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Non Alcoholic Fatty Liver Disease (NAFLD) Positive Correlation with Metabolic Disorders Has Positive Outcome with UDCA (Urso-Deoxy Cholic Acid) Associated with Life Style Modification

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ABSTRACT

Nonalcoholic fatty liver disease (NAFLD) is currently the most common liver disease worldwide, the prevalence of which had progressively increased over the past 10 years where other liver diseases remained at the same prevalence rates or are expected to decrease as in the case of hepatitis C virus (HCV). The treatment of NAFLD is of prime concern to health care professionals and patients due to the significant mortality and morbidity it implies; the problem is further escalated by the fact that standard of care medications targeting NAFLD remain experimental and without evidence base. Treatment nowadays is focused on lifestyle modification and managing the comorbid associated diseases, with a possible role for some hepatic protective agents.

Medications include agents for weight loss, insulin sensitizers, drugs that reduce blood lipids, glucagon-mimetics, drugs that may reduce fibrosis, angiotensin receptor blockers, and medicines believed to reduce endoplasmic reticular stress such as vitamin E, ursodeoxycholic acid, and S-adenosyl methionine. Ursodeoxycholic acid (UDCA) is a metabolic by-product of intestinal bacteria, showing hepatoprotective effects. However, its underlying molecular mechanisms remain unclear. The action mechanisms underlying the protective effects of UDCA and vitamin E against liver dysfunction using metabolomics and metagenomic analysis is common these days. Nonalcoholic fatty liver disease (NAFLD) is a leading cause of chronic liver disease.

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It affects 20%–40% of the general population and 20% of patients with NAFLD will progress to **nonalcoholic steatohepatitis (NASH**). It is well known that NASH patients may progress to liver cirrhosis and even hepatocellular carcinoma. NASH is currently the most rapidly growing indication for liver transplantation (LT) in patients with HCC in the United States. NASH/NAFLD is predicted to soon become the leading LT indication as a result of major advances in hepatitis C therapy and the increasing prevalence of obesity and associated conditions. **Ursodeoxycholic acid (UDCA),** which is one of the first-line therapeutic agents for treatment of NAFLD, is reported to have a beneficial effect on dyslipidemia and ASCVD risk because of antioxidant properties. Non-alcoholic steatohepatitis (NASH) is a condition that occurs during the progression of non-alcoholic fatty liver disease. Effective therapy for NASH is still lacking. In this study, we investigated the effects of Ursodeoxycholic acid (UDCA) in the treatment of NASH.

INTRODUCTION

Nonalcoholic-fatty-liver-disease/nonalcoholic steatohepatitis (NAFLD/NASH) is expected to become the leading liver disease worldwide. Typical liver-related complications are fibrosis, cirrhosis, and the development of **hepatocellular cancer (HCC**) with the need for liver transplantation. Up to now there is no approved pharmacotherapy. Indeed, this might be due to the complexity of this disease. While the cheapest therapeutic approach is still a lifestyle change leading to weight loss, the proportion of

people achieving sufficient weight reduction without additional support is low. Newly developed drugs are expensive and lack a breakthrough in therapeutic success. Over the last couple of years, more systematic approaches have been developed to find people at risk of nonalcoholic fatty liver disease (NALFD) or nonalcoholic steatohepatitis (NASH). Risk factors include type 2 diabetes (T2DM), obesity, hypertension, and dyslipidemia with or without elevated liver enzymes. When NAFLD/NASH is suspected, further measurements are necessary such as liver stiffness (fibroscan), CT-scan (sensitive and specific, but exposes the patient to radiation), or MRI, which is the gold standard, but currently the most expensive method to identify liver steatosis. Currently, the only way to reliably diagnose steatohepatitis (NASH) is a liver biopsy with histological evaluation. Its presence and the fibrotic stage of the liver are the best predictors of cirrhosis. Ursodeoxycholic acid is able to reduce serum levels of hepatic enzymes in patients with nonalcoholic fatty liver disease, but this effect is not related to modifications in liver fat content.[1]

