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REVIEW ARTICLE

Non-alcoholic fatty liver disease: An emerging liver disease in Taiwan

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Non-alcoholic fatty liver disease (NAFLD) is the most common liver disorder in Western countries, and has become increasingly recognized as a public health problem in Taiwan. Patients with non-alcoholic steatohepatitis, a more severe form of NAFLD, may progress to cirrhosis and its related complications, including hepatocellular carcinoma. Since NAFLD is highly linked to metabolic syndrome, such patients may have increased risks of complications related to both liver disease and metabolic syndrome. Therefore, if we fail to cope with this growing health problem, NAFLD may gradually replace viral hepatitis as the major etiology of liver disease in Taiwan.
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Abbreviations: ALT, alanine aminotransferase; APASL, Asian Pacific Association for the Study of Liver; CHB/C, chronic hepatitis B/C; HB/CV, hepatitis B/C virus; HCC, hepatocellular carcinoma; HOMA-IR, homeostasis model assessment-insulin resistance; NAFLD, non-alcoholic fatty liver disease; MetS, metabolic syndrome; NASH, non-alcoholic steatohepatitis; T2DM, type 2 diabetes mellitus.

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Introduction

Non-alcoholic fatty liver disease (NAFLD), which describes a condition of fat accumulation in the liver in the absence of excessive alcohol consumption and specific causes of hepatic steatosis,[1] is the most common liver disorder in the world, affecting 20—40% of the general population in Western countries and 5—40% in the general population across the Asia-Pacific region.[2,3] The prevalence of NAFLD, including the more aggressive non-alcoholic steatohepatitis (NASH), is increasing in parallel with the growing pandemics of obesity, type 2 diabetes mellitus (T2DM), and metabolic syndrome.[4] A certain proportion of NASH patients progress to cirrhosis and its related complications, such as hepatocellular carcinoma (HCC).[5] Previous studies showed that 10—29% of NASH patients may develop cirrhosis within 10 years,[6] and 4—27% of these cirrhosis patients may have HCC[4] (Fig. 1). Therefore, NAFLD/NASH will gradually become the major etiology of chronic liver disease worldwide.

Large population-based surveys in the Asia-Pacific region indicated that the prevalence rates of NAFLD range from 12% to 24% in population subgroups, depending on age, gender, ethnicity, and geographic location (urban vs. rural). In Taiwan, the prevalence of NAFLD is about 11.4—41% in two studies,[7,8] and the rates are higher in population subgroups, from 66.4% in healthy taxi drivers[9] to 80% in obese individuals who attended weight reduction programs.[10] Although viral hepatitis continues to rage in Taiwan, the health impact of NAFLD has become increasingly recognized, and is likely to be a huge disease burden in the future. Therefore, it is time for us to formulate strategies in advance to cope with this growing health problem.

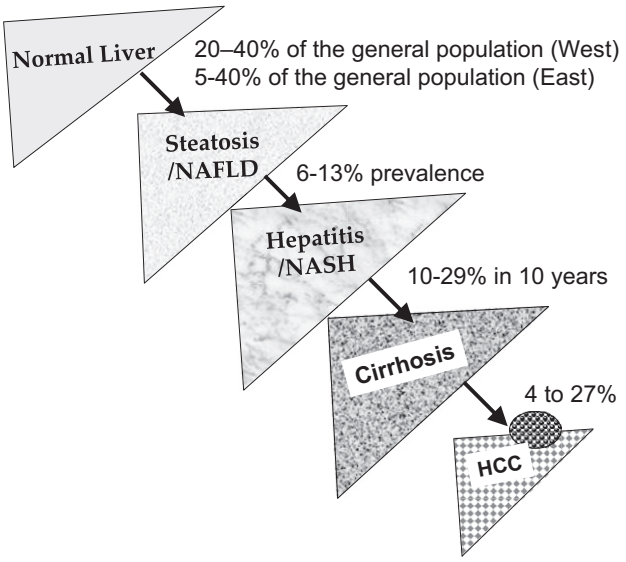

Figure 1 Natural history of nonalcoholic fatty liver disease (NAFLD). NAFLD affects 20—40% of the general population in Western countries and 5—40% across the Asia-Pacific region. The prevalence of its more aggressive form, nonalcoholic steatohepatitis (NASH), is about 6—13%. About 10—29% of NASH patients progress to cirrhosis within 10 years, 40—62% of them develop a complication of cirrhosis, and 4—27% of patients with NASH-related cirrhosis may have hepatocellular carcinoma (HCC) over time.

