J MEDICINE 2007; 8 : 17-27

REVIEW ARTICLE

NONALCOHOLIC FATTY LIVER DISEASE (NAFLD) - A DISEASE OF NEW ERA

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Abstract

Non-alcoholic fatty liver disease (NAFLD) is the term used to describe the alcohol-like liver injury that occurs in the absence of alcohol abuse (alcohol consumption of over 20 g / day excludes the condition). It includes a range of histological abnormalities including simple steatosis or fatty liver, non-alcoholic steatohepatitis (NASH) and NAFLD induced cirrhosis. Its increasing prevalence in western countries, the diagnostic difficulties by noninvasive tests, and the possibility of progression to advanced fibrosis and even cirrhosis make NASH a challenge for physicians. NASH is frequently associated with type 2 diabetes and the metabolic syndrome, and several genetic and acquired factors are involved in its pathogenesis. Insulin resistance plays a central role in the development of a steatotic liver, which becomes vulnerable to additional injuries. Several cyclic mechanisms leading to self-enhancement of insulin resistance and hepatic accumulation of fat have been recently identified. Excess intracellular fatty acids, oxidant stress, tumor necrosis factor, and mitochondrial dysfunction are causes of hepatocellular injury, thereby leading to disease progression and to the establishment of NASH. Intestinal bacterial overgrowth also plays a role, by increasing production of endogenous ethanol and proinflammatory cytokines. Therapeutic strategies aimed at modulating insulin resistance, managing risk factors, including reduction of weight normalizing lipoprotein metabolism, and down regulating inflammatory mediators with probiotics have promising potential.

Introduction

NAFLD comprises a spectrum of liver disease characterized from simple fatty liver (macrovascular fatty change), to nonalcoholic steatohepatitis (NASH), and to cirrhosis in absence of alcohol consumption in amounts considered detrimental to the liver[1]. In 1980, Dr. J. Ludwig from the Mayo Clinic in Rochester, Minnesota was the first to coin the term NASH. Synonyms of NASH are pseudoalcoholic hepatitis, alcohol-like hepatitis, fatty liver hepatitis, steatonecrosis, and diabetic hepatitis.

Cryptogenic cirrhosis is a common cause of liver-related morbidity and mortality in USA. NAFLD is now recognized as the most common cause of cryptogenic cirrhosis[2]. NAFLD affects 10 to 24% of general population in various countries. The prevalence increases to 57.5%[3] to 74%[4] in obese persons. NAFLD affects 2.6% of children and 22.5% to 52.8% of obese children[5]. The prevalence of T_2 Diabetes Mellitus varied between 10 to 75% and the prevalence of hyperlipidemia varied between 20 to 92 %[6].

Staging / spectrum of NAFLD

NAFLD begins with fatty liver, progressing through NASH, and ending with cirrhosis. Fatty liver (steatosis), a harmless condition, is characterized by accumulation of fat in the liver cells without inflammation or scarring. Fatty liver is defined as fat, largely triglyceride exceeding 5% of the liver weight. When the fat content in the liver is 10%, fat begins to appear in many hepatocytes, and exceeds 30% of the weight; almost all of the hepatocytes contain a large drop of fat. It can be roughly estimated by how much of the acinus has fat laden hepatocytes; the involvement is characterized as mild for the pervienular third only, moderate for two-thirds, and severe for the entire acinus[7].

Only a fraction of patients with simple fatty liver will develop NASH, which involves fat accumulation

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(steatosis), inflammation (hepatitis), and scarring (fibrosis) in the liver. NASH can ultimately lead to scarring of the liver (fibrosis) and then irreversible, advanced scarring (cirrhosis). Cirrhosis is the last and most severe stage in the NAFLD spectrum.

Causes of non-alcoholic fatty liver disease[8,9]
Arbitrarily, NASH is subcategorized into "primary" and "secondary" NASH.

Primary: Primary NASH refers to steatohepatitis that is associated with metabolic syndrome and is the predominant form of NASH.

Secondary:

- **Nutritional:** Rapid weight loss, gastrointestinal bypass surgery, total parenteral nutrition, short bowel syndrome, small bowel bacterial overgrowth (small bowel diverticulosis) and protein-calorie malnutrition.
- **Drugs:** Glucocorticoids, oestrogen, amiodarone, methotrexate, tamoxifen, diltiazem, aspirin, tetracycline, valproate, cocaine, protease inhibitors, nucleoside reverse transcriptase inhibitors.
- **Rare metabolic syndomes:** Lipodystrophy, hypothyroidism, abetabetalipoproteinaemia, hypobetalipoproteinaemia, and Weber- Christian disease.
- **Toxins:** Amanita phalloides mushroom, phosphorus poisoning, bacillus cereus toxin
- **Infections:** HIV, hepatitis C
- **Chronic inflammatory disorders**: Rheumatoid arthritis and systemic lupus erythematosus.

Metabolic Syndrome/ Syndrome X[10]

The predominant risk factor for NAFLD appears to be insulin resistance related to the metabolic syndrome. In non-diabetic subjects with high insulin resistance 90% had moderate or severe steatosis. Metabolic syndrome is a set of risk factors that includes: abdominal obesity, hyperinsulinemia, insulin resistance, diabetes, hypertriglyceridemia, and hypertension. Recent research has determined that people with syndrome X also have a liver disease. NAFLD appears to be the liver component of this syndrome. In fact, people with syndrome X often have more advanced forms of NAFLD – i.e. fibrosis or cirrhosis.