Nonalcoholic fatty liver disease (NAFLD) has been diagnosed with a higher frequency in the last years because of improved imaging methods. Most patients are asymptomatic and show no signs of disease. Serum levels of hepatic enzymes (mainly aminotransferases and g-glutamyltransferase, g-GT) may or may not be increased. Hepatic ultrasound, computed tomography (CT) and magnetic resonance imaging (MRI) have good sensitivity and specificity for the diagnosis of hepatic steatosis, but only CT and MRI are considered to be reliable methods for the grading of liver fat content. Nonalcoholic fatty liver disease (NAFLD) is a disorder characterized by excess fat accumulation in the liver in the absence of significant amounts of alcohol consumption, usually defined as less than 20 g of ethanol per day.Comparison of nonalcoholic steatohepatitis (NASH) and NAFLD in Eastern and Western showed a similar age at presentation, that is, 4th to 8th decade, prevalence of 20%-30% in the West, whereas 10% in the East. [2]

In 2007, **The Asia-Pacific Working Party** formulated guidelines for NAFLD in the Asia-Pacific region. The Working Party estimated the prevalence of NAFLD in adult population from 5% to 30%. There is a rapid change in the socioeconomic status in Asia, which has led to inappropriate diet and sedentary lifestyle. The management of patients with NAFLD consists of treating liver disease as well as the associated metabolic comorbidities such as obesity, hyperlipidemia, insulin resistance, and Type 2 Diabetes Mellitus. A variety of drugs have been tried for treatment of NASH, including metformin, pioglitazone, Vitamin E, Ursodeoxycholic Acid (UDCA), omega-3 fatty acids, anti-hypertensives, antiobesity drugs, antioxidants, and many more. The most controversial of these drugs is UDCA with some studies favoring its use and others not. UDCA, a secondary bile acid produced by intestinal bacteria as metabolic byproduct, has been shown to be effective in the nonsurgical treatment of cholesterol gallstones and primary biliary cirrhosis (PBC). Studies have investigated UDCA (conventional and high doses) to improve aminotransferases and steatosis in patients with NAFLD and liver histology in patients with NASH. A single large multicenter randomized controlled trial (RCT) showed that UDCA offers no benefit over placebo in patients with NASH. Recent Chinese studies favor UDCA as monotherapy or in combination. However, the **American Association for the Study of Liver Diseases (AASLD)** recommends the use of Vitamin E administered at daily doses of 800 IU/day in nondiabetic adults with biopsy-proven NASH and is considered as a first line pharmacotherapy for this patient population. We carried out this study to compare the efficacy of these two drugs for treatment of NAFLD.[3]

Some existing medications, including pioglitazones and angiotensin receptor antagonists, may be repurposed to help treat this condition. **Vitamin E** may improve histology in NASH, but safety issues limit its use. Recently, a number of novel agents specifically targeting nonalcoholic fatty liver disease pathogenesis have entered clinical trials, including the farnesoid X receptor agonist obeticholic acid, which has shown significant histological improvements in steatohepatitis and fibrosis. Diet/lifestyle modification remains the mainstay of treatment. For patients with NASH and advanced fibrosis, current liver-directed pharmacotherapy with vitamin E and pioglitazone offer some benefits; obeticholic acid appears promising and is currently being tested. Comorbidities must be diagnosed and treated; cardiovascular disease remains a primary cause of death in these patients.

DISCUSSION

The **Clinical Practice Guidelines** propose recommendations for the diagnosis, treatment and follow-up of non-alcoholic fatty liver disease (NAFLD) patients and are the product of a joint effort by the European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD) and European Association for the Study of Obesity (EASO). They update a position statement based on the 2009 EASL Special

Conference. By improving obesity and diabetes, bariatric (metabolic) surgery reduces liver fat and is likely to reduce NASH progression; prospective data have shown an improvement in all histological lesions of NASH, including fibrosis (B1). Pioglitazone is the only agent that has shown consistent benefit and efficacy in clinical trials. Pentoxifylline, rosiglitazone, and ursodeoxycholic acid had both positive and negative results from clinical trials. There is also evidence for vitamin E and metformin. Other drugs, including bicyclol, cysteamine bitartrate, l-carnitine, liraglutide, obeticholic acid, oligofructose, selonsertib, silymarin, and statins, each had a single clinical study.[4]

