examination, but liver biopsy is often not appropriate in this disorder for logistic reasons. An alternative set of operational definitions is proposed here. Clinicians need guidelines as how best to diagnose and manage NAFLD and its associated metabolic disorders in countries with scant healthcare resources. The Asia–Pacific Working Party (APWP) for NAFLD was convened to collate evidence and deliberate these issues. Draft proposals were presented and discussed at Asia–Pacific Digestive Week at Cebu, Philippines, in late November 2006, and are published separately in this issue of the *Journal* as an Executive Summary. The present document reviews the reasoning and evidence behind the APWP-NAFLD proposals for definition, assessment, and management of NAFLD in the Asia–Pacific region.

Introduction

Non-alcoholic fatty liver disease (NAFLD) encompasses a spectrum of liver disorders characterized by macrovesicular hepatic fat accumulation alone (steatosis), or accompanied by signs of hepatocyte injury, mixed inflammatory cell infiltrate, and variable hepatic fibrosis (non-alcoholic steatohepatitis, NASH), through to cirrhosis.^{1–6} The histological characteristics of NAFLD are indistinguishable from alcoholic liver disease;^{7–9} excluding patients with a history of excessive alcohol use is critical in defining who has NAFLD. The 'typical' patient is likely to have one or more metabolic disorders associated with insulin resistance, such as central or overall obesity, type 2 diabetes mellitus (T2DM), hypertension, dyslipidemia, or metabolic syndrome.^{2–6,10–14} Other causes such as drugs (amiodarone, perhexiline maleate, tamoxifen), certain bariatric operations (jejunio-ileal bypass), total parenteral nutrition, and inherited or acquired lipodystrophies account for a

tiny fraction of all cases of steatosis or steatohepatitis;⁵ these will not be discussed further in this overview.

A Western perspective of NAFLD

Large scale surveys in the United States (NHANES III) and Europe (Dionysus study in Italy) have shown that NAFLD is prevalent in at least 20% of the general population,^{15–18} and as high as 30% (>40% in Hispanic men) if sensitive tools such as proton magnetic resonance spectroscopy are used to detect increased hepatic triglyceride levels.¹⁸ Although non-alcoholic steatohepatitis (NASH) is present in only 10% to 30% of these individuals,¹⁷ its prevalence increases with obesity (six-fold) and T2DM,^{10,11,19} both of which are part of a burgeoning pandemic.¹

Most physicians in the West accept that fatty liver is widely prevalent but disagree about its clinical relevance.^{2,20} This largely

stems from the variable natural history of NAFLD, which is now known to differ considerably according to the underlying histological lesion present,^{20–25} and the characteristics of the population surveyed (age, community versus hospital-based, obese versus non-obese).^{25–28} On the one hand, hepatic steatosis is essentially a non-progressive entity,^{21–23} whereas on the other, up to one-third of cases with NASH will develop progressive hepatic fibrosis.^{21,24,26}

Overall, 5% to 20% of subjects with NAFLD in community cohorts and tertiary hospital series, respectively, will progress to cirrhosis over a 10-year period.^{2,20} As expected, this also translates to differences in clinical outcome by study location. For instance, Matteoni *et al.* from the Cleveland Clinic reported liver-related mortality of 12% in their NAFLD cohort over a decade of follow up.²¹ By contrast, the natural history of individuals diagnosed with NAFLD in the Olmsted County community study (Rochester, USA) appeared somewhat better (liver-related mortality of 1.7% over 7 years).²⁶ However, it is relevant to note that deaths from liver disease ranked third among the causes of death in this cohort, versus 13th in those without NAFLD.

Other reports have highlighted the relentless decline in liver function in individuals with NASH-related cirrhosis (liver-related complications in 30% within 7 years).^{25,28} It therefore appears that the course of NAFLD is not completely benign and that a subset of patients with NAFLD have advanced hepatic fibrosis and are likely to develop liver-related complications and die from liver failure or hepatocellular carcinoma (HCC).^{2,20,25,28–32}

Steatosis, and the metabolic factors that are so strongly associated with it, may also have a negative impact on other liver diseases. With hepatitis C, obesity, insulin resistance, and steatosis are predictors of progression to advanced hepatic fibrosis,^{33,34} and are also associated with lower sustained viral response rates to interferon-based therapies.^{35,36} A proportion of cases of HCC have also been attributable to NAFLD,^{29–32} but the overall contribution of metabolic risk factors to HCC is an unresolved issue at present.² As discussed in more detail in the third of these reviews,¹⁰ there is also evidence that the outcome of alcoholic liver disease is worse in the obese and those with metabolic syndrome. Fatty liver disease attributable to metabolic risk factors is increasingly noted in those infected with hepatitis B virus (HBV) in more affluent parts of Asia, but whether this has any implications for disease outcomes remains unclear.