The criteria proposed for diagnosing the metabolic syndrome by the Third Report of the National Cholesterol Education Program (NCEP) expert Panel on detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) are the most current and widely used. According to the ATP III criteria, the metabolic syndrome is identified by the presence of three or more of these components:

1. Central obesity as measured by waist circumference:
   - Men- greater than or equal to 40 inches and
   - Women- Greater than or equal to 35 inches
2. Fasting blood triglycerides greater than or equal to 150 mg/dl
3. Blood HDL cholesterol: (Men- <40mg/dl & Women- <50mg/dl)
4. Blood pressure greater than or equal to 130/85 mmHg
5. Fasting glucose greater than or equal to 100 mg/dl

The factors contributing genesis of fatty liver are gender (male), obesity, high alcohol consumption, glucose intolerance and hypertriglyceridaemia, majority are linked to metabolic syndrome.

Pathogenesis of NAFLD

The exact cause of NASH is still unknown. A net retention of lipids within hepatocytes, mostly in the form of triglycerides, is responsible for the development of NAFLD. The primary metabolic abnormalities leading to lipid accumulation are not well understood, but they could consist of alterations in the pathways of uptake, synthesis, degradation, or secretion in hepatic lipid metabolism resulting from insulin resistance.

Insulin resistance:
The metabolic syndrome involving insulin resistance is associated with NAFLD. Protein tyrosine phosphatase 1B (PTP1B) negatively regulates the insulin receptor (IR). Increased PTP1B expression is seen in obesity and possibly is responsible for the insulin resistance seen in the metabolic syndrome[11].

Insulin resistance owing to inhibition of tumor necrosis factor-a (TNF-a) leads to the accumulation of fat in hepatocytes by two main mechanisms:

Lipolysis, which increases circulating fatty acids and hyper insulinemia. Increased uptake of fatty acids by hepatocytes leads to mitochondrial -oxidation overload, with the consequent accumulation of fatty acids within hepatocytes. Hyperinsulinemia resulting from insulin resistance increases the synthesis of fatty acids in hepatocytes by increasing glycolysis and favors the accumulation of triglycerides within hepatocytes by decreasing hepatic production of apolipoprotein B-100. Since weight reduction leads to decrease in TNF-a and other factors it may improve the liver disease. As regards the cause of extracellular matrix deposition in liver tissue, the hepatic sinusoidal lumens are narrowed by swollen hepatocytes containing fat droplets and abundant enlarged endoplasmic reticulum in their cytoplasm, and the hepatic sinusoidal microcirculation is impaired. Consequently, ischemia occurs in the perivenular or intralobular spaces, and hepatic fibrogenesis appears to be enhanced by ischemia, which may lead to liver cirrhosis[7].

Although these patients are euglycemic, overweight or obesity is still clues that they are insulin resistant; the euglycemic clamp test can detect insulin resistance. Ultimately this insulin resistance leads to elevated blood sugars and T2 DM. Whereas diabetes mellitus type 1 (DM1) is due to defect in insulin secretion. NAFLD may be considered an additional feature of the metabolic syndrome, with specific hepatic insulin resistance[12].

Insulin resistance can also occur in congenital genetic abnormalities in the insulin receptors and becomes evident later in life as a result of acquired obesity. Increased HTGL activities and elevated apo A-II levels can explain accumulation of triglycerides in the liver, a co-factor of HTGL. In fact, BMI directly correlates with the amount of fat in the liver. Almost all patients with NASH are insulin resistant to some degree, but only minorities of patients who are insulin resistant develop NASH[13].

The process whereby liver inflammation and death of liver tissue develop in NASH remains to be clearly explained. Several theories, however, have been advanced[14]. Day and James[15] proposed that additional oxidative stress was required for disease progression from steatosis to NASH, although others feel that one-hit e.g., insulin resistance alone is sufficient to explain the full NAFLD spectrum[16].

One hit hypothesis. According to this theory, the large quantity of fat in the liver is thought to be a source of peroxidation (removal of electrons from molecules), and thereby generates free radicals. These free radicals damage proteins and organelles in the liver cells. Finally, this damage leads to cell death and/or an inflammatory cell cascade that removes the affected cells.

Two-hit hypothesis. With this theory, the first hit is the steatosis. Then, a second event, or *second hit*, leads to the development of NASH. Kupffer cells are a major immune effector cell may play a pivotal role in the pathogenesis of steatohepatitis. Multiple potential second hits have been suggested.

1. Cytokines, such as tumor necrosis factor-alpha, secreted by cells and involved in inflammation, may induce cell death and even increase insulin resistance.
2. Intracellular organelles (mitochondria) that provide energy to the cell may malfunction and thereby cause a decrease in cell energy and lead to cell death.
3. Enzymes (cytochromes) that are involved in multiple metabolic pathways may lead to increased peroxidation and its consequences.
4. Receptors in the cell nucleus that are involved in triggering the effects of insulin (*peroxisome proliferator activating receptors, PPAR*) may fail and lead to insulin resistance, inflammation, and scarring of the liver.