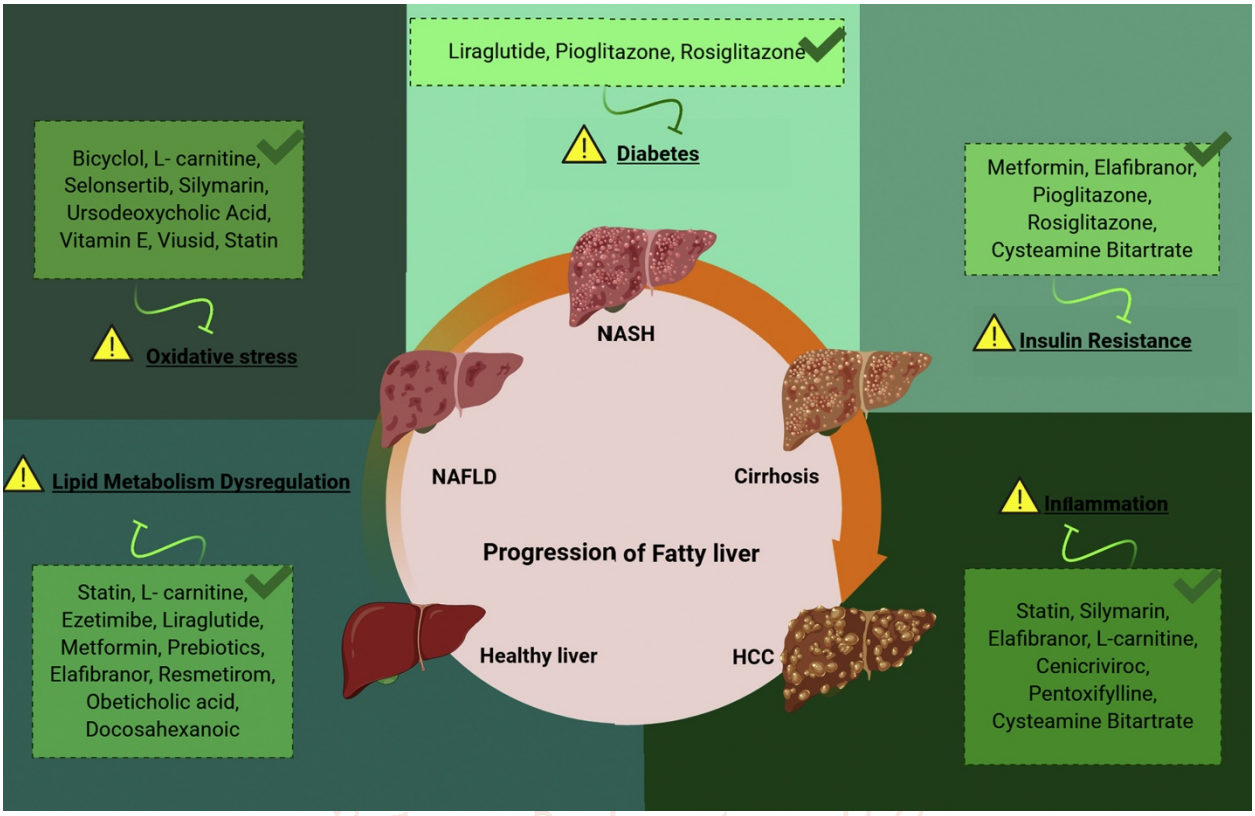

Figure 1 Possible mode of action of agents used in clinical trials for non-alcoholic fatty liver disease and steatohepatitis that used pre-treatment and post-treatment liver biopsy as the endpoints.

Multiple non-invasive tests are available for diagnosis of NAFLD, and its different stages however gold standard test is liver biopsy. NALFD without NASH and significant fibrosis is treated by lifestyle modifications which include moderate to vigorous exercise and diet modification. To improve hepatic steatosis, minimum of 3–5% of body weight loss is necessary, but > 7–10% weight reductions is required for histological improvement in NASH and fibrosis. Pharmacotherapy is indicated when patient is having NASH with significant fibrosis.

Because most pediatric NAFLD patients have obesity, addressing this is the first step. An open-label study(280) in 84 Italian children with biopsy-proven NAFLD showed that >20% body weight reduction over 12 months resulted in improvement in serum ALT and steatosis by ultrasonography in most children with NAFLD. Reportedly, 94% of the 70 enrolled subjects were able to achieve this weight loss goal using caloric restriction and exercise advice. Because liver biopsies were not performed at the end of the study, the effect of lifestyle intervention on liver histology could not be determined. [5]