Diagnosis of NAFLD

Fatty liver or hepatic steatosis is characterized by triglyceride accumulation within the cytoplasm of hepatocytes, and includes a spectrum of liver disease from a benign simple steatosis, steatohepatitis, to fibrosis, and may progress to liver cirrhosis, liver failure, and hepatocellular carcinoma.[11] Several conditions have been linked to fatty liver. Among them, alcoholic liver disease and NAFLD are most common.

NAFLD is a more widely used term than "non-alcoholic steatohepatitis," which was originally developed by Ludwig in 1979 to describe an alcoholic-like liver disease in patients who do not drink alcohol[12,13] on the basis of histological findings. Patients with NAFLD usually have slightly elevated liver enzyme values, deny excessive alcohol consumption, and have negative laboratory tests suggestive of viral hepatitis, autoimmune liver disease, and congenital causes of chronic hepatitis.

Although fatty liver may be identified by imaging modalities including ultrasonography, computed tomography (CT), and magnetic resonance imaging with a reasonably high sensitivity (~80% for 30% steatosis),[14] steatohepatitis and fibrosis cannot be judged merely on image findings. Several new imaging modalities and biomarkers are emerging and may provide more detailed information about hepatic tissue or even replace biopsy, although most of them are not available on clinical practice, are expensive, need further validation, and remained research tools up to now.[1,15,16] Accordingly, liver histology remains the gold standard for the diagnosis of NAFLD/NASH.[12,16,17] Because it is often impractical to use a pathological definition in clinical practice and research studies, an operational definition of NAFLD has been proposed in the Asia-Pacific region.[18]

According to the proposed Asian Pacific Association for the Study of Liver operational definition, fatty liver can be defined by the presence of at least two of three abnormal findings on abdominal ultrasonography: diffusely increased echogenicity ("bright") liver with liver echogenicity greater than kidney or spleen, vascular blurring, and deep attenuation of ultrasound signal. NAFLD is highly likely provided that the other causes of liver disease have been rigorously ruled out, particularly significant alcohol intake (more than 140 g weekly in men, 70 g weekly in women), hepatitis B, hepatitis C, and medication use. Alternatively, in patients with otherwise unexplained alanine aminotransferase (ALT) elevation, NAFLD is highly likely to be the cause if hepatic imaging results compatible with fatty liver, and metabolic risk factors are also present. However, in some clinical settings, liver biopsy is usually the first-line procedure for the diagnosis of NAFLD, such as in cases whose diagnosis are uncertain, who are at risk of advanced hepatic fibrosis (in the absence of clinical or imaging evidence of cirrhosis), or had both chronic liver diseases other than NAFLD and metabolic risk factors, or enrolled in clinical trials, or subjected to laparoscopy for another purpose (because of

reduced risk and greater convenience, e.g., cholecystectomy, gastric banding),[18] or during elective surgical procedure (such as anti-obesity surgery).[16] On the other hand, liver biopsy should not be performed in patients with recent weight change. A watchful period (4–6 months) is useful, aimed at enforcing diet and lifestyle measures. If these measures failed in weight loss, ALT normalization, and a reduction of insulin resistance (IR), liver biopsy should be considered after balancing the risk for advanced fibrosis (age, diabetes, IR), patient motivation, and competing comorbidities.[16]

Prevalence, clinical significance, and risk factors of NAFLD worldwide

With the rising prevalence of obesity and T2DM worldwide, NAFLD has become a major public health problem.[19] Although NAFLD and NASH are now considered to be common causes of chronic liver disease, an increasing indication for liver transplantation and a possible cause of HCC,[12] it is difficult to determine the true prevalence of NAFLD worldwide because of the problematic interpretation of data from various studies, such as referral bias, population heterogeneity, study design, imaging modalities used, and use of liver biopsies. On the basis of hepatic imaging and/or quantification of hepatic triglyceride content, the prevalence of fatty liver disease in Western countries is estimated to be 24–42%, depending on gender and ethnicity,[12,13] and is higher in population subgroups, such as 80% in obese individuals.[20] Of particular note, about 3–15% of the general population has NASH.