Obesity is an inflammatory state and adipose tissue is now recognized to be a hormonally rich tissue that secretes a number of physiologically active peptides. These peptides or "adipocytokines" can be classified as proinflammatory, such as leptin, TNF-á and IL-6, or anti-inflammatory and anti-steatotic, such as adiponectin. They all have a role in the regulation of adipocyte metabolism, with a direct role in several insulin-mediated processes[17].

TNF-α[18]

Several studies have shown that FFAs activate a kinase cascade that results in IR via abnormal phoshorylation of IRS-1. During this process TNFα is synthesized, leading to further IR and release of FFA and TNFá from adipose tissue. TNFα promotes release of mitochondrial ROS and is fibrogenic. Chronically elevated TNFα levels promote

hepatocellular death through alterations in ATP levels or apoptosis. In the absence of any extrahepatic inflammatory conditions, TNFá plasma levels correlate with BMI and increased expression of adipose tissue TNFá mRNA has been shown in patients with a histological diagnosis of NASH.

Adiponectin [19, 20]

This is an anti-steatotic adipocytokine that enhances FFA oxidation and decreases FFA synthesis in the liver and thus it is regarded as a hepatic insulin sensitizer. Serum adiponectin is markedly decreased in patients with obesity, T2DM, and NASH. Adiponectin's hepatic receptor (adipoR2) in patients with NASH is also down regulated. Administration of recombinant adiponectin relieves the metabolic derangement and liver damage in animal models of NASH.

Leptin resistance:

Leptin is a very small hormone that is secreted by the brain, fat, and stomach cells in response to eating. Decreased expression of leptin or of functional leptin receptors results in hyperphagia, decreased energy expenditure, and obesity. Patients with NASH have abnormally elevated levels of leptin but experience no loss of appetite. That is, they are resistant to the appetite-curbing effect of leptin. The leptin also helps control the processes of inflammation and scarring within the liver cells. Furthermore, interestingly enough, leptin also increases insulin sensitivity. But the fact that patients with NASH are insulin resistant supports the idea that the leptin receptors are malfunctioning[21].

Other adipocytokines, which may be implicated in NAFLD or IR are resistin, visfatin and acetylated stimulating protein[17].

Finally, not all patients with NASH will develop cirrhosis. Cirrhosis may simply develop over time as a result of chronic inflammation and repair, or may be due to yet a *third hit*. This varying susceptibility of individuals to these diseases coupled with multiple disease-producing pathways suggests that the cause of primary NASH is a multi-faceted process. The cause is thought to involve altered lipid metabolism that results from environmental factors and genetic predisposition.

Role of intestinal bacterial overgrowth in the pathogenesis of NASH

A clear link between intestinal bacterial overgrowth and liver damage during NASH has recently been established[22]. Bacterial overgrowth has been detected in NASH patients with breath tests with lactulose and D-xilose[23], as well as in some forms of secondary NASH, such as that associated with obesity-related intestinal surgery[24].

Clinical features of NAFLD/NASH[16]

Patients are usually asymptomatic but commonly have features of the metabolic syndrome such as high BMI, hypertension, dyslipidaemia and impaired glucose tolerance/T2DM. Vague dull and aching right upper-quadrant abdominal pain due to the stretching of the liver capsule may be present. Hepatomegaly is present in around 50% and acanthosis nigricans may be present in children.

In contrast to ALD, HBV, and HCV, symptoms of severe, acute (rapid onset) liver failure i.e. jaundice, intense fatigue, loss of appetite, nausea, vomiting, and confusion is not observed in NAFLD. The cirrhosis stage of NAFLD usually occurs later in life (age 50 to 60 years), presumably after many years of NASH. Fatty liver has also been described in several medical syndromes like polycystic ovarian syndrome, congenital lipodystrophy syndromes.

Complications of NASH

The complications of NASH include cirrhosis (also considered the last stage of NAFLD) and hepatocellular carcinoma (HCC).

The risk of developing cirrhosis in a patient with NASH varies perhaps from 8% to 15%. In most instances when cirrhosis develops, the fatty infiltration disappears (regresses) along with the inflammation, referred to as burned-out cirrhosis. This may result from less fat coming to the liver by way of the portal vein. The progression to cirrhosis in NASH is thought to be slow and the cirrhosis diagnosis is typically made in patients in there sixties. A study from France suggests that patients with NASH have a similar risk of developing cirrhosis, as do patients with HCV[25].

Indeed, the incidence of HCC in NASH cirrhosis appears to be similar to that observed in HCV cirrhosis (1-2% per year). HCC may develop as a result of liver repair and regrowth (hepatocellular regeneration). Some authors, however, have suggested that insulin resistance in this situation may promote the development of liver cancer[26].

Diagnosis

The most frequent biochemical abnormality is persistent, fluctuating, and mild to moderately elevated transaminases (ALT and AST). The AST to ALT ratio appears to be a useful index for distinguishing NASH from ALD. Values <1 suggest NASH, whereas a ratio of e" suggestive of ALD. Unfortunately, however, no biochemical test or imaging procedure can differentiate simple fatty liver from NASH Serum bilirubin and alkaline phosphate is usually normal in patients with NASH. Gamma glutamyl transferase is usually abnormal (> 35 U/L) and alkaline phosphatase may be up to twice normal, sometimes giving rise to a cholestatic variant. [27] Other causes of raised aminotransferese must be excluded (table-1) [28]. Serum ferritin can be significantly elevated, but transferrin saturation is usually normal. These iron studies suggest the presence of only mild, if any, deposition of iron in the liver (iron overload) [29].