The connotations of a diagnosis of NAFLD go beyond its impact on liver function. By virtue of its almost universal association with insulin resistance and the metabolic syndrome,^{10–14} NAFLD is emerging as a marker for this syndrome, bringing with it implications for cardiovascular risk assessment and predisposition to diabetes and some cancers; the practical implications are discussed in the fourth review of this series.³⁷

NAFLD is an emerging problem in the Asia-Pacific region, and is likely to increase in the future

In a region overwhelmed with viral hepatitis and with inequalities in access to healthcare, recognition of fatty liver disorders as a distinct and common entity has been slow in coming.^{3,38} However, several key population surveys and hospital-based case series have been instructive in delineating the nature of NAFLD in this region.

These are detailed in the second and third of these reviews,^{10,39} the key findings will be summarized briefly here.

Prevalence

NAFLD is now well documented in most countries within the region. Its prevalence in the general population, determined principally by ultrasonography, is higher than previously anticipated, with values ranging from 2% to 37%. Prevalence figures of 10% to 29% obtained from large surveys in China, Japan, and Korea are very similar to those described in Western surveys.^{10,11,14,40–43}

Trends

Three longitudinal studies from Japan and China indicate that the prevalence of NAFLD is increasing.^{10,11,14,40} Over a 12-year period, the prevalence of NAFLD in Japan has more than doubled from ~13% in 1988–9 to ~30% in 2004.^{14,40,41} Similar trends are documented in China,^{10,11} and have been noted anecdotally in the rest of Asia, particularly in urban centres.³⁹ Studies in North America have noted an ethnic predisposition to NAFLD among Asian-Indian men, Hispanics, and East Asians,^{18,44,45} despite similarity in metabolic risk factors between races.^{44,45} Together with the emergence of obesity and T2DM, NAFLD is clearly now an important public health issue in the Asia-Pacific region.

Demographics

The profile of Asian patients with NAFLD is similar to cases reported in contemporary publications outside the region. Men outnumber women in most of the published series^{42,46–60} (Table 1), but larger community-based studies indicate age-related trends. Thus, a bimodal age distribution is generally observed: the peak prevalence of NAFLD in men occurs earlier (40–49 years) than for women (over 50 years),¹⁰ explaining the male predominance in younger populations.⁴⁵

Clinicopathologic profile

The diagnosis of fatty liver is often made when abdominal imaging is performed for evaluation of abnormal liver tests or for other indications. Initial symptoms are often non-specific (fatigue, right upper quadrant discomfort). The presence of hepatomegaly can draw attention to the need for further evaluation. Features of advanced liver disease are unusual. This is consistent with the liver histologic appearances of mild-moderate necroinflammatory activity in the majority of cases. However, there have been well-documented cases of advanced hepatic fibrosis, including cirrhosis, across the region.²⁷ Deaths from hepatic decompensation and HCC have been noted in published series, especially those from Japan and Korea.^{27,32,61}

Limited studies on cryptogenic cirrhosis (three reports; two from Japan, one from India) suggest that a proportion of these cases can be attributed to NAFLD,^{62–64} as has been suggested in European populations.^{2,65} Thus, Japanese patients with cryptogenic cirrhosis are more likely to be obese; have greater amounts of visceral adiposity; and also a higher frequency of T2DM, raised triglycerides, or low HDL-cholesterol than matched controls with alcohol-related or hepatitis B- or C-associated cirrhosis.^{62,63}

Table 1 Non-alcoholic fatty liver disease in Asia: associated metabolic diseases

Location	N	M/F	Age (mean)	Mean BMI (kg/m ²)	Central obesity (%)	Obesity (%)	DM (%)	↑ TG (%)	↑ T. Chol (%)	↓ HDL-C	Metabolic syndrome (%)	Ref.
China (Guangzhou)	301						49	56	16	12		46
China (Hong Kong)	60	38/22	46 [†]	>25 (90%); >30 (47%)	92	90	62	70	68		58	47
China (Hong Kong)	80	52/28	45	29	85	51		66	63	36	56-70; all had ≥1 features of metabolic syndrome	48
India (Lucknow)	65	46/19	39	27.4	98	73	8				20-36; 25-32% had ≥1 features of metabolic syndrome	49
India (Chandigarh)	31	25/6	38	>25 (74%)	92		10	32		42		50
India (New Delhi)	51	46/10	34 [†]	26.7 [†]		69	10	41		36	21	51
Japan (Tokyo)	148	78/70	52 [†]	26.5		97	41					52
Malaysia (Kuala Lumpur)	45	21/24	48	27.4		73	43	71	51			53
Pakistan (Karachi)	21	15/6	32	32.6								54
Philippines (Manila)	17	8/9	43			70	23	17	23			55
South Korea (Seoul)	180	108/72	53	25.6	63		11% had IFG [‡]	59		51		56
South Korea (Seoul)	1240	23%/14%	48	23.9		79	35	35	27	24		57
Sri Lanka	100	79/21	37			52	55		54			58
Taiwan	372	224/148	51			83	32	68	24		99 had ≥1 features of metabolic syndrome	59
Taiwan	124	104/20	50	27.6		18	6	21	12		16	60
Thailand	31	20/11				71		45				61

