

Non-alcoholic fatty liver disease in 2015

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Author contributions: Ahmed M solely contributed to this work.

Conflict-of-interest: None to declare.

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Received: August 23, 2014

Peer-review started: August 25, 2014

First decision: November 3, 2014

Revised: April 18, 2015

Accepted: April 28, 2015

Article in press: April 30, 2015

Published online: June 18, 2015

Abstract

There is worldwide epidemic of non-alcoholic fatty liver disease (NAFLD). NAFLD is a clinical entity related to metabolic syndrome. Majority of the patients are obese but the disease can affect non-obese individuals as well. Metabolic factors and genetics play important roles in the pathogenesis of this disorder. The spectrum of disorders included in NAFLD are benign macrovesicular

hepatic steatosis, non-alcoholic steatohepatitis, hepatic fibrosis, cirrhosis of liver and hepatocellular carcinoma. Although the disease remains asymptomatic most of the time, it can slowly progress to end stage liver disease. It will be the most common indication of liver transplantation in the future. It is diagnosed by abnormal liver chemistry, imaging studies and liver biopsy. As there are risks of potential complications during liver biopsy, many patients do not opt for liver biopsy. There are some noninvasive scoring systems to find out whether patients have advanced hepatic fibrosis. At the present time, there are limited treatment options which include lifestyle modification to loose weight, vitamin E and thio-glitazones. Different therapeutic agents are being investigated for optimal management of this entity. There are some studies done on incretin based therapies in patients with NAFLD. Other potential agents will be silent information regulator protein Sirtuin and antifibrotic monoclonal antibody Simtuzumab against lysyl oxidase like molecule 2. But they are still in the investigational phase.

Key words: Fatty liver; Hepatic steatosis; Non-alcoholic fatty liver disease; Non-alcoholic steatohepatitis

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Core tip: While non-alcoholic fatty liver disease is a very common clinical problem in our day-to-day clinical practice, the management of this disease is still in its infancy. This article focuses on the epidemiology, pathogenesis, pathology, clinical presentation, investigations including noninvasive scoring systems, current treatment options and future potential agents.

Ahmed M. Non-alcoholic fatty liver disease in 2015. *World J Hepatol* 2015; 7(11): 1450-1459 Available from: URL: <http://www.wjgnet.com/1948-5182/full/v7/i11/1450.htm> DOI: <http://dx.doi.org/10.4254/wjh.v7.i11.1450>

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a universal disorder which is now considered as the most common liver disease in the western world. NAFLD is defined as the accumulation of excessive fat in the liver in the absence of excessive drinking of alcohol and any secondary cause. Although initially benign, the disease can progress slowly from simple non-alcoholic steatosis (NAS) to non-alcoholic steatohepatitis (NASH) and subsequently to hepatic fibrosis, cirrhosis of liver and hepatoma. At the present time, there is no specific test which can predict progression of NAS to NASH. Although cirrhosis of liver secondary to hepatitis C is now the most common indication of liver transplantation in the United States, as the prevalence of NAFLD is increasing, NASH-related cirrhosis and hepatocellular carcinoma will be a major health care problem and the leading indication of liver transplantation in the future. As the epidemic of NAFLD is mainly related to insulin resistance, different therapies are now being directed to improve insulin resistance.

EPIDEMIOLOGY

Twenty percent to 30% of the general population in the western world suffer from NAFLD^[1]. The prevalence is increased in type 2 diabetes mellitus (70%) and morbid obesity (90%). This correlates with the rising incidence of obesity and metabolic syndrome in the western world. In the United States, the National Health and Nutrition Examination Surveys from 2009-2010 showed obesity rates of 35.5% among men and 35.8% among women^[2]. In Asia, similar prevalence of NAFLD has been found in the range of 15% to 30% in the general population and over 50% in patients with diabetes and metabolic syndrome^[3]. In the general population of United States, the prevalence of NASH is about 3% but could be more than 25% in obese individuals^[4].

PATHOGENESIS

Obesity is an important risk factor for the development of NAFLD. Obesity may lead to insulin resistance and metabolic syndrome which is diagnosed in the presence of 2 or more of the criteria: (1) impaired glucose tolerance (fasting blood glucose > 110 mg/dL); (2) hypertension; (3) hypertriglyceridemia (> 250 mg/dL); (4) low high density lipoprotein (HDL) level (< 40 mg/dL for men and < 50 mg/dL for women); and (5) abdominal obesity (waist > 40 inches for men and > 35 inches for women).