Table 1
Causes of chronically elevated aminotransferase levels

Hepatic Causes
• Alcohol abuse
• Medication
• Chronic hepatitis B and C
• Steatosis and NASH
• Hereditary Hemochromatosis
• Wilson's disease (in patients<40 years old)
• Alpha 1- antitrypsin deficiency
Non-hepatic causes
• Celiac Sprue
• Inherited disorders of muscle metabolism
• Acquired muscle disease
• Strenuous exercise

Abnormal biochemistry tests associated with insulin resistance include elevated total cholesterol, LDL-C, triglycerides, and blood sugar and decreased HDL-C. The diagnosis of NAFLD or NASH can be considered after excluding other causes of hepatitis.

Ultrasound is comparatively cheap and readily available but is less sensitive at detecting minimal (<30%) steatosis or among obese patients (BMI of 35-40 kg/m$^{2)}$. Thus a negative ultrasound does not necessarily exclude NAFLD. A good quality ultrasound can be highly sensitive and specific in diagnosing fatty liver. The classic finding is a hyperechoic (bright) liver. But this finding is non-specific (positive predictive value 62%), but sensitive (85-95%)[30]. The sonogrphic findings[31] are graded as follows:

- Grade 0: normal echogenicity
- Grade 1:slight diffuse increase in fine echo's in liver parenchyma with normal visualization of the diaphragm and intra hepatic blood vessels borders
- Grade 2: moderate diffuse increase in fine echo's in liver parenchyma with slightly impaired visualization of the diaphragm and intra hepatic blood vessels borders
- Grade 1:marked diffuse increase in fine echo's in liver parenchyma with poor or non-visualization of the diaphragm, intra hepatic blood vessels borders and posterior lobe of the liver.

CT scan can detect fatty liver, even the degree of fat infiltration, but may be hampered by any liver iron deposition. Hepatic steatosis decreases the CT attenuation of the liver. While these features allow hepatic steatosis to be defined with a 76% positive predictive value[30]. The severity of hepatic fatty infiltration is graded as follows[31].

- Grade 0: normal;
- Grade 1: liver attenuation is slightly less than spleen;
- Grade 2: more pronounced difference between liver and spleen and intra hepatic vessels not seen or slightly higher attenuation than liver;
- Grade 3: markedly reduced liver attenuation with sharp contrast between liver and intra hepatic vessels.

MRI is the overall best, most expensive imaging exam for fatty liver[30]. The minimal advantages of MRI are balanced against wider availability and lower cost of ultrasonogram[31].

Thus, a presumptive diagnosis of NAFLD can be made in an individual based on the following criteria.

- Clinical and/or biochemical signs of insulin resistance
- Chronically (long duration) elevated ALT
- Signs of fatty liver on ultrasound
- Exclusion of other causes of elevated ALT and fatty liver

Only a liver biopsy can establish a definite diagnosis and determine the severity of the condition.

Liver biopsy

In NASH, fibrosis heterogeneity is substantial and is greater than in HCV, and parenchymal injury, fibrosis, and healing might vary in different regions of the liver, demanding individual needle cores should be longer than 1.6cm for acute diagnosis[32].

The lesions most commonly accepted for NASH include steatosis, ballooning degeneration, mild diffuse lobular mixed acute and chronic inflammation, and perivenular, perisinusoidal collagen deposition. Zone 3 accentuation may be detected. Mallory's hyaline, vacuolated nuclei in periportal hepatocytes, lobular lipogranulomas, and PAS-diastase- resistant Kupffer cells are common. In children, portal inflammation may be more prominent than in adults[33,34].

A staging score was developed to reflect both location and extent of fibrosis. The fibrosis score was derived from the extent of zone 3 remodeling. The score is as follows: Stage1: Zone 3 perisinusoidal fibrosis; Stage 2: as above with portal fibrosis; Stage 3: as above with bridging fibrosis; and Stage: cirrhosis[35].

As no specific treatment is available for NAFLD or NASH, the result of a biopsy would not impact the patient's treatment. It may be important to know whether an individual has severe NASH, especially if she or he is young, as the risk of developing cirrhosis later on is high. So a liver biopsy has a prognostic value and can exclude the presence of other liver diseases. The decision to do liver biopsy to diagnosis NASH in clinical practice should be made on a case-by-case basis.

Risk factors assessment of NASH

Risk factors for adverse clinical symptoms include patients older than the age of 45, the presence of diabetes or significant obesity (BMI greater than 30 kg/m^2), an AST/ ALT ratio >1 and hepatic histology[36]. Poor outcomes are more frequent in patients in whom biopsies show ballooning degeneration and Mallory hyaline or fibrosis[26].

Iron deposition in the liver appears to be more common at the stage of severe, irreversible liver scarring (cirrhosis). Testing for serum iron markers, however, turns out to be of little use in predicting any degree of liver scarring (fibrosis) [29].

Treatment

No single truly effective treatment has been found to date. Treatment is important to prevent the development of cirrhosis and its complications. Patients with NAFLD will usually have features of the metabolic syndrome, treatment of which is important to reduce cardiovascular risk. Four main strategies have been employed in the treatment of NAFLD, usually in those with the intermediate phase of NASH; lifestyle intervention, dyslipidaemia therapy, insulin sensitizing drugs and anti-oxidant/ anti-cytokine agents as well as discontinuation of potentially hepatotoxic drugs[37].