[†]Median

[‡]Patients with type 2 diabetes were excluded

BMI, body mass index; DM, diabetes mellitus; IFG, impaired fasting glucose; TC, total cholesterol; TG, triglycerides

Fibrosis progression and predictors of advanced hepatic fibrosis

Serial histologic data are yet to accrue, but one study from Hong Kong found that nine of 17 (53%) patients with NAFLD who underwent a second liver biopsy had an increase in fibrosis stage by one to two grades over 6 years.⁶⁶ It is pertinent to note that eight of these nine patients had NASH, not steatosis alone. Thus, histologic progression of NASH can occur in Asian subjects. With respect to predictors of advanced hepatic fibrosis, as in Western studies, T2DM was shown to be a risk factor in some studies.⁴⁷ Additional variables identified as independent markers of fibrotic severity include a platelet count of $\leq 160\,000/\mu\text{L}$, a hepatic necro-inflammatory grade of ≥ 2 , and aspartate aminotransferase (AST) ≥ 2 times the upper limit of normal.⁴⁷ Older individuals tend to be over-represented in cirrhotic cohorts, but age by itself has not been selected in multivariate analyses.⁴⁷ Other variables selected by univariate, but not multivariate analyses, include female gender, obesity, hypertension, and the AST/ALT ratio.^{47,52} Hepatic iron overload and the presence of hemochromatosis gene mutations do not correlate with fibrotic severity. Biomarkers of hepatic fibrosis, such as hyaluronic acid, appear promising and are being evaluated, as discussed in more detail in the review by Chan *et al.*³⁷

Natural history

The general impression is that most individuals with NAFLD are unlikely to develop significant hepatic decompensation. However, this view is likely incorrect, as underscored by a report from Japan. Of 247 patients with NAFLD, 89 (36%) had stage 3 and stage 4 hepatic fibrosis, respectively.²⁷ Over a mean follow up period of 44 months, 10 (11%) developed liver-related complications. Six presented with variceal bleeding, four with ascites, and two with hepatic encephalopathy. Further, HCC developed in five patients; four died from their liver cancer. The 5 years cumulative incidence for HCC was 20%. The overall mortality (six of 247) was 2.4% and six of 89 patients with advanced hepatic fibrosis (7%) died.²⁷

Assessment of metabolic risk factors requires application of appropriate anthropometric standards

Applying Western anthropometric standards has previously failed to identify Asian patients at risk of cardiovascular disease, and led to an upsurge in studies identifying metabolic thresholds for Asian subjects. The criteria proposed by the International Diabetes Federation reflect these changes (Table 2).^{67,68} The most striking of these is the lowering of the cut-off for waist circumference in Asian men and women. The World Health Organization has also defined obesity in Asians as a body mass index (BMI) $\geq 25\text{ kg/m}^2$; overweight is correspondingly 23–25 kg/m^2 .⁶⁹ As shown in Table 1, the mean BMI in the majority of the studies cited is below 27.5 kg/m^2 . This is in contrast to studies outside Asia where the mean BMI levels have often exceeded 32 kg/m^2 .

Metabolic risk factors, insulin resistance, metabolic syndrome

As shown in Table 1, Asian studies have reiterated the central role

Table 2 International Diabetes Federation definition of the metabolic syndrome

The metabolic syndrome is defined by central obesity *plus* any two of the following factors

Central obesity	Waist circumference ≥ 94 cm (Europid men), ≥ 80 cm (Europid women); ≥ 90 cm (Asian men) and ≥ 80 cm (Asian women)
Triglycerides	≥ 150 mg/dL (1.7 mmol/L) or receiving specific treatment for this lipid abnormality
Reduced HDL-cholesterol	< 40 mg/dL (1.03 mmol/L) in men and < 50 mg/dL (1.29 mmol/L) in women or receiving specific treatment for this lipid abnormality
Raised blood pressure	Systolic BP ≥ 130 or diastolic BP ≥ 85 mmHg or receiving treatment for hypertension
Fasting plasma glucose	≥ 100 mg/dL (5.6 mmol/L)* or previously diagnosed type 2 diabetes