Risk factors associated with the development of NAFLD include older age, obesity, T2DM, as well as dyslipidemia.[21] Therefore, NAFLD was conceptualized as a part of metabolic syndrome (MetS).[12,13,22,23] However, the association of NAFLD with metabolic risk factors is only evident when regional definitions of anthropometry are used.

NAFLD in the Asia-Pacific region

In the past, NAFLD has been thought 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.[2,3] However, the major risk factors for NAFLD, like glucose intolerance and T2DM, obesity, dyslipidemia, and metabolic syndrome, are widely prevalent in the Asia-Pacific region and increasing in geometric proportions.[19,24] Therefore, recent surveys by using ultrasonography indicated that the prevalence of NAFLD in the general population across Asia-Pacific region varies from 5% to 30%.[20] In addition, a study from Japan demonstrated a 2.4-fold increasing prevalence of fatty liver over a 12-year period,[25] an implication that the prevalence is indeed increasing in this region.

Prevalence and risk factors of NAFLD in Taiwan

Although some studies use laparoscopy or liver biopsy to diagnose NAFLD in obese patients,[26,27] the diagnostic criteria for NAFLD among most epidemiologic studies in Taiwan are based on the history without excessive alcohol intake, chronic viral hepatitis, as well as known etiologies of liver disease and ultrasonographic findings consistent with fatty liver (Table 1).[7–10,24,26,28,30–32,40,50,51] Several studies on the general population and those undergoing a health checkup showed the prevalence of NAFLD, ranging from 11.4% to 41% in Taiwan.[7,8] The prevalence is higher in population subgroups, from 66.4% among 1635 volunteer healthy taxi drivers (1541 males and 94 females)[9] to 80% in 210 apparently healthy obese individuals who attended weight reduction programs.[10] In adolescents, the prevalence of NAFLD increased progressively from 16.0% in the normal group to 50.5% in the overweight group, and 63.5% among obese individuals.[28]

On the other hand, in a general population study that included 11.4% (372/3260) individuals with elevated ALT, NAFLD appears to be the most common cause of ALT elevation and presumed liver injury in Taiwan, with a prevalence of 33.6%, and followed by HBV (28.5%), unexplained cause (21.8%), HCV (13.2%), both HBV and HCV (2.2%), and excess alcohol consumption (0.8%). In addition, the prevalence of ALT elevation in NAFLD was 18.1% (125/691) in adults[29] and 23.3% (20/86) in adolescents.[28]

Risk factors associated with the presence of NAFLD in Taiwan have been examined in the general population, obese persons, or individuals who received laparoscopy, and male gender, older age, BMI, obesity, waist circumference, diabetes, hypercholesterolemia, hypertriglyceridemia, hypertension, elevated ALT, homeostasis model assessment-insulin resistance (HOMA-IR), and hyperuricemia are the identified risk factors.[7,10,28,30,31] Of patients with metabolic disorders, waist circumference and IR are independently associated with fatty liver in obese individuals,[10] and only hypertriglyceridemia was related to NAFLD in non-obese individuals. In addition, presence of MetS, high blood pressure, and high fasting glucose are independent factors related to an increased risk of NASH.[26]

Therefore, the development of NAFLD in Taiwan is closely associated with metabolic derangements, as observed in other Asian countries. Metabolic disorders are also related to ALT elevation in patients without known etiologies of liver disease.