Antioxidant therapy did not improve liver histology, but children groups who had already reduced their weight through designated lifestyle changes showed significant improvement in steatosis, inflammation, ballooning, and the NAS. In one study consisting of children with severe obesity (BMI z-score >3.5) and NAFLD, intensive lifestyle modification (either in an inpatient or ambulatory setting) offered sustained biochemical benefits in comparison to usual care. No information exists on recommending any particular type of diet or exercise. Similarly, the degree of weight loss needed to improve various histological aspects of NASH in children is unknown. Further studies are needed to assess the efficacy of specific diets. Recommendations for overweight pediatric NAFLD patients should include consultation with a registered dietitian to assess quality of diet and measurement of caloric intake, adoption of American Heart Association dietary strategies, and regular aerobic exercise, progressing in difficulty as fitness allows. As in adults, clinical trials for pediatric NAFLD generally targeted IR or oxidative stress. Open-label, proof-of-concept studies have utilized changes in serum ALT or liver brightness on

ultrasound as endpoints.Agents evaluated thus far include metformin, vitamin E, UDCA, and delayed-release cysteamine. A large, multicenter RCT using change in histology as a secondary endpoint, called TONIC, compared the efficacy of vitamin E or metformin to placebo in 8- to 17-year-olds with NAFLD. [6]

Although the primary outcome of sustained reduction of ALT was not different among the three groups, there were statistically significant improvements in NAS and resolution of NASH ($P < 0.006$) with vitamin E treatment compared to placebo over 96 weeks. In this study, metformin administered at a 500-mg, twice-daily dose had no effect on liver biochemistries or liver histology. The results from another large, multicenter RCT comparing the effect of delayed-release cysteamine to placebo were just reported.In this trial, the primary outcome, requiring reduction in NAS of 2 or more without worsening of fibrosis, was not achieved over the 52- week treatment interval. Interestingly, a secondary outcome comparing reduction in serum ALT on treatment to placebo did achieve significance. There has been some interest to evaluate omega-3 fatty acids to treat NAFLD in children. Whereas a combination of eicosapentaenoic acid and docosahexaenoic acid failed to show significant therapeutic benefit in one study,docosahexaenoic acid administered at 250 mg/day for 6 months showed significant improvement in hepatic fat as well as cardiometabolic risk factors in another study.

RESULTS

Fatty liver is a condition in which the cells of the liver accumulate abnormally increased amounts of fat. Although excessive consumption of alcohol is a very common cause of fatty liver (alcoholic fatty liver), there is another form of fatty liver, termed nonalcoholic fatty liver disease (nonalcoholic fatty liver disease), in which alcohol has been excluded as a cause. In nonalcoholic fatty liver disease, other recognized causes of fatty liver that are less common causes than alcohol also are excluded.[7]

Nonalcoholic fatty liver disease is a manifestation of an abnormality of metabolism within the liver. The liver is an important organ in the metabolism (handling) of fat. The liver makes and exports fat to other parts of the body. It also removes fat from the blood that has been released by other tissues in the body, for example, by fat cells, or absorbed from the food we eat. In nonalcoholic fatty liver disease, the handling of fat by liver cells is disturbed. Increased amounts of fat are removed from the blood and/or are produced by liver cells, and not enough is disposed of or exported by the cells. As a result, fat accumulates in the liver. Nonalcoholic fatty liver disease is classified as either fatty liver (sometimes referred to as isolated fatty liver or IFL) or steatohepatitis (NASH). In both isolated fatty liver and NASH there is an abnormal amount of fat in the liver cells, but, in addition, in NASH there is inflammation within the liver, and, as a result, the liver cells are damaged, they die, and are replaced by **scar tissue**.

When the liver disease is far advanced (cirrhosis), signs and symptoms :-

1. Excessive bleeding due to the inability of the liver to make blood-clotting proteins
2. Jaundice due to the inability of the liver to eliminate bilirubin from the blood
3. Gastrointestinal bleeding due to portal hypertension that increases the pressure in intestinal blood vessels
4. Fluid accumulation due to portal hypertension that causes fluid to leak from blood vessels and the inability of the liver to make the major blood protein, albumin
5. Mental changes (encephalopathy) due to the liver's inability to eliminate chemicals from the body that are toxic to the brain. Coma may occur.
6. Liver cancer

The diagnosis of NAFLD requires that (a) there is hepatic steatosis by imaging or histology, (b) there is no significant alcohol consumption, (c) there are no competing etiologies for hepatic steatosis, and (d) there are no co-existing causes for chronic liver disease. Common alternative causes of hepatic steatosis are significant alcohol consumption, hepatitis C, medications, parenteral nutrition, Wilson's disease, and severe malnutrition. When evaluating a patient with newly suspected NAFLD, it is important to exclude co-existing etiologies for chronic liver disease including hemochromatosis, autoimmune liver disease, chronic viral hepatitis, and Wilson's disease.3 Mildly elevated serum ferritin is common in patients with NAFLD and it does not necessarily indicate increased iron stores.3,64 Elevated serum ferritin and transferrin saturation in patients with suspected NAFLD should lead to testing for genetic hemochromatosis. **Mutations in the HFE gene occur with variable frequency in patients with NAFLD** and their clinical significance is unclear. One should consider a liver biopsy to assess hepatic iron concentration and to exclude significant hepatic injury and fibrosis in a patient with suspected NAFLD with elevated serum ferritin and a homozygote or compound heterozygote C282Y mutation in the HFE gene.65 Elevated serum