*If FPG is ≥ 100 mg/dL (5.6 mmol/L) *, a glucose tolerance test is strongly recommended but is not necessary to define the syndrome
Source: references ^{67,68}

Waist circumference is measured with the subject standing. Measurements should be taken at the mid-point between the lower border of the rib cage and the iliac crest.

of insulin resistance in NAFLD.^{10,11,14,27,41,42} Overall, one or more characteristics of the metabolic syndrome are observed in at least a third of participants in some studies, and practically all in other reports. Central obesity is the most frequently observed manifestation of the metabolic syndrome, but has not always been mentioned in NAFLD reports from this region. It seems evident from the systematic review of available data presented in the review by Fan *et al.* in the third of these articles,¹⁰ that the failure to measure central obesity and/or the failure to use Asian-specific criteria for central obesity and BMI (see Table 3) almost entirely accounts for the hitherto widespread claim of 'NASH in lean Asians'. Most cogently, the presence of the metabolic syndrome is also a strong predictor of future development of NAFLD.¹⁴

More detailed consideration of methods used to study insulin resistance and its relationship to NAFLD in Asian studies is given in Dr Fan's review.¹⁰ Insulin resistance has been identified as an independent predictor of NAFLD both in obese and more recently in apparently non-obese persons (BMI $< 25\text{ kg/m}^2$). However, the latter studies may be misleading because subgroups with diminished insulin sensitivity have probably inadvertently included individuals who should be regarded as overweight (BMI 23.7–25 kg/m^2) by Asian standards,^{68,69} and also centrally obese individuals with normal BMI who could also be considered 'metabolically obese'. Despite these limitations, these reports underscore the key role of insulin resistance in NAFLD in persons not usually considered to be at risk of this condition by Western standards. A few studies that have examined adipokine profiles in NAFLD have also confirmed the relationship of NASH with low serum adiponectin levels in Asians.⁴⁸

Table 3 World Health Organization criteria for defining the metabolic syndrome in the Asia–Pacific region

The metabolic syndrome is defined by diabetes mellitus[†], impaired glucose regulation,[‡] and/or insulin resistance[§] with 2 or more of the following:

Central obesity	Waist-hip ratio ≥ 0.90 cm (men) and ≥ 0.85 cm (women)
Triglycerides and/or low HDL-cholesterol	Triglycerides ≥ 150 mg/dL (1.7 mmol/L); HDL-cholesterol < 40 mg/dL (1.03 mmol/L) in men and < 50 mg/dL (1.29 mmol/L)
Raised arterial blood pressure	Systolic BP ≥ 140 or diastolic BP ≥ 90 mmHg or receiving treatment for hypertension
Microalbuminuria	Urinary albumin/creatinine ratio of 20 mg/g or urinary albumin excretion rate of 20 mg/min

Source: reference ⁶⁹.

[†]Diabetes mellitus: fasting plasma glucose ≥ 7.0 mmol/L and/or 2-h plasma glucose ≥ 11.1 mmol/L

[‡]Impaired glucose regulation: by fasting plasma glucose 6.1–6.9 mmol/L and/or 2-h plasma glucose 7.8–11.1 mmol/L

[§]Insulin resistance: below lowest quartile of glucose uptake in the euglycemic clamp

Evaluation and management of NAFLD and NASH in the Asia–Pacific region

How should NAFLD be defined?

Liver histology remains the gold standard for the diagnosis of NAFLD, particularly in defining steatohepatitis (NASH) versus simple steatosis, and for assessing the stage of hepatic fibrosis, both of which have prognostic implications.^{2,7–9,17} However, a requirement of liver biopsy to define NAFLD is often impractical for several reasons. First, its widespread application poses logistic problems (cost, access, acceptability) in a region already overwhelmed with chronic viral hepatitis, both hepatitis B and hepatitis C. Second, there are definite (albeit low) risks of intraperitoneal bleeding and death (1 in 10 000) associated with liver biopsy,⁷⁰ but much higher rates of pain and other discomfort.⁷¹ Third, problems also arise with biopsy interpretation in NAFLD due to sampling variability⁷² and because of interobserver variation in interpreting some aspects, notably necroinflammatory activity.⁹ Finally, a contemporary view on the place of liver biopsy is that it is indicated only when the resultant information has a high probability of informing subsequent patient management.^{70,73} It is therefore not surprising that in the absence of effective therapy for NASH, treating physicians are unwilling to refer their patients for a liver biopsy.