In fact, hepatic manifestation of metabolic syndrome is NAFLD^[5]. Insulin resistance may also be responsible for the development of NAFLD even in non-obese and lean individuals. How does insulin resistance cause hepatic steatosis? Insulin suppresses lipolysis in adipose tissue. Insulin resistance in the adipose tissue leads to continued lipolysis, increased plasma free fatty acid (FFA) and FFA influx into the hepatocytes. Beta-oxidation of

fatty acid is also inhibited in the liver. Other factors which play roles in hepatic lipogenesis include dietary factors, *de novo* hepatic synthesis of lipid and genetics. Dietary fat in the form of chylomicron supplies FFA to the liver. Carbohydrate metabolism leads to *de novo* synthesis of FFA from acetyl CoA. Glucose also activates carbohydrate responsive element binding protein and promotes hepatic lipogenesis. Hepatic triglyceride is generally exported into the blood as very low density lipoprotein (VLDL) with the help of apolipoprotein B (APOB). Mutation in APOB may lead to hepatic steatosis^[6]. Insulin resistance can also occur in liver and skeletal muscle. Normally, insulin inhibits gluconeogenesis and promotes lipogenesis in the liver. In insulin resistant liver, gluconeogenesis continues leading to hyperglycemia and hyperinsulinemia while fatty acid synthesis is maintained in the liver. In the normal state, insulin also inhibits the production of VLDL. So in an insulin resistant state, the overproduction of VLDL in the fasting state leads to high triglyceride and low HDL in the blood. Why do obese individuals develop insulin resistance, *i.e.*, failure of insulin receptors to function? Obesity leads to hyperlipidemic and pro-inflammatory state^[7]. Hepatic insulin resistance occurs when there is excess FFA influx into hepatocytes. Metabolites of FFA - long-chain acyl-CoAs and diacylglycerol - relocate cytoplasmic several protein kinase C to the membrane. Protein kinase Cs then phosphorylate intracellular portion of insulin receptors with the development of insulin resistance. It has been proposed that excessive intraperitoneal fat can cause excessive FFA reflux directly into the liver *via* the portal vein^[8].

"Multiple hit" theory has been proposed in the pathogenesis of NAFLD^[9]. In the first hit, there is an accumulation of triglyceride as lipid droplets within the cytoplasm of hepatocytes (steatosis) in more than 5% of hepatocytes. Insulin resistance contributes to this hepatic steatosis. This phase of benign hepatic steatosis is reversible and can be self-limited but makes the liver susceptible to the second hit which advances the liver to a necroinflammatory stage, *i.e.*, NASH. The second hit includes oxidative stress (free radical formation due to excessive fatty acid oxidation), cardiolipin (present on inner mitochondrial membrane) peroxidation leading to mitochondrial dysfunction and more reactive oxygen species formation, pro-inflammatory cytokine formation, apoptosis and gut-derived bacterial endotoxemia.

The third hit includes palatine-like phospholipase 3 (*PNPLA3*) gene involvement, and impaired hepatocyte regeneration. A small proportion (29%) of patients with NAFLD have normal BMI. There are different genomic studies done to find out the genetic predisposition to NAFLD^[10-12]. Certain single nucleotide polymorphisms (SNPs) have been found to be associated with higher frequency, severe histologic changes and more progression of NAFLD. Variant SNPs in *PZP* and *PNPLA3* genes were found to be independent risk factors for the development of NAFLD. Hence genetics play an important role along with metabolic factors in the development of NAFLD.

CLINICAL PRESENTATION

Most patients with NAFLD remain asymptomatic until they develop cirrhosis of liver when they complain of fatigue. Even before development of cirrhosis, some patients may complain of right upper quadrant discomfort or pain due to hepatomegaly and stretching of the hepatic capsule^[13]. Physical examination may reveal obesity and hepatomegaly. When they develop cirrhosis of liver, they may present with cutaneous stigmata of liver disease (palmar erythema, spider nevi) or features of hepatic decompensation which include jaundice, ascites, edema, gastrointestinal bleeding and encephalopathy. Some of the clinical symptoms and signs are due to associated metabolic conditions such as diabetes mellitus, hypertension, and hyperlipidemia.