A. Lifestyle Modification [38,39]

As most patients with NAFLD have the metabolic syndrome, lifestyle interventions that decrease weight and increase exercise are a logical initial approach as they reduce insulin resistance and cardiovascular risks. Losing weight has a beneficial effect on ALT and steatosis in patients with NASH. In addition there is evidence that weight loss reduces leptin and IL-6. Orlistat, sibutramine and rimonabant are licensed for the treatment of obesity. Combination of medications and orlistat or sibutramine as a monotherapy plus lifestyle modification was more effective than either intervention alone. Orlistat also improves

steatosis[40]. Gastric reduction operations for morbid obesity may result in substantial weight loss, a marked reduction in transaminases and a regression of fatty liver. However, rapid weight loss can also induce the occurrence of NASH, perhaps inflammatory cytokines and the fat that produce the fatty liver and inflammation come from the body fat. Moreover, small bowel bypass surgery entails the risk of bacterial overgrowth and worsening steatosis.

Even in non-obese, a healthy diet and daily physical activity may reduce inflammation, lower elevated levels of liver enzymes and decrease insulin resistance.

B. Dyslipidaemia Therapy

Gemfibrozil lowers transaminases and serum triglycerides. A one-year trial of clofibrate showed that it lowered blood fats, however, had no positive effect whatsoever[41]. Statins may decrease fatty liver.

C. Insulin Sensitising Agents

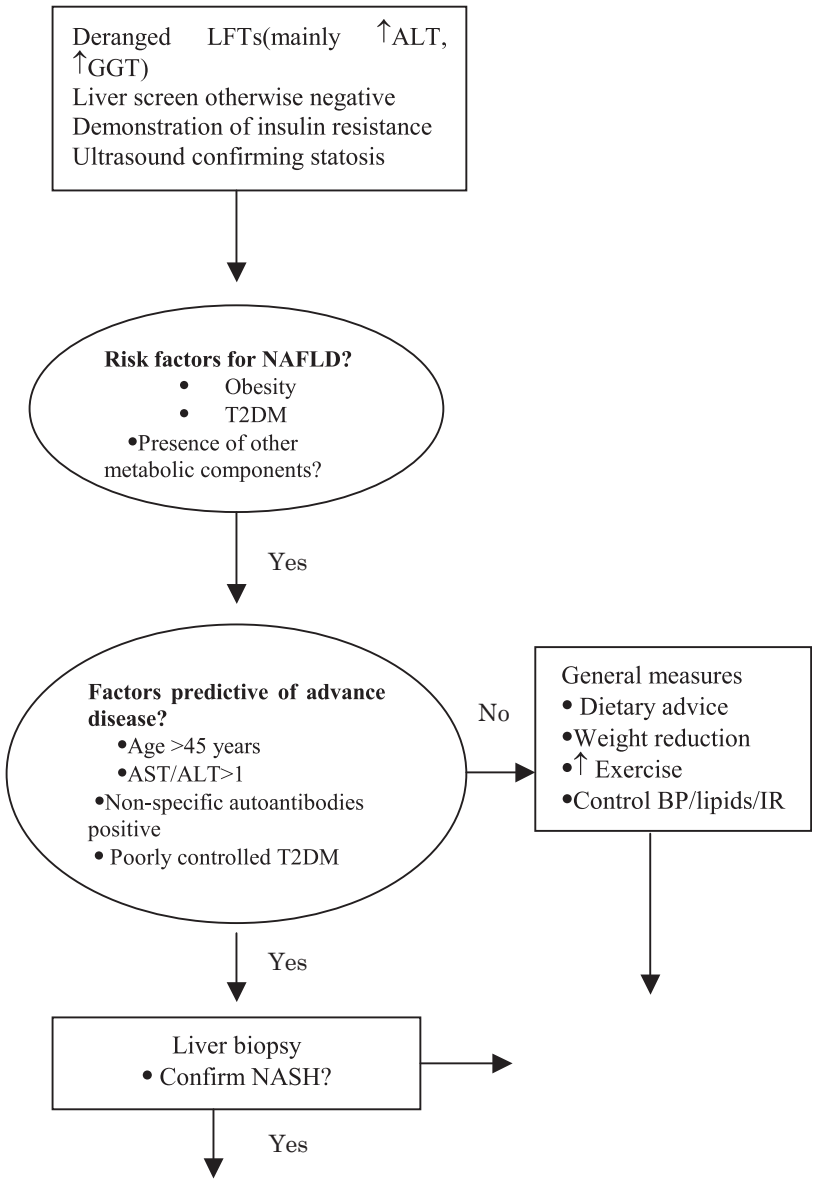
Metformin[42] causes fall in ALT, a 20% decrease in liver volume and improvement in insulin sensitivity and perhaps decreases inflammation and scarring in the liver. Thiazolidinediones (rosiglitazone and pioglitazone), peroxisome proliferator-activator receptor (PPAR)- gamma agonist[43], also increases insulin sensitivity and perhaps improves steatosis.

D. Anti-oxidant/anti-cytokine Agents

A number of agents exist in this class and include UDCA, Vitamin E, beta-carotene, pentoxifylline, selenium and betaine.