Unlike hospital-based studies, population surveys have defined NAFLD by biochemical criteria (increased serum aminotransferases and/or alkaline phosphatase and gamma-glutamyl transpeptidase) or by hepatic imaging (hepatic ultrasound, computerized tomography, magnetic resonance imaging), or both. In both Western series and in the large Asian population-based surveys discussed in the third article,¹⁰ NAFLD is identified as the principal underlying cause of abnormal liver tests in persons

without excessive alcohol use or viral hepatitis. Many of the subjects identified in these studies had one or more coexisting metabolic disorders, lending support to a primary diagnosis of NAFLD. Therefore, an operational definition of NAFLD based on hepatic imaging, when supported by appropriate exclusion criteria, appears sustainable and can overcome some of the problems associated with liver biopsy.

In considering what would be the most appropriate imaging modality to recommend for an operational definition of NAFLD in the Asia–Pacific region, cost and access were noted to be important issues. There appear to be no major advantages of computerized tomography (CT) over ultrasonography in terms of diagnostic accuracy,⁷⁴ and although it may be useful in difficult cases (such as focal fatty change), it is more expensive. Magnetic resonance imaging (MRI) can quantify hepatic triglyceride stores, which may be very useful in assessing the efficacy of therapeutic interventions, but it is more expensive and the technology is not widely available in many Asian countries. The appearance of ‘bright’ liver (increased echogenicity) at hepatic ultrasonography is not entirely specific for steatosis and more subtle cases can be subject to operator interpretation. To avoid this limitation, the working party considered a more rigorous definition of steatosis by hepatic ultrasonography that is the current standard in Japan.⁷⁵ Specifically, comparison with a nonaffected parenchymal organ (kidney or spleen) is encouraged, and two additional features are sought: blurring of hepatic vessels and deep attenuation of the ultrasound signal.⁷⁵ It has been suggested that two of these criteria are required for interpretation of an abnormal ultrasonographic appearance as indicating steatosis.

On the other hand, there are limitations when using either hepatic imaging and/or liver enzymes as diagnostic tools. It has been long recognized that current imaging modalities cannot distinguish hepatic steatosis from NASH, nor identify the stage of hepatic fibrosis unless complications of cirrhosis are present.^{2,74} In one comparative study, which used liver histology (at least 30% steatosis) as the gold standard, the sensitivity and specificity of hepatic ultrasonography for steatosis was good (89% and 93%, respectively), but somewhat less for hepatic fibrosis (77% and 89%, respectively).⁷⁴ With respect to biochemical tests, the whole range of NAFLD, including advanced hepatic fibrosis (bridging fibrosis and cirrhosis) can occur in persons with normal liver enzymes.⁷⁶ Further, the definition of normal reference intervals for serum AT is under scrutiny. Recent studies suggest that the upper limit of normal for serum ALT (generally between 40 and 55 IU/L) needs to be lowered to ≤ 30 U/L for men and to ≤ 19 U/L for women.⁷⁷ At present, this remains an unresolved and controversial issue. In one study where both the current and proposed new reference ranges were compared, the diagnostic utility with respect to NASH (not steatosis) remained unaltered.⁷⁸

It is not yet clear whether the sensitivity for detection of NAFLD is higher with ultrasound or with ALT, although the specificity is likely to be higher with ultrasound. However, in clinical practice, patients often present with a raised ALT of unexplained cause, i.e. not due to alcohol, medications, hepatitis B, hepatitis C, or other evident hepatobiliary disease.⁷⁹ The working party therefore extended its proposal on the operational definition of NAFLD to encompass the diagnostic needs of physicians and their patients who are confronted with abnormal liver biochemistry. In such patients, compatible findings on hepatic ultrasonography, particu-

larly in the presence of metabolic risk factors, are regarded as sufficient to make the diagnosis of NAFLD, provided alcoholic liver disease and other disorders have been satisfactorily excluded. This latter aspect called for separate iteration of appropriate exclusions before the diagnosis of NAFLD can be established.

What are the exclusion criteria for NAFLD?