DIAGNOSIS: BIOCHEMISTRY, IMAGING AND HISTOLOGY

As most of the patients with NAFLD are free of symptoms during the pre-cirrhotic stage, they come to our attention when we find abnormal liver function tests or abnormal imaging studies done for some other reasons^[13]. Abnormal liver function test with mild to moderate elevation (1.5 to 4 fold) of serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels and greater elevation of ALT than AST (AST/ALT: < 1) unlike alcoholic liver disease can be found in patients with NASH. Sometimes this is picked up during routine Laboratory test or during routine monitoring of statin therapy for hyperlipidemia. In fact, in the western world, NAFLD is the commonest cause of incidental abnormal liver function test (LFT)^[14]. However, AST and ALT are not reliable markers of NASH as they can be normal even in advanced NAFLD. Generally, the AST:ALT ratio increases as the NAFLD advances from the necroinflammatory stage (NASH) to the fibrotic stage^[15].

Imaging studies may show abnormalities suggestive of fatty liver. In clinical practice, transabdominal ultrasound is most widely used as an initial imaging modality because of its availability, low cost and no radiation exposure. Positive findings may include hyperechogenicity of the liver parenchyma, *i.e.*, bright liver relative to spleen and right kidney, hepatomegaly and blurring of vascular margins. But abdominal ultrasound cannot detect mild hepatic steatosis and cannot differentiate simple steatosis, NASH and hepatic fibrosis^[16]. It is operator dependent, interfered by intra-abdominal gas and technically difficult with poor image quality in obese patients.

Non-contrast computed tomography (CT) scan may show hypodensity of the liver parenchyma as compared to spleen^[17]. Contrast-enhanced CT if done on a specific protocol (time interval 2 min and liver-spleen differential of 18.5 Hounsfield units) increases the sensitivity of detection of steatosis^[18].

CT involves ionizing radiation and cannot differentiate

different stages of NAFLD. Transabdominal ultrasound is more sensitive than CT in detecting hepatic steatosis^[19].

Magnetic resonance imaging (MRI) shows lower signal intensity of the hepatic parenchyma as compared to surrounding muscle and is more sensitive than CT scan for detection of hepatic steatosis. Hepatic triglyceride content can also be measured by MR techniques which decompose the liver signal into fat signal and water signal. Conventional MR technique (MR spectroscopy) measures the fraction of the liver signal attributable to hepatic fat. But in this technique, there can be many biological and technical confounding factors (T1 bias, T2* decay) and measurement of fat content may not be reliable^[20]. New MRI technique can detect the proton density fat-fraction (PDFF) attributable to hepatic fat and thus can measure hepatic fat content directly and generally shows correlation with histologic grades of NAFLD. As the disease progresses towards fibrosis, there is less steatosis, and this can be detected by MRI-determined PDFF^[21].

Histologic diagnosis of fatty liver disease by liver biopsy is the gold standard. As the histologic features of alcoholic and non-alcoholic liver disease are similar, history is very important in distinguishing these two entities. The person with NAFLD is a nondrinker or a social drinker but does not drink excessive amount of alcohol, *i.e.*, > 30 gm a day for men and > 20 gm a day for women within the last 5 years. According to Center for Disease Control and Prevention, a standard drink contains 14 gm (0.6 ounces) of pure alcohol. The standard drink could be 5 ounces of wine (12% alcohol) or 12 ounces of beer (5% alcohol) or 1.5 ounces of shot or liquor, *e.g.*, vodka, whiskey, gin, rum (40% alcohol) or 8 ounces of malt liquor (7% alcohol). As per the National Institute on Alcohol Abuse and Alcoholism, > 4 drinks on any given day or > 14 drinks per week in case of men, and > 3 drinks on any given day or > 7 drinks per week in case of women are considered heavy alcohol drinking. Thus detailed history of drinking of alcohol is very important despite the chance of inaccurate estimation. Diagnosis of NAFLD is established if there is no significant alcohol drinking history and there is fatty liver on imaging. Then the question comes whether the patient has simple steatosis, steatohepatitis, hepatic fibrosis or cirrhosis of liver. Liver biopsy is still the gold standard of finding out the histological picture of NAFLD as mentioned before.