NAFLD and HCV in Taiwan

As hepatic steatosis is a well-known feature for patients with HCV infection and may affect disease progression and therapeutic response of antiviral therapy for Western chronic hepatitis C (CHC) patients, it is thus important and interesting to know the impact of hepatic steatosis on Taiwanese CHC patients. To this end, Liu et al[32] enrolled 95 naive Taiwanese patients infected with either hepatitis C virus (HCV) genotype 1 ($n = 57$) or 2 ($n = 38$), receiving interferon alone ($n = 41$) or in combination with ribavirin ($n = 54$) therapy, and had available liver histological data. In their study, about 44 (46%) patients had steatosis and four (4%) patients had steatohepatitis. They demonstrated the associations of steatosis and hyperglycemia ($p = 0.01$), hypertriglyceridemia ($p = 004$), as well as body mass index ≥ 27 ($p = 0.009$), while not with HCV genotype or viral load. Of note, the grade of steatosis correlated well with the

Table 1 NAFLD studies in Taiwan.

Key issue	Authors (year)	Case number	Diagnosis	What is known	Reference
Prevalence and Risk factors	Hsiao et al (2004)	210	Ultrasonography plus elevation of serum ALT levels	The prevalence of NAFLD was 20.5% in obese patients. Both insulin resistance and ferritin elevation were significantly associated with NAFLD in obese patients.	10
	Lin et al (2005)	187 (33 with NAFLD)	Ultrasonography plus elevation of serum AST and ALT levels	The HFE mutations may not contribute to iron accumulation in CHC or NAFLD patients in Taiwan.	8
	Chen et al (2006)	3245	Ultrasonography and history	NAFLD is closely associated with elevated ALT, obesity, diabetes mellitus, hypercholesterolemia, hypertriglyceridemia, and hyperuricemia. Serum ALT level was not a good predictor in individuals with NAFLD.	7
	Huang et al (2007)	111	Laparoscopic bariatric surgery	MetS and NASH were common in severely obese Taiwanese adults. Presence of MetS, high blood pressure, and high fasting glucose increased the risk of NASH.	26
	Fan et al (2008)	126	Laparoscopic bariatric surgery	Laparoscopic inspection of the abdominal cavity provides important and additional information for the final diagnosis of chronic liver diseases and detection of possible pathology in patients.	24
	Fu et al (2009)	220	Ultrasonography and testing negative for serum HBsAg and anti- HCV antibody	Obesity, ALT abnormality and elevated non-HDL-cholesterol are risk factors for NAFLD in adolescents. However, ALT alone is not a sufficient indicator; and ultrasonography of the liver should be part of the routine health examination of obese adolescents.	28
	Tung et al (2011)	1635	Ultrasonography	Gender-related differences of NAFLD. Hypertension, hyperuricemia, higher AST, higher ALT, hypertriglyceridemia, and higher fasting plasma glucose were significantly related to NAFLD in males but not related to NAFLD in females.	9
				Risk factors of NAFLD include male gender, older age, BMI, obesity, waist circumference, diabetes, hypercholesterolemia, hypertriglyceridemia, hypertension, elevated ALT, homeostasis model assessment-insulin resistance (HOMA-IR) and hyperuricemia.	7,10,26,28,30,31
NAFLD and HCV	Liu et al (2005)	95	Pathology	Hepatic steatosis in Taiwanese patients with CHC was associated with metabolic syndrome, but not with HCV genotype, advanced fibrosis or the response to antiviral therapy.	32
Pathophysiologic studies	Chu et al (2007)	144 (94 with NAFLD)	Ultrasonography	Modest correlations between plasma levels of TNF-alpha with ALT and triglyceride, and NAFLD patients with abnormal ALT had significantly higher plasma TNF-alpha levels than controls.	40

	Lin et al (2005)	187 (33 with NAFLD)	Ultrasonography and elevated serum AST or ALT	HFE mutations may not contribute to iron accumulation in the CHC or NAFLD group even when serum iron overload is observed in more than one-third of these patients in Taiwan.	[8]
Treatments for NAFLD	Wang et al (2006)	68	Ultrasonography and elevated serum AST and/or ALT	Rosiglitazone is well tolerated and might improve liver function of one-third patients with NAFLD and type 2 diabetes.	[51]
	Chen et al (2008)	54	Ultrasonography	Diet-plus-exercise and exercise-only therapeutic lifestyle programs are effective for improving anthropometric indices, insulin sensitivity, ultrasound findings and physical fitness in NAFLD patients. Only the diet-plus-exercise program resulted in significant improvement in liver biochemistry.	[52]