- **Ursodeoxy cholic acid:** decreases transaminases, gamma- glutamyl transpeptidase and improves histological grades of steatosis. Ursodeoxycholic acid has several mechanisms of action that justify its use in NASH: hydrophilic effect (resulting in the displacement of toxic hydrophobic biliary salts), and immuno-modulatory and cytoprotective properties. An oral dose of 13–15 mg/day for 12 months may be efficacious in improving liver biochemistry alterations and steatosis, although no favorable changes occurred in the rest of the histological lesions of NASH [43].
- **Vitamins E and C: In NASH, serum ALT level** and histological findings improve after 1-year vitamin E (300mg/day) treatment. The plasma transforming growth factor-beta1 (TGF-b1) level in NASH patients was significantly elevated compared with that in NAFLD patients and healthy controls, and decreased with vitamin E treatment. The measurement of TGF-b1 represents a possible method to distinguish NASH and NAFLD. Long-term alpha-tocopherol treatment may be safe and effective for NASH[44]. Since both vitamins (E& C) are antioxidants, it's thought that they may reduce liver damage caused by oxidants, unstable oxygen molecules that damage cell membranes. A 6 months trial with 45 patients showed that 6 months of vitamins E and C combination (1000 IU and 1000 mg, respectively) resulted in significant improvement in fibrosis score ($P = 0.002$) [9].
- **Betaine:** Betaine, a naturally occurring metabolite of methionine, raises S-adenosylmethionine (SAM) levels that may in turn play a role in decreasing hepatic steatosis[44].
- **Pentoxyfylline:** Tumour necrosis factor-alpha (TNF-alpha) is one of the primary events in many types of liver injury. TNF-alpha triggers the production of additional cytokines that collectively recruit inflammatory cells, which destroy hepatocytes and induce fibrogenesis. Patients with NASH have been shown to have higher levels of TNF-alpha. Pentoxifylline (PTX) is a methylxanthine compound known to inhibit the production of TNF-alpha. Biochemical improvement was demonstrated in two studies; however, histological follow-up was not obtained and gastrointestinal side effects lead to a high rate of withdrawal[9].

Algorith of investigation and treatment of NAFLD[17]



Aggressive control of components of metabolic syndrome

- **Other treatment options**[9,46,47]**:**
- A number of complementary and alternative therapies — many of them herbs and nutritional supplements — purport to improve liver heath. Among these are milk thistle, alpha-lipoic acid (thioctic acid), N-acetyl cysteine (an amino acid byproduct) and omega-3 fatty acids.
- **Antibiotics:** Because bacterial overgrowth–derived lipoproteins may be involved in the development of NASH; oral metronidazol (0.75–2 g/day for 3 months, followed by a similar period without treatment) may be efficacious in reverting steatosis and, in some cases, inflammation and fibrosis. Oral polymixin B may improve parenteral nutrition–associated NASH by reducing liver exposure to intestinal flora-derived endotoxin.
- **Probiotics:** The knowledge of the role of bacterial overgrowth in the pathogenesis of NASH has led to the proposal of probiotics as a therapeutic strategy for this disorder. Probiotics

may interfere with the development of NASH at various levels: *1*) decreases in proinflammatory cytokines, such as TNF-; *2*) alteration of the inflammatory effects of pathogenic strains of intestinal bacteria, through changes in cytokine signaling; *3*) replacement of pathogenic strains of bacteria; and *4*) improved epithelial barrier function (thereby avoiding excessive exposure of the liver to LPS and bacterial ethanol).

- Certain nutritional deficiencies, which are common among people with NAFLD, may provide a clue in the search for a successful treatment. Some people who receive intravenous feedings for prolonged periods of time develop fatty liver in addition to a choline (Choline is a B vitamin) deficiency and correcting the choline deficiency resolve the fatty liver as well.
- Coenzyme A is a substance that is essential for the metabolism of carbohydrates, fats, and certain amino acids. It contains pantothenic acid, a B vitamin that is necessary for growth. In some studies, people with NAFLD were supplemented with a form of coenzyme A, and this caused the extent of fat deposits in the liver to decrease. More research must be done to confirm the efficacy of this type of nutritional supplementation.
- Biotin, a B vitamin has been shown to decrease insulin resistance. Studies on people with NAFLD have not been conducted at this time, but biotin supplementation would be an interesting area of exploration for people with NAFLD.
- Metadoxine restores hepatic glutathione concentrations and acts as an antifibrogenic agent and has proved efficacious in the treatment of alcoholic liver steatosis.
- Silymarin also possesses antioxidant and antifibrogenic properties, with beneficial effects in alcoholic liver disease. S-adenosyl-methionine has anti-steatotic, anti-inflammatory, anti-oxidant, and anti-fibrotic properties. Oral treatment with 600 mg/day or intramuscular administration of 50–100 mg/day have shown efficacy in terms of biochemical, histological, and echographic parameters of liver steatosis, in the absence of adverse effects.

Conclusion:

NAFLD is probably the single most common liver abnormality in the United States. It appears to be linked directly to the growing epidemic of obesity in adults as well as in children. Thus, in a sense, NAFLD is a sell-inflicted liver disease, much like alcoholic liver disease. But only a minority of patients who are obese or diabetic will develop severe liver disease and this is most likely determined genetically. In addition, increasing evidence suggests that obesity and diabetes can worsen alcoholic liver disease and liver disease due to HCV.