In NAFLD, the simple steatosis is generally macrovesicular but mixed macro and microvesicular steatosis can also occur. There is fat deposition in the form of triglyceride in the cytoplasm of more than 5% of hepatocytes. In macrovesicular steatosis, the nucleus is displaced to the periphery of the hepatocyte by a single large fat globule or multiple small fat globules in the cytoplasm. In microvesicular steatosis, the nucleus remains in the center with many minute fat globules in the cytoplasm^[22]. The steatosis is more prominent in the perivenular regions of the hepatocytes (zone 3). NASH is characterized by the triad of steatosis, ballooning degeneration and inflammation^[23]. Ballooning

Table 1 Brunt classification of steatohepatitis^[27]

Grades of NASH	
Grade 1 (mild)	Steatosis up to 66%. Occasional ballooned hepatocytes predominantly in zone 3. Scattered intra-acinar neutrophils
Grade 2 (moderate)	Steatosis of any degree. Ballooned hepatocytes predominantly in zone 3. Intra-acinar neutrophils. Zone 3 perisinusoidal fibrosis. Mild to moderate portal and intra-acinar chronic inflammation
Grade 3 (severe)	Panacinar steatosis. Widespread ballooned hepatocytes predominantly in zone 3. Intra-acinar inflammation. Scattered neutrophils associated with ballooned hepatocytes. Mild to moderate portal inflammation
Stages of NASH	
Stage 1	Extensive zone 3 perisinusoidal fibrosis
Stage 2	Zone 3 perisinusoidal and portal or periportal fibrosis
Stage 3	Bridging fibrosis
Stage 4	Cirrhosis

NASH: Non-alcoholic steatohepatitis.

Table 2 Non-alcoholic steatosis or non-alcoholic fatty liver disease activity score is determined by evaluating the steatotic and inflammatory activity

NAS	Steatosis	Ballooning	Inflammation, lobular
0	< 5% (0)	None (0)	None (0)
3	5%-33% (1)	Rare or few (1)	1-2 foci per 20 × field (1)
6	34%-66% (2)	Many (2)	2-4 foci/20 × field (2)
8	> 66% (3)	Many (2)	> 4 foci/20 × field (3)

NAS: Non-alcoholic steatosis.

degeneration also considered as the hallmark of steatohepatitis is recognized by a swollen hepatocyte with foamy, pale cytoplasm and enlarged hyperchromatic nucleus. Loss of normal hepatocyte keratins 8/18 immunostaining can be helpful in the detection of the ballooned hepatocytes^[24]. Mild inflammation mainly involving the acini and sometimes the portal tract is the central feature in NASH. Mixed inflammatory cells consisting of lymphocytes, plasma cells, monocytes, eosinophils and neutrophils are found. Ballooned hepatocytes surrounded by neutrophils, a lesion called "satellitosis" can be rarely seen in NASH. Sometimes, intracytoplasmic inclusions (ubiquitin-rich) called Mallory's hyaline are found in the hepatocytes. As the disease progresses, portal inflammation becomes more severe. Hepatic fibrosis generally begins in zone 3. There is pericellular and perisinusoidal fibrosis giving characteristic "chicken wire" appearance. Portal and periportal fibrosis occurs as well. Then bridging fibrosis with central to portal, and central to central fibrous septa formation is seen, ultimately leading to macronodular or mixed cirrhosis of liver. At this stage, the characteristic triad of NASH and perisinusoidal fibrosis becomes less prominent or disappear. As a result, many times NASH-related cirrhosis are labeled as cryptogenic cirrhosis. This may lead to hepatic failure and hepatoma. One study showed that the chance of developing hepatoma in patients with cirrhosis secondary to NAFLD was 7% over 10 years time period^[25]. Non-cirrhotic NAFLD patients may also develop hepatoma possibly because of associated metabolic syndrome^[26].

As mentioned before that NAFLD is a spectrum of

disorders:

Simple steatosis → NASH → cirrhosis

NAFLD classification: type 1: Simple steatosis; type 2: steatosis + inflammation (lobular and portal) → NASH; type 3: steatosis + ballooned hepatocytes → NASH; type 4: steatosis + fibrosis → NASH.

Grades of hepatic steatosis: Hepatocytes containing fat vacuoles are subjectively visualized and graded. grade 0 (normal): < 5% of hepatocytes are affected; grade 1 (mild): 5% to 33% of hepatocytes are affected; grade 2 (moderate): 34% to 66% of hepatocytes are affected; grade 3 (severe): > 66% of hepatocytes are affected (Table 1).

NAS or NAFLD activity score is determined by evaluating the steatotic and inflammatory activity as Table 2.

Although liver biopsy is widely available and very helpful in staging and grading NAFLD, it is an invasive procedure with inherent risks of complications like pain at the biopsy site, intraperitoneal bleeding, subcapsular hematoma, infection and accidental injury to other organs. After liver biopsy, patients may need to stay at the hospital for several hours for recovery. Rarely (1%-3% of cases), patients may need to get admitted to the hospital and the mortality is 1 in 10000^[28]. Many patients are also reluctant to have liver biopsy done. As advanced hepatic fibrosis can eventually lead to cirrhosis of liver and hepatoma, assessment of patients with NAFLD and hepatic fibrosis is important (Table 3).