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; CHC = chronic hepatitis C; MetS = metabolic syndrome; NAFLD = non-alcoholic fatty liver disease; NASH = non-alcoholic steatohepatitis.

number of MetS parameters ($p = 0.018$), but not with lower sustained response rate. And the improvement of steatosis after treatment ($n = 19$) did not correlate with HCV genotype ($p = 0.850$) or sustained response to antiviral therapy ($p = 0.246$). Therefore, they concluded that hepatic steatosis in Taiwanese patients with CHC was associated with features of the metabolic syndrome, but did not correlate with HCV genotype, advanced fibrosis, or the response to antiviral therapy.[32]

Pathogenesis of NAFLD

In the traditional "two hit" model of NASH pathogenesis, steatosis (the "first hit") will sensitize the liver to the "second hit," such as oxidative stress, cytokines, free fatty acids, as well as endoplasmic stress, and then leads liver to inflammation, fibrosis, and ultimately cirrhosis.[33] However, because all of these "second hits" can contribute to both steatosis and progressive liver disease, current lines of evidence have implied that steatosis may be a part of the liver's early adaptive response to stress, rather than a prerequisite "hit," and the "second hit," oxidative stress, free fatty acids, endoplasmic stress, as well as cytokines are the true "hit."[33–35] Therefore, in consideration of the mechanisms of cellular injuries and fibrosis in NAFLD patients, the "second hit" deserves much more attention.

Accordingly, many hepatic and extrahepatic mediators have been identified to play important roles in the development of inflammation and fibrosis of NASH/NAFLD patients.[16] Some of them are produced directly as results of steatosis, hepatocyte injury, and apoptosis, such as IR,[36] reactive oxygen species, and cytokines, or derived from Kupffer cell, T-cell, hepatic stellate cells, and other inflammatory cells[37]; meanwhile, others are released indirectly as a response to hepatocyte injury or gut-derived bacterial products,[38] including lipopolysaccharide and adipocytokines.[39] Since all of them are potentially therapeutic targets for NAFLD, studies focusing on these mediators and mechanisms have increased dramatically and worldwide in recent decades.

Pathophysiologic studies of NAFLD in Taiwan

Several studies in Taiwan have also examined the pathophysiologic mechanisms of NAFLD. For example, Chu et al[40] compared the differences of proinflammatory cytokines, IL-6, and IL-8, as well as disease severity between 94 NAFLD patients and 50 matched controls. They found that, compared with control group, NAFLD patients had significantly higher BMI ($p < 0.001$), fasting sugar ($p = 0.002$), cholesterol ($p = 0.017$), and triglyceride ($p < 0.001$) level. NAFLD patients with abnormal serum ALT had higher plasma IL-8 levels (42.87 ± 16.58 pg/mL) than control groups (9.19 ± 1.75 pg/mL, $p = 0.028$), but with comparable plasma IL-6 levels.[40] In addition, the authors also evaluated the role of TNF-alpha in the pathogenesis of NAFLD and demonstrated differential plasma TNF-alpha levels between NAFLD and healthy individuals. They found that there were modest correlations between plasma levels of TNF-alpha with ALT ($r = 0.25$, $p < 0.005$) and triglyceride ($r = 0.40$, $p < 0.001$), and NAFLD patients with abnormal

ALT had significantly higher plasma TNF-alpha levels than controls (2.63 ± 0.44 vs. 1.56 ± 0.10 pg/mL, $p = 0.016$).[41]

On the other hand, Lin et al[8] examined HFE mutations and iron accumulation among 125 healthy individuals, 29 patients with CHC, and 33 patients with NAFLD in Taiwan. They found that all the enrolled participants were free from C282Y mutation, and the distributions of H63D mutation were comparable among healthy individuals, the CHC group, and the NAFLD group. Although 34.48% of CHC patients and 36.36% of NAFLD patients had increased serum iron store, there was no significant difference in the prevalence of HFE mutations between patients with increased serum iron store and those without in CHC or NAFLD group. Therefore, they concluded that HFE mutations may not contribute to iron accumulation in the CHC or NAFLD group even when serum iron overload is observed in more than one-third of these patients in Taiwan.[8]