For these reasons, basic science researchers, liver specialists, nutritionists, and endocrinologists are combining their efforts to better understand and contain this process that has been recognized for only the past 30 years.

The single most effective treatment for obese people with NASH is to simply lose weight through diet and exercise. Unfortunately, this is no easy task in our present society, which is dominated by a sedentary lifestyle and high-calorie, high-carbohydrate, high-fat diets. With great effort, however, weight loss is achievable.

References:

1. Contos MJ, Sanyal AJ. The clinopathologic spectrum and management of nonalcoholic Fatty liver disese. Adv Anat Pathol 2002; 9(1): 37-51.
2. Clark JM, Diehl AM. Nonalcoholic Fatty Liver Disease: an unrecognized cause of cryptogenic cirrhosis. JAMA 2003; 289(22): 3000-4.
3. Nomura H, Kashiwagi S. Prevalence of fatty liver in a general population of Okinawa, Japan. Jpn J Med 1988; 27: 142-9.
4. Bellentani S, Saccoccio G. Prevalence of and risk factors for hepatic steatosis in northern Italy. Ann Intern Med 2000; 132: 112-7.
5. Tominaga k, Kurata JH. Prevalence of fatty liver in Japanese children and relationship to obesity: an epidemiological ultrasonographic survey. Dig Dis Sci 1995; 40: 2002-9.
6. Ratziu V, Giral P. Liver of fibrosis in overweight patients. Gastroenterology 2000; 118: 1117-1123.
7. Ravanshad S, Amirkalai B, Saberfirozi M, Zare NE, Maram S. Therapeutic Effects of Restricted Diet in Obese Patients with Non-Alcoholic Fatty Liver Disease (NAFLD) Pak J Med Sci 2005; 21 (4): 472-475.

8. Diehl AM, Li ZP, Lin HZ, Yang SQ. Cytokines and the pathogenesis of non-alcoholic steatohepatitis. Gut 2005; 54:303-306.

9. Comar KM, Sterling RK. Review article: drug therapy for non-alcoholic fatty liver disease. Alimentary Pharmacol & Therapeutics 2006; 23:207.

10. NCEP Expert Panel. JAMA 2001; 285: 2486-2497.

11. Sanderson SO, Smyrk TC. The use of Protein tyrosine phosphatase 1B and Insulin Receptor Immunostains to differentiate Nonalcoholic from Alcoholic Steatohepatitis in Liver Biopsy Specimens. Am J Clin Pathol; 123:503-509.

12. Marchesini G, Brizi M, Bianchi G, Tomassetti S, Bugianesi E, Lenzi M, et al. Nonalcoholic fatty liver disease: a feature of the metabolic syndrome. Diabetes 2001; 50(8): 1844-50.

13. Osono Y, Nakajima K, Hata Y. Hypertriglyceridaemia and fatty liver: clinical diagnosis of fatty liver and lipoprotein profiles in hypertriglyceridaemic patients with fatty liver. J Atheroscler Thromb 195; 2 Suppl 1: S47-52.

14. Lefkowitch JH, Haythe JH, Regent N. Kupffer cell aggregation and perivenular distribution in steatohepatitis. Mod pathol 2002; 15(7): 699-704.

15. Day CP, James OFW. Steatohepatitis: a tale of two 'hits'. Gastroenterology 1998; 114:842-5.

16. Cortez-Pinto. Concluding remarks: metabolic syndrome, liver and HCV. Aliment Pharmacol Therapeutics 2005; 22(suppl 2): 83-5.

17. McAvoy NC, Ferguson JW, Campbell IW, Hayes PC. Non-Alcoholic Fatty Liver Disease: Natural History, Pathogenesis and Treatment Br J Diabetes Vasc Dis. 2006; 6(6): 251-260.

18. Crespo J, Cayon A, Fernandez-Gil P. Gene expression of tumour necrosis factor alpha and TNF-receptors, p55 and p75, in non-alcoholic steatohepatitis patients. J Hepatol 2001; 34:1158-63.

19. Yamauchi T, Kamon J, Minokoshi Y. Adiponectin stimulates glucose utilization and fatty-acid oxidation by activating AMP-activated protein kinase. Nat Med 2002; 8:1288-95.

20. Hui JM, Hodge A, Farrell GC. Beyond insulin resistance in NASH: TNF-alpha or adiponectin? Hepatology 2004; 40:46-54.

21. Loffreda S, Yang SQ, Lin HZ, Karp CL, Brengman ML, Wang DJ, et al. Leptin regulates proinflammatory immune responses. *The FASEB Journal.* 1998; 12:57-65.

22. Solga SF, Diehl A: Non-alcoholic fatty liver disease: lumen-liver interactions and possible role for probiotics. *J Hepatol* 38:681–687, 2003.

23. Wigg AJ, Roberts-Thomson I, Dymock R, McCarthy P, Grose R, Cummins A: The role of small intestinal bacterial overgrowth, intestinal permeability, endotoxaemia, and tumour necrosis factor alpha in the pathogenesis of non-alcoholic steatohepatitis. *Gut* 48:206–211, 2001.