The Fibrosis 4 index was found to be superior when comparison was made among the non-invasive markers of fibrosis in patients with NAFLD.

Hepatic fibrosis can also be evaluated by hepatic elastography which measures liver stiffness. Hepatic elastography can be done by ultrasound or MRI^[34]. In ultrasound elastography also known as Fibroscan or Transient Elastography, a transducer on an ultrasound probe transmits ultrasound wave (50-MHz) into the liver which then produces an elastic shear wave (meter/sec). The shear wave passes faster through the fibrous tissue. The shear wave is then converted into liver stiffness (kilopascals)^[35]. Fibroscan is very sensitive (70%) and specific (84%) in detecting the stages of hepatic fibrosis^[36]. There are some technical issues

Table 3 Several noninvasive scoring systems based on indirect serologic markers of fibrosis are available to predict the presence or absence of advanced hepatic fibrosis

BARD (BMI > 28, AST/ALT \geq 0.8 and diabetes mellitus) score ^[29] : Score ranges from 0 to 4. BMI > 28 (yes = 1, no = 0) + AST/ALT (> 0.8 = 2, \leq 0.8 = 0) + diabetes mellitus (yes = 1, no = 0)	Score 0 to 1 means low probability of advanced hepatic fibrosis (negative predictive value 96%) and score 2 to 4 means high probability of hepatic fibrosis (positive predictive value 43%)
NAFLD fibrosis score: depends on age, BMI, diabetic status, AST, ALT, Platelet Count and albumin ^[30] : $-1.675 + 0.037 \times \text{age (yr)} + 0.094 \times \text{BMI (kg/m}^2\text{)} + 1.13 \times \text{IFG/diabetes (yes = 1, no = 0)} + 0.99 \times \text{AST/ALT ratio} - 0.013 \times \text{Platelet (10}^9\text{/L)} - 0.66 \times \text{albumin (g/dL)}$	If the score is < -1.455, there is low probability of advanced hepatic fibrosis (negative predictive value \geq 87%) and if the score is > 0.676, there is high probability of advanced hepatic fibrosis (positive predictive value \geq 78%). If the score is intermediate (between -1.455 and 0.676), there is indeterminate probability and these patients need to have liver biopsy for further assessment
Fibrosis 4 index: Uses age, AST, ALT and platelet count ^[31] : $\text{Age (yr)} \times \text{AST (U/L)/platelet (10}^9\text{/L)} \times [\text{ALT (U/L)}]^{1/2}$	If the score is < 1.30, there is low probability of advanced hepatic fibrosis (negative predictive value 90%), if the score is > 2.67, there is high probability of advanced hepatic fibrosis (positive predictive value 80%). If the score is intermediate (1.30 to 2.67), the possibility of having advanced hepatic fibrosis is indeterminate and liver biopsy is warranted
APRI ^[32] : $\text{AST level (IU/L)/AST upper limit of normal (IU/L)}/[\text{platelet count (10}^9\text{/L)}] \times 100 =$	If the score is \leq 0.5, there is low probability of hepatic fibrosis negative predictive value 83% and if the score is > 1.5, there is high probability (positive predictive value 68.4%) of hepatic fibrosis ^[33] . The intermediate score is indeterminate and liver biopsy should be done in those patients

BMI: Body mass index; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; NAFLD: Non-alcoholic fatty liver disease; IFG: Impaired fasting blood glucose; APRI: AST platelet ratio index.

which limit performance of doing Fibroscan, including morbid obesity, ascites, narrow intercostal spaces and excessive chest wall fat.

MR elastography (MRE) has a vibration device which produces shear waves in the liver. The shear waves are detected by the modified MRI machine, generating a color image (elastogram) that represents wave velocity and hence stiffness of the liver. MRE is superior in differentiating different stages of fibrosis (sensitivity 85.4%, specificity 88.4%)^[37]. The limitations will be cost and claustrophobia.

MANAGEMENT

The goal of management will be to diagnose the disease early, prevent further progression of the disease from one stage to the next stage, regression of the disease as much as possible and improvement of the underlying metabolic syndrome. When the patient becomes cirrhotic, standard treatment of cirrhosis should be offered including liver transplantation in the decompensated state. NAFLD can recur in the transplanted liver.