By definition, it is critical to exclude individuals with a history of excessive alcohol use. On the other hand, insisting that only non-drinkers of alcohol be included would be necessarily restrictive because small amounts of alcohol are not toxic to the liver. The threshold of permissible alcohol intake within definitions of NAFLD has been variously defined, ranging from complete abstinence up to 40 g of ethanol/day. The National Institutes of Health (NIH) Clinical Research Network (CRN) limits alcohol intake to less than two standard drinks per day for men (140 g of ethanol/week) and one standard drink per day for women (70 g of ethanol/week). These levels are one-third to one-quarter of those usually regarded as toxic to the liver (≥ 60 g/day in men, ≥ 40 g/day in women). Within Asian countries, similar or even more rigorous definitions of alcohol intake have been applied for NAFLD, including 0–20 g/day in some studies, and up to 30 g/day in Korea.^{11,14,42} However, studies from China have used the same definition as the NIH CRN,^{10,11} and because there is no evidence for ethnic differences in dose thresholds for alcohol-induced liver injury, the working party accepted this definition as appropriate for the Asia-Pacific region. The working party did note that socio-cultural factors can contribute to concealment of significant alcohol use and/or difficulty with its quantitation; for instance, the equivalent of a 'standard drink' for home-brewed alcoholic beverages does not exist. For these reasons, clinicians need to make rigorous attempts to corroborate accounts of patient's alcohol intake with their spouse, other family members, and family doctor. The life-time history of alcohol exposure may also be more important than the history in the year leading up to presentation.⁸⁰

Patients should be screened for HBV and HCV serology. Minimal screening should include testing for hepatitis B surface antigen (HBsAg) and anti-HCV (by 3rd generation ELISA). Other routine tests to exclude autoimmune and metabolic disorders, biliary tract disease, and hepatic malignancy or infection are necessary. These may include antinuclear (ANA), smooth muscle, and antimitochondrial antibodies; serum caeruloplasmin and alpha-1-antitrypsin levels; tests for celiac disease (transglutaminase antibodies); and abdominal ultrasonography to exclude biliary obstruction. If tests for iron overload are performed (recognizing that iron storage disorder does not usually cause abnormal liver tests in the absence of alcohol excess or fatty liver disease), it is noted that a raised ferritin is very common in NAFLD (about 60% of cases). Raised serum ferritin does not, of itself, indicate iron overload. In the Asia-Pacific region, clinicians need to be aware of the relative frequency of the above disorders in their own area of practice so that the battery of tests is appropriately tailored to the local context in order to contain costs.

How should patients with NAFLD be assessed?

In considering this third issue, the working party recommended that patients with suspected NAFLD should undergo baseline tests

that allow definition of NAFLD (discussed earlier in relation to proposal 1), identification of the underlying metabolic factors, exclusion of other disorders, and assessment of the likely severity of NAFLD/NASH. These tests encompass biochemical and hematological indices, anthropometry, hepatic imaging, and determination of insulin sensitivity. In light of the need to reconcile economic factors and the strength of evidence for different indicators, we chose to stratify available tests into those of highest priority ('minimal assessment') and those that might represent a 'council of perfection'; the latter were labeled as 'optional tests' (once the diagnosis of NAFLD is established), or 'research tools'. In general, the evidence that factors listed under 'minimal assessment' corroborate the likely presence of NAFLD and/or give weight to its probable severity is Level II or Level III. For most tests listed as optional, there are logistic constraints despite Level I or II evidence of their value; examples are liver biopsy (discussed earlier), MRI (for quantitation of hepatic triglyceride), and more detailed assessment of insulin resistance. Alternatively, the evidence appears weaker, as for novel biomarkers.

Three types of tests or bodily measurements are singled out for special comment.

Tests of insulin sensitivity (i.e. how to detect insulin resistance and its consequences)

The working party strongly endorsed the principle that full diagnosis and investigation of the health of persons with NAFLD requires laboratory tests to establish evidence for insulin resistance (Level Ia evidence). It is also vital to know whether a person is at high risk of T2DM; it can be reasoned that all patients with NAFLD are at high risk of diabetes, but an even higher risk group is comprised of those with glucose intolerance.^{10–13,41,42} Conversely, we were again cognizant of the cost of some tests, including multiple serum insulin determinations that are required for a dynamic 'assay' for insulin resistance, and the limitations of a static estimation, such as the homeostatic model assessment of insulin resistance (HOMA-IR). To balance these opposing arguments, we have recommended that *all* patients with or suspected to have NAFLD have a fasting blood glucose (FBG) performed, and that if this is abnormal (≥ 5.6 mmol/L), the person should have an oral glucose tolerance test (OGTT). The validity of this recommendation comes from analyses and recommendations of the IDF (Level Ia).^{67,68} There is some evidence that fasting hyperglycaemia is insensitive for detecting insulin resistance, or even glucose intolerance in NAFLD patients.⁸¹ Thus, many of us would perform an OGTT on *all* patients with NAFLD irrespective of FBG. Finally, better (more direct, more sensitive) evidence of insulin resistance in patients with NAFLD is given by fasting and post-prandial insulin levels, and by serum C-peptide, which reflects the rate of pancreatic β -cell production of insulin (increased with insulin resistance, before the phase of β -cell failure).¹³ For the reasons already outlined, these additional (and more expensive) tests have been relegated to the list of optional tests or research tools.