24. Drenick EJ, Fisler J, Johnson D: Hepatic steatosis after intestinal bypass: prevention and reversal by metronidazole, irrespective of protein-calorie malnutrition. *Gastroenterology* 82:535–548, 1982.

25. Matteoni CA, Younossi ZM, Gramlich T, Boparai N, Liu YC, McCullough AJ. Nonalcoholic fatty liver disease: a spectrum of clinical and pathological severity. Gastroenterology 1999; 116(6): 1413-9.

26. Marrero JA, Fontana RJ, Su GL, Conjeevaram HS, Emrick DM, Lok AS. NAFLD may be a common underlying liver disease in patients with hepatocellular carcinoma in the United States. Hepatology 2002; 36(6): 1349-54.

27. Sorbi D, Boynton J, Lindor KD. The ratio of aspartate aminotransferase to alanine aminotransferase: potential value in differentiating nonalcoholic steatohepatitis from alcoholic liver disease. Am J Gastroenterol 1999; 94(4): 1018-1022.

28. Mendler MH, Turlin B, Moirand R, Jouanolle AM, Sapey T, Guyader D, et al. Insulin resistance-associated hepatic iron overload. Gastroenterology 1999; 117(5): 1155-63.

29. Pratt DS, Kaplan MM. New Enngl J Med 2000; 342:1266-1271.

30. Ramesh S, Sanyl AJ. Evaluation and management of non-alcoholic steatohepatis. Hepatology 2005; 42: Suppl S2-12.

31. Saadeh S, Younossi ZM, Remer EM, Gramlich T, Ong JP, et al. The utility of radiological imaging in nonalcoholic fatty liver disease. Gastroenterology 2002; 123:745-750.

32. Goldstein NS, Hastah F, Galan MV, Gordon SC. Fibrosis heterogeneity in nonalcoholic steatohepatitis and hepatitis C virus needle core biopsy specimens. Am J Clin Pathol 2005; 123(3): 382-7.

33. Brunt EM. Nonalcoholic steatohepatitis: definition and pathology. Semin Liver Dis 2001; 21(1): 3-16.

34. Gramlich T, Kleiner DE, McCullough AJ, Matteoni CA, Boparai N, Younossi ZM. Pathologic features

associated with fibrosis in nonalcoholic fatty liver disease. Hum Pathol 2004; 35(2): 196-9.

35. Brunt EM, Janney CG, Di Bisceglie AM, Neuschwander- Tetri BA, Bacon BR. Nonalcoholic steatohepatitis: a proposal for grading and staging the histological lesions. Am J Gastroenterol 1999; 94(9): 2467-74.

36. Falck-Ytter Y, Younossi ZM, Marahesini G, McCullough AJ. Clinical features and natural history of nonalcoholic steatosis syndromes. Semin Liver Dis 2001; 21(1): 17-26.

37. Angulo P, Lindor KD. Treatment of nonalcoholic fatty liver: present and emerging therapies. Semin Liver Dis 2001; 21(1): 81-88.

38. Harrison SA, Ramarakhiani S, Brunt EM, anabari MA, Cortese C, Bacon BR. Orlistat in the treatment of NASH: a case series. Am J Gastroenterol 2003; 98(4): 926-30.

39. Hickman IJ, Jonsson JR, Prins JB. Modest weight loss and physical activity in overweight patients with chronic liver disease results in sustained improvements in alanine aminotransferase, fasting insulin, and quality of life. Gut 2004; 53:413-19.

40. Kugelmas M, Hill DB, Vivian B, Marsano L, McClain CJ. Cytokines and NASH: a pilot study of the effects of lifestyle modification and vitamin E. Hepatology 2003; 38:413-19.

41. Laurin J, Lindor KD, Crippin JS, Gossard A, Gores GJ, Ludwig J et al,. Ursodeoxycholic acid or clofibrate in the treatment of non- alcoho- induced steatohepatitis: a pilot study. Hepatology 1996; 23(6): 1464-7.

42. Uygun A, Kadayifci A, Isik AT, Ozgurtas T, Deveci S, Tuzun A etal. Metformin in the treatment of patients with non-alcoholic steatohepatitis. Aliment Pharmacol Ther 2004; 19(5): 537-44.

43. Brunt EM, Neuschwander-Teri BA, Oliver D, Wehmeier KR, Bacon BR. Nonalcoholic steatohepatitis: histologic features and clinical correlations with 30 blinded biopsy specimens. Hum Pathol 2004; 35(9): 1070-82.

44. Hasegawa T, Yoneda M, Nakamura K, Makino I, Terano A. Plasma transforming growth factor-beta1 level and efficacy of alpha-tocopherol in patients with non-alcoholic steatohepatitis: a pilot study. Aliment Pharmacol Ther 2001; 15(10): 1667-72.

45. Abdelmalek MF, Angulo P, Jorgensen RA, Sylvestre PB, Lindor KD. Betaine, a promising new agent for patients with nonalcoholic steatohepatitis: results of a pilot study. Am J Gastroenterol 2001; 96(9): 2711-7.

46. Adams LA, Angulo P. Treatment of non-alcoholic fatty liver disease.Postgrad Med J 2006; 82: 315-22.

47. Medina J, Fernández-Salazar LI, García-Buey L, Moreno-Otero R. Approach to the Pathogenesis and Treatment of Nonalcoholic Steatohepatitis. Diabetes care 2004; 27:2057-2066.