Lifestyle modification

As most of the patients with NAFLD are overweight or obese and have associated metabolic syndrome, gradual weight loss is advocated as the first line of intervention^[38]. Diet and exercise (30 min of aerobic exercise 4 times a week, *i.e.*, moderate physical activity) are the preferred methods of weight loss. There are many studies showing the benefit of weight loss in NAFLD^[39]. Five percent to 10% of body weight loss can reduce a significant amount of liver fat and improve steatohepatitis. But as it is difficult to maintain body weight, many patients regain lost body weight with the recurrence of NAFLD. Dietary modification is also very important. High sugar consumption in the Western diet is the major cause of obesity. Diet rich in fructose particularly high fructose corn

syrup (Granola bars, condiments, sweetened beverages, prepared desserts, baked goods, snacks, breakfast cereal, cookies) may impair insulin sensitivity leading to development of NAFLD^[40]. Thus sugar consumption should be less than 10% of one's total caloric intake and food rich in high fructose corn syrup should be avoided. Western diet is also rich in saturated fat and omega-6 fatty acid but deficient in omega-3 fatty acid^[41]. Omega-3 fatty acids normally coordinate with upregulation of fatty acid oxidation and downregulation of fatty acid synthesis. Dietary omega-3 fatty acid deficiency associated with increase in omega-6 fatty acid in the body has been found to cause NAFLD in rats and mice. Cooking oils high in omega-6 fatty acid (soybean, sunflower, corn) should be changed to cooking oils high in omega-3 fatty acids (Canola, Olive, Chia, Perilla). Patients should be encouraged to eat more fish as they contain omega-3 fatty acid. Fish oil supplementation helps in improving the lipid profile and reducing the inflammatory markers of metabolic syndrome^[42] although further studies are needed to find out its beneficial effects on metabolic syndrome. One study showed diet and exercise were superior to insulin sensitizers metformin and rosiglitazone in ALT normalization in NAFLD^[43].

Pharmacotherapy

As NAFLD is associated with metabolic syndrome, the associated comorbidities like obesity, diabetes mellitus, hypertension and hyperlipidemia should be managed well concurrently as part of the treatment of NAFLD. There is a practice guideline developed by American Association for the study of Liver Diseases and approved by American College of Gastroenterology and the American Gastroenterological Association on the management of NAFLD. The guideline was published in *Hepatology* in 2012^[44].

The broad categories of pharmacotherapy for the treatment of NAFLD include: (1) Antioxidants; (2)

Insulin-sensitizing agents; (3) Hepatoprotective and miscellaneous agents; and (4) Bariatric surgery.

Antioxidants

As oxidative stress is considered to be the main mechanism of progression of steatosis to steatohepatitis, the antioxidant Vitamin E has been studied in different trials. Vitamin E 800 units per day was studied in the PIVENS trial^[45]. It showed improvement in steatosis and steatohepatitis and decrease in serum transaminases in nondiabetic patients but there was no improvement of fibrosis histologically. Currently it is recommended as the first line agent in nondiabetic individuals with biopsy proven NASH.

INSULIN SENSITIZING AGENTS

Metformin

Metformin is a common and first line antidiabetic agent as it increases insulin sensitivity by upregulating AMP-activated protein kinase which results in the reduction of hepatic glucose production^[46]. Although there was initial enthusiasm about Metformin on its therapeutic effect on NAFLD, subsequent studies did not find much benefit. A pilot study showed little effect of Metformin on serum transaminases and liver histology in NAFLD^[47]. Currently metformin is not recommended as a specific treatment of NAFLD.

THIOGLITAZONES

Thioglitzones (Pioglitazone and Rosiglitazone) are agonists of peroxisome proliferator-activated receptor gamma that controls transcription of insulin receptor genes involved in the transport, utilization and production of glucose and lipid^[48].

These nuclear receptors are found in liver, muscle and fat cells. Thioglitzones act as insulin sensitizers in NAFLD by helping to redistribute fat from the liver and muscles to the adipose tissue. In the PIVENS trial^[49], pioglitazone improved serum transaminases, steatosis and steatohepatitis in nondiabetic patients with NASH but histological improvement was not statistically significant in comparison to placebo. Thioglitzones can cause weight gain and carry increase risk of congestive cardiac failure. At the present time, thioglitzones can be recommended to treat NASH, but long term safety and efficacy are not known.