Recently, Hsiao et al[42] studied the beneficial effects of pioglitazone in NAFLD patients by using a high fat diet mice model and demonstrated the diminished oxidative damage of pioglitazone in "NAFLD" mice. They found that the high-fat diet induced hepatic steatosis may be improved by adding pioglitazone. Moreover, the increased oxidative stress and DNA damage, such as increased malondialdehyde concentration and 8-oxoG staining in the high-fat diet group, were attenuated by pioglitazone, and decreased gene expressions of antioxidant defense mechanism—Sod1, Sod2, Ogg1, and MutY in the high-fat diet group—were reversed by pioglitazone coadministration.[42]

In addition, different kinds of animal models were used to explore the pathophysiologic mechanisms of NAFLD in Taiwan. For examples, Lin et al. studied the mechanisms that androgen/androgen receptor signaling regulates insulin sensitivity in hepatic androgen receptor-knockout mice [43]. Yeh et al[44] examined the effects of high energy infusion and insulin treatment in diabetic rats. Chen et al[45] examined the effects of Metformin on gene expression and post-translational processing in laying hens. Amali et al[46] used TAA-treated zebrafish as a model of steatohepatitis, and Her et al[47] also used zebrafish to study the link between gankyrin, microRNAs, and liver steatosis. Interestingly, soft-shelled turtle was also used to examine the effect of dietary highly unsaturated fatty acids on lipid peroxidation of muscle and liver tissues in Taiwan.[48]

Assessment and management of NAFLD patients

Because of the possibility of disease progression and a close link with metabolic syndrome, patients with NAFLD should be monitored for the changes in liver disease severity, components, and complications of the MetS.[15,18] Therefore, several assays need to be used for the evaluation of liver function and complications of cirrhosis, such as ALT, platelet count, serum albumin, bilirubin, and prothrombin time. Abdominal ultrasonography may also be performed for the surveillance of HCC, particularly in patients with NASH-related cirrhosis (cryptogenic cirrhosis). Nevertheless, more studies are required to determine the benefit and cost-effectiveness of HCC surveillance in NAFLD patients. In addition, insulin resistance (HOMA-IR) score, which is calculated by serum glucose (mg/dL × 0.05551) × serum insulin (mU/L) divided by 22.5),[49] and complications of MetS are required for screening and assessment, such as waist circumference (central obesity for Asian criteria), body height and weight (BMI), fasting blood glucose, serum lipids, blood pressure, and oral glucose tolerance test (if fasting blood glucose is ≧5.6 mmol/L, no history of diabetes).[15]

The rationale for NAFLD/NASH treatment is to prevent or reverse hepatic injury induced by lipotoxicity.[16] Although the best management strategy for NAFLD is yet to be defined, two strategies have been proposed at the 2009 European Association for the Study of the Liver meeting. The first strategy is to correct IR and hyperinsulinemia as well as reduce visceral adiposity, and the second is to prevent or reverse hepatic cellular injury.[16] For the first strategy, weight loss, physical exercise, diet changes, reduction of sedentary lifestyle, insulin-sensitizing agents, and anti-obesity surgery are options, while lifestyle measures including diet control and increasing physical activity such as aerobic exercise are the first-line treatment and mainstay of management recommended by the Asia-Pacific Working Party on NAFLD.[18] Accordingly, some weight reduction is usually required, and even limited physical activity more than none or any increase over baseline in physical exercise is preferable. Although the minimal amount of weight loss and physical activity has not been determined, targets supported by several International Societies for diabetes prevention could be applied in NAFLD/NASH patients. Ideally, the best regimen for NAFLFD/NASH is a long-term, multidisciplinary, and personalized approach,[50] while the most effective regimen and long-term adherence remain unclear and need future studies.[18]