Anthropometry

The general importance of recognizing NAFLD as a metabolic disorder inextricably related to visceral adiposity and insulin resistance has already been made: the extensive evidence to support the relevance of this concept in Asia is presented in the next two

reviews.^{10,39} In making the recommendation that anthropometric measurements are an *essential* aspect of assessing the patient likely to have NAFLD, this working party is exhorting liver physicians to think and behave in the same manner as diabetologists and nutritionalists/obesity or metabolic physicians. This means introducing BMI and waist circumference measurements into the liver clinic. A technical and logistic aspect is that measuring waist circumference requires the measurer to be trained (or calibrated): the subject should be standing, and the circumference is determined at the midpoint between the lower margin of the rib cage and the iliac crest (in centimeters). Normal values and cut-off values are given in Table 2.

Liver biopsy

More new ground is covered by these recommendations in making clear statements about the necessity (or otherwise) for liver biopsy in patients with NAFLD. In agreement with international opinion,⁸² the working party that examined management strategies concluded that there is no specific treatment for NAFLD.³⁷ The evidence that knowledge of liver histology really alters management in fatty liver disorders is therefore lacking, so that it seems reasonable to conclude that liver biopsy is not always essential for the diagnosis of NAFLD or for initial assessment of patients who have this disorder. However, this is not the same as saying a liver biopsy should not be performed. In fact, the working party recommends that liver biopsy be considered when the diagnosis is not unambiguously clear, in patients with high risk of advanced fibrosis (assuming the person wants to know that, and are prepared to be screened for complications like portal hypertension and HCC), and for those involved in clinical trials. Having accepted that the main reason for not mandating liver biopsy in all patients with NAFLD are logistic and pertain to acceptability of the procedure (which can cause pain or dangerous complications)^{70,71} it also seemed reasonable to recommend that greater consideration be given to liver biopsy in those coming to surgery for other procedures, particularly cholecystectomy and gastric banding: both these procedures will be performed in a large number of patients with NAFLD.

How should liver biopsies be evaluated?

Semiquantitative liver histologic scoring systems in use in contemporary studies of NAFLD include those proposed by Brunt *et al.* (1999) and the Pathology Committee of the NIH NASH CRN.^{7,9} The Brunt classification has separate categories for the grade of hepatic necroinflammation and stage of hepatic fibrosis.⁷ After assessing individual components within these categories (steatosis, ballooning, lobular and portal inflammation, hepatic fibrosis), liver biopsies are graded as mild, moderate, or severe steatohepatitis and staged as 1–4 (from perivenular, perisinusoidal fibrosis through to cirrhosis). The CRN classification draws on the Brunt scheme but differs from it by providing a single score (NAFLD activity score, NAS) to categorize liver biopsies as: NASH, borderline NASH, and no NASH.⁹ The stage of fibrosis is evaluated separately, and broadly similar to the Brunt scheme except that stage 1 is subdivided to three components to include portal/periportal hepatic fibrosis. The CRN scheme is applicable across the spectrum of NAFLD and has reasonable interrater

agreement (kappa weighted scores of 0.84 for fibrosis, 0.79 for steatosis, 0.56 for hepatic injury, 0.45 for lobular inflammation, and 0.61 for diagnostic category). Unpublished data also validate the use of CRN scheme in therapeutic trials, and in animal models (M Yeh, personal communication, October 2006). For this reason, the working party recommends that the NAS now be incorporated into routine reporting of NAFLD, as well as for clinical trials.

While the framework of the CRN scheme appears reasonably straightforward, clarification has been sought with respect to patients with cirrhosis. In particular, ballooning hepatocytes are common in cirrhosis of any cause. Hui *et al.* therefore proposed different categories for NASH-associated cirrhosis: definite, probable, possible, and cryptogenic.²⁵ In this scheme, liver biopsies with cirrhosis showing steatosis and intralobular mixed inflammatory infiltrate would be marked 'definite', those with steatosis and lobular mononuclear infiltrates as 'probable', and cases of cirrhosis with either steatosis or intralobular mixed inflammation as 'possible NASH-associated cirrhosis', respectively. The term 'cryptogenic' was reserved to designate cirrhosis in the absence of steatosis or necroinflammation, but occurring in persons with metabolic risk factors. Now that cryptogenic cirrhosis is generally regarded as the endstage of NASH (largely because of the high rate of metabolic comorbidity, such as diabetes, hypertension and obesity, but also because of a high rate of recurrence after liver transplantation), the working party was concerned that cases of cirrhosis due to other occult causes could be mislabeled. It therefore recommended (proposal 4.3) that caution should be applied to including cryptogenic cirrhosis as part of NAFLD/NASH in the absence of any histologic characteristics of steatohepatitis. In such cases, a rigorous search should be made for secondary disorders, including viral hepatitis, surreptitious alcohol use, sclerosing cholangitis, and drug-induced liver disease, etc.