MISCELLANEOUS AGENTS

Ursodeoxycholic acid

A naturally occurring secondary bile acid found in small quantities in the human small intestine, is produced by intestinal bacteria as a metabolic by-product and it is found in large quantities in the bile of certain types of bear. It has cytoprotective effects along with the ability to alter lipid properties. The acid can reduce transaminases in NAFLD^[50] but long-term study failed to improve any

liver histology^[51,52]. As a result, ursodeoxycholic acid is not a treatment option for NAFLD.

Pentoxifylline

Pentoxifylline is a xanthine derivative and is being used in peripheral vascular disease because of its beneficial effects like relaxation of smooth muscle, flexibility of red blood cells and deaggregation of platelets. Because of anti-tumor necrosis factor activity, it has been used in alcoholic hepatitis, and studied in NAFLD. A randomized placebo controlled trial by Zein *et al*^[53] showed that pentoxifylline 400 mg 3 times a day over 1 year improved steatosis and lobular inflammation with no significant effect on ballooning degeneration^[53]. However, in a similar study done by Van Wagner *et al*^[54], pentoxifylline improved transaminases, hepatic steatosis and ballooning degeneration when compared to baseline but when compared to placebo, the improvement was not clinically significant. Pentoxifylline did not improve any metabolic marker of insulin resistance. These findings warrant further studies to determine the role of pentoxifylline in NAFLD.

Statins

NAFLD and hyperlipidemia frequently coexist as part of the metabolic syndrome. Statins are used as one of the main line therapies for hyperlipidemia. Statins may cause mild elevation of transaminases but they have been found to be safe in patients with chronic liver diseases including NAFLD^[55]. One randomized study showed that Atorvastatin improved both biochemical and ultrasound evidence of NAFLD^[56]. But at the present time, there is no randomized controlled study evaluating the effect of statin on the histology of NAFLD. Statins are not currently recommended specifically for the treatment of NAFLD.

Omega-3 fatty acids

In the western diet, omega-6 fatty acid consumption is high and omega-3 fatty acid consumption is low - a phenomenon that may lead to an increased amount of pro-inflammatory arachidonic acid derivatives (eicosanoids) production and impaired hepatic lipid metabolism, predisposing to NAFLD. A meta-analysis showed treatment with omega-3 polyunsaturated fatty acid improved hepatic steatosis but not transaminases but the correct dose is currently not known^[57]. Further randomized controlled trials are needed. At the present omega-3 fatty acid supplementation is not recommended for the treatment of NAFLD.

Orlistat

Orlistat is a reversible enteric and pancreatic lipase inhibitor. It promotes fat malabsorption, and decreases free fatty-acid influx into the liver leading to weight loss and improvement of insulin sensitivity. In a randomized controlled trial, Orlistat reduced serum transaminases and hepatic steatosis as determined by abdominal ultrasound^[58]. Another study demonstrated that significant

weight loss of > 9% improved serum transaminases and liver histology irrespective of intake of Orlistat^[59]. Currently, Orlistat is approved for weight loss in obese patients but not recommended solely for the treatment of NAFLD.

Incretin-based therapies

Glucagon-like peptide 1 (GLP-1) secreted by the L cells of the intestinal mucosa after nutrient ingestion is an incretin hormone. It increases insulin secretion by stimulating pancreatic β cells, decreases glucagon secretion and delays gastric emptying. Thus it lowers blood glucose in diabetes mellitus and has other beneficial effects including central appetite suppression, weight reduction and improvement of insulin sensitivity^[60]. Because of rapid degradation by dipeptidyl-peptidase IV (DPPIV), GLP-1 has a short half life. GLP-1 receptor agonists (exenatide, liraglutide) are long acting as they are DPP IV resistant. They are primarily developed for type 2 diabetes mellitus for maintenance of blood glucose. There are case reports in which diabetic patients with NAFLD when treated with exenatide showed significant decrease in liver fat. In obese mouse, exendin-4 improved insulin sensitivity and reversed hepatic steatosis^[61]. Hepatic DPP IV expression and serum DPPIV activity are significantly higher in NAFLD patients and they correlate with hepatic steatosis^[62]. DPPIV inhibitor sitagliptin treated diabetic NAFLD patients displayed a decrease in transaminases and hepatic steatosis^[63,64]. Thus considering the experimental and clinical data, incretin-based therapies (GLP-1 analogues and DPPIV inhibitors) can be considered as potential novel agents in the treatment of NAFLD. Further randomized controlled trials are needed before starting incretin-based therapies as therapeutic agents for NAFLD.