The role of pharmacotherapy remains investigational and is not recommended for clinical practice. Specific pharmacological treatment is not recommended for NAFLD patients, but identified metabolic risk factors, such as diabetes mellitus and dyslipidemia, should be treated and screened for regularly. For example, use of statins to treat hypercholesterolemia is safe and recommended. Obese patients who do not respond to attempted lifestyle measures should be referred to centers specializing in obesity management. In those refractory to medical measurements, consideration should be given to bariatric surgery or gastric ballooning.[15,18] For specific liver-directed therapy to prevent or reverse hepatic cellular injury, as there is still no approved medication for NAFLD/NASH, all these liver-directed therapies should be considered experimental for now and need to be further examined especially for their long-term effects on histological endpoints and safety in the near future.

Managements studies for NAFLD in Taiwan

In Taiwan, two studies examined the effects of treatments on patients with ultrasound-diagnosed NAFLD.[51,52] First, Wang et al[51] evaluated the safety and effectiveness of rosiglitazone in 68 inadequately controlled type 2 diabetes patients with NAFLD, and found that it was reasonably well tolerated and might improve one-third of patients' liver function after treatment. In their study, only two (2.9%)

patients discontinued the treatment due to increase of aspartate aminotransferase (AST) or ALT levels to more than three times the upper limit of normal, and among the 60 patients who completed the study treatment, mean fasting plasma glucose, A1C, fasting plasma insulin, mean ALT, and HOMA-IR were all significantly reduced, whereas body weight was increased by a mean of 2.6 $\pm$ 2.4 kg ($p < 0.001$). In addition, 20 (33.3%) patients maintained their normal AST and ALT levels for at least three consecutive measurements and through the end of the study period. Second, Chen et al investigated the effects of varied therapeutic lifestyle programs on 54 patients with ultrasound-diagnosed NAFLD. They divided the participants into three groups—(1) diet plus exercise group ($n = 16$), (2) exercise group ($n = 23$), (3) control group ($n = 15$) —and found that both 10-week diet-plus-exercise and exercise-only therapeutic lifestyle programs are effective for improving anthropometric indices, insulin sensitivity, ultrasound findings, and physical fitness in NAFLD patients. However, only the diet-plus-exercise program resulted in significant improvement in liver biochemistry.[52]

Perspectives

The prevalence of NAFLD in Taiwan is similar to other Asian countries. Along with the increasing trends in westernized lifestyle (including overnutrition, sedentary lifestyle), obesity, diabetes mellitus, as well as metabolic syndrome, a further increase in the clinical significance of NAFLD/NASH is anticipated. Of particular note is that NASH, albeit mild and slowly progressive, indeed exists in Taiwan.[53] Therefore, after the control of chronic hepatitis B and C, NAFLD/NASH will become the most prominent liver disease and prophylactic measure, and active management strategies should be planned and implemented in time. Unfortunately, essential information regarding the active management of NAFLD remains deficient and more data are needed before the development of a practical and effective guideline. For example, clinical trials including active prophylactic measures and studies with long-term follow-up, especially on the durability of management, are needed. In addition, the diagnostic accuracy of all noninvasive measurements used to identify liver fibrosis seldom exceeds 75% to 80%.[54] Furthermore, most of these measurements are not available in our daily clinical practice[55,56] and may not substitute for liver biopsy in the management of NAFLD. Therefore, effective and practical measurements to assess the severity of NAFLD are still lacking. Finally, interaction between NAFLD and other liver diseases is a concern, especially in Taiwan where viral hepatitis is rampant. For example, diabetes and obesity have been linked to several important malignancies, including HCC, which is a well-known complication of chronic hepatitis in Taiwan.[57] However, patients with chronic HCV infection are usually associated with a lower serum lipid profiles than healthy adults,[58] and a clearance of HCV may increase the risk of cardiovascular diseases in some participants.[59] Therefore, the situations are more complicated than ever, and not just a question of treat-or-not. Several issues remain unsolved and need further studies, such as the impact of NAFLD on disease progression of other liver diseases or therapy, interactions, and pathophysiological mechanisms.

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