Management

At the present time, the initial approach involves dietary modification based on the metabolic profile (obesity, diabetes, hyperlipidemia, hypertension) and getting patients to increase levels of physical activity. The assistance of a dedicated dietician is critical in achieving target outcomes. Besides its impact on fatty liver, such a program would have salutary effects on prevention of diabetes and cardiovascular disease. Earlier studies suggested that reduction of body weight by 10% can normalize liver tests, but recent data have shown that even smaller changes in body weight (0.5–3 kg) can achieve improvement in hepatic necroinflammatory activity and/or radiologic resolution of hepatic steatosis and/or reversal of insulin resistance.^{83,84} While robust evidence to confirm the effectiveness of lifestyle measures is yet to accrue,⁸⁵ the working party considered that this should remain the cornerstone of management. The evidence for this is considered further in the review by Chan *et al.* in this issue of JGH.³⁷

Another important aspect of patient care is that those with NAFLD have a high risk of developing new complications of insulin resistance and metabolic syndrome, such as hypertension, diabetes, and dyslipidaemia. Thus, the working party felt obliged to emphasise for practitioners and affected persons alike the importance of engaging patients in regular screening for these disorders, as well as for the cancers for which obesity and insulin resistance are risk factors. The working party also considered the

evidence in respect of putative pharmacologic therapies, up to and including those present in late October 2006. As others have pointed out,⁸² there is some promise and much interest in this field, particularly for agents such as metformin and the thiazolidinediones ('glitazones'). However, to-date there is insufficient evidence of benefits, as well as outstanding concerns about treatment course, adverse effects, and cost, to warrant recommendation for pharmacotherapy against NAFLD in the immediate future. Finally, the most consistent and spectacular evidence for treatment efficacy against NASH comes from literature on obesity surgery (Level 1a), in which highly reproducible benefits against steatosis, steatohepatitis, and hepatic fibrosis have been reported.^{2,86} For this reason, the working party endorsed referral to specialized obesity management centers those patients with NAFLD who are obese and fail to respond to lifestyle measures. There is no evidence of harm from contemporary surgical and endoscopic approaches to bariatric surgery, and in the working party's view, patients should not be denied the opportunity to undergo a procedure that could radically improve their metabolic and hepatic health.

Concluding remarks: a view of the future

In seeking to make evidence-based recommendations on definition, assessment, and management of NAFLD, the Asia-Pacific Working Party was aware that there were no similar guidelines from other regions or authoritative bodies, and that this is a relatively new and rapidly changing field. Nonetheless, it seemed timely to focus attention on the realities of this burgeoning problem, and to assemble the data from studies in this region, not all of which have been published in English, so as to dispel forever the myth that fatty liver disease occurs in lean subjects in Asia. Doubtless the attempt to provide operational definitions of NAFLD will attract critical comment: this is an anticipated challenge that will, hopefully, lead to the search for new evidence that may ultimately support stronger definitions in future. Studies of biomarkers and of imaging techniques to quantify hepatic fat partitioning are promising approaches and should be encouraged in future research.

Use of the proposed definitions (or inevitable improvements in their iteration) will allow investigators to pool their resources of clinical and community based databases, thereby allowing more adequate definition of the natural history of NAFLD in this region. Further, if NAFLD is part of metabolic syndrome,¹⁰⁻¹⁴ as so strongly asserted by the evidence reviewed by this working party (see particularly the next two reviews in references 39 and 10 respectively), then there are implications for earlier recognition of metabolic risk factors during assessment of patients with fatty liver^{14,87} and there are clear obligations for long-term management, as stipulated by the fourth review.³⁷

Finally, while we were unable to recommend any present pharmacologic agent for treatment of NAFLD (albeit some show promise in small, short-term randomized controlled trials), we were able to make an evidence-based recommendation for lifestyle intervention (and not simply weight reduction) in this disorder. Ultimately, if as contended here, NAFLD affects at least one-quarter of the urbanized Asian population at this time of economic development, drug therapy is going to be an expensive option. Metabolic disorders like NAFLD, diabetes, and metabolic syn-

drome are classic chronic diseases in which genetically susceptible individuals are challenged by environmental circumstances that ultimately lead to disease. With metabolic disorders the environmental 'stress' is over-nutrition, imbalance between energy needs, and energy (food) intake. Concerted action by regional societies, and public health policies by governments, are needed to effectively tackle over-nutrition as a cause of liver disease.

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