BARIATRIC SURGERY

Most of the patients who undergo bariatric surgery have NAFLD. Common bariatric surgeries practiced in the United States are Roux-en-Y gastric bypass, laparoscopic adjustable gastric banding, sleeve gastrectomy, and biliopancreatic diversion with duodenal switch^[65]. Steady and profound weight loss increases insulin sensitivity, promotes visceral fat loss and can potentially improve liver histology in NAFLD. Although beneficial effects including improved liver histology were seen in few studies, a randomized controlled trial that has evaluated bariatric surgery as the treatment of NAFLD has not been pursued. There is concern of hepatic failure in cirrhotic patients due to rapid weight loss^[66]. Bariatric surgery in cirrhosis of liver due to NAFLD could be risky. Although bariatric surgery is frequently done in morbidly obese individuals with non-cirrhotic NAFLD to reduce obesity, it is not recommended as a primary treatment for NAFLD.

FUTURE THERAPY

Research is ongoing to find out prevention and better

therapeutic options of NAFLD. Sirtuins (SIRT) are silent information regulator proteins which act as nicotinamide adenine dinucleotide dependent deacylases and thus can modulate activation and deactivation of certain proteins^[67]. In mammals, there are 7 different types of SIRT 1-7. SIRT1 has been found to increase insulin sensitivity and secretion, decrease oxidative stress and inflammatory activity, and help in glucose and lipid metabolism. In the rat model, significantly decreased SIRT expression in the liver was found in NAFLD and moderate SIRT1 overexpression in the liver was protective from developing NAFLD^[68]. In another murine model, resveratrol, a natural SIRT1 activator, showed improvement of insulin resistance and liver histology in NAFLD^[69]. Thus pharmacological activation of SIRT1 can be a potential target in the treatment of NAFLD but human studies (randomized controlled trials) are needed.

Hepatic fibrosis at a more advanced stage leads to cirrhosis of the liver. Lysyl Oxidase Like Molecule 2 (LOXL2) is an enzyme that causes cross linkage of type 1 collagen and promotes fibrosis^[70]. Its serum level correlates with the stage of hepatic fibrosis^[71]. Simtuzumab is a humanized antifibrotic monoclonal antibody (IgG4) against LOXL2. It was well tolerated in patients with liver disease of diverse etiology in a small study^[72]. In multicenter clinical trials, Simtuzumab is currently being evaluated for its safety and efficacy in patients with compensated cirrhosis due to NASH, and also in patients with advanced hepatic fibrosis but not cirrhosis secondary to NASH^[73].

PROGNOSIS

Most of the patients with NAFLD will die from cardiovascular events. Simple steatosis has a benign course and can be reversible. NASH is a progressive disease leading to hepatic fibrosis and ultimately cirrhosis of the liver in 20% of the time. The chance of developing hepatoma is also high in NAFLD, particularly in cirrhotic liver. Besides the liver disease, the associated components of metabolic syndrome give rise to morbidity and mortality. Cardiovascular disease, cancer and cirrhosis are the top three causes of death^[74]. Recently a long-term (> 12 years) international study found that although lean patients (body mass index < 25 kg/m²) with NAFLD had less insulin resistance and less advanced hepatic fibrosis, they had twice (28% vs 14%) the mortality than their overweight and obese counterparts^[75].

CONCLUSION

NAFLD is the most common cause of incidental abnormal LFT, and the most prevalent chronic liver disease in the world. Because of the epidemic of NAFLD, it is predicted to be the commonest indication of liver transplantation in the near future. Good preventive measures, better understanding of the underlying mechanisms of the disease, reliable non-invasive diagnostic tests and

effective therapies are essential for optimal management of the disease. At the present time, we have practical guidelines but only few options which include life-style modifications to achieve targeted weight loss, vitamin E and pioglitazone in non-diabetic patients with biopsy-proven NASH. Although metabolic syndrome plays a major role in most of the patients with NAFLD, the pathogenic mechanism is heterogenous as evidenced in the recent finding of higher mortality in lean NAFLD patients who are more likely to be men, non-white, especially Asian and Hispanic, with few metabolic conditions like diabetes, hypertension, hyperlipidemia, less elevated transaminases and less fibrosis. In future, treatment should be more individualized depending on the underlying pathogenic mechanism.

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P- Reviewer: Bian JM, Huang SF, Schemmer P **S- Editor:** Ji FF
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