autoantibodies are common in patients with NAFLD and are generally considered to be an epiphenomenon.3 In a recently published large study from the NASH Clinical Research Network, positive serum autoantibodies, defined as ANA 1:160 or ASMA 1:40 were present in 21% of patients with well-phenotyped NAFLD and were not associated with more advanced histologic features.[8]

NAFLD has become the most common chronic liver disease worldwide and represents the liver manifestation of metabolic syndrome. As NAFLD prevalence will increase, the prevalence of NASH, liver cirrhosis, and HCC will also inevitably increase. NAFLD is also associated with extrahepatic manifestations of cardiovascular disease. Due to the overall burden of the disease, both prevention and treatment of NAFLD at any possible stage gain paramount importance. Despite several new drugs and molecular targets are promising, many clinical trials conclude that the optimal pharmacological approach still to come due to the complex pathogenesis of NAFLD and NASH. One logical approach would be to target some subcellular organelles involved in the pathogenic process while searching for genetic risk variants and reducing metabolic and environmental stressors. Novel therapies may act both on mitochondrial function and energy supply other than on intracellular regulators of lipid metabolism. Adequate duration and power are needed to evaluate the long-term efficacy and safety of each potential therapeutic option. The beneficial effects of combination therapies are under close scrutiny and await convincing results.

CONCLUSION

No definitive pharmacologic therapy has been approved for treatment of nonalcoholic fatty liver disease (NAFLD). Management of NAFLD should include treating the associated obesity, hyperlipidemia, insulin resistance, and type 2 diabetes.[9]

Although alcohol-induced hyperhomocysteinemia (which has been associated with endoplasmic reticulum stress leading to apoptosis and up-regulation of lipid synthesis) and its correction by betaine have been studied in animal models, no definite role of the use of betaine to treat alcoholic fatty liver in humans is available.Weight loss and control of comorbidities appear to slow the progress of NAFLD and may reverse some of the steatosis and fibrosis. In a randomized trial, improvement on liver biopsy was seen after a 7% weight loss resulting from lifestyle changes (improved diet, exercise, and behavioral modification). No established treatment is available for nonalcoholic steatohepatitis (NASH).Although no proven medical therapy is available, Atorvastatin 20 mg, combined with vitamins C and E, is effective in reducing the odds of having hepatic steatosis by 71% in healthy individuals with NAFLD after 4 years of active therapy. [10]

Some points of treatment and management:-

- Weight loss of 3%-5% of body weight generally reduces hepatic steatosis, but up to 10% weight loss may be needed to improve necroinflammation.
- A combination of reduced calorie diet and moderate intensity exercise may aid in sustaining weight loss, along with aggressive modification of cardiovascular risk factors.
- Patients with NAFLD should not consume heavy amounts of alcohol; data are insufficient to make recommendations with regard to nonheavy alcohol consumption.
- Pharmacologic treatments should be limited to individuals with biopsy-proven NASH and fibrosis.
- Vitamin E 800 IU/day improves liver histology in nondiabetic adults with biopsy-proven NASH; it should therefore be considered as a first-line pharmacotherapy for this patient population, and the risks and benefits should be discussed with the patient prior to starting treatment.
- Omega-3 fatty acids may be considered for hypertriglyceridemia in patients with NAFLD, but it is premature to recommend them for the specific treatment of NAFLD or NASH.
- Metformin is not recommended as a specific treatment for liver disease in adults with NASH.
- Pioglitazone may be used to treat steatohepatitis in both patients with and without type 2 diabetes with biopsy-proven NASH, but the risks and benefits should be thoroughly discussed with the patient prior to initiation of treatment.
- Glucagon-like peptide (GLP)-1 agonists have been studied to treat liver disease in patients with NAFLD or NASH; however, it is still premature to consider these agents as treatment options at this time.[11]
- Foregut bariatric surgery is not contraindicated in otherwise eligible obese individuals with NAFLD or NASH but without established cirrhosis; however, it is premature to consider foregut bariatric surgery as an established option to treat NASH specifically..

- Statins can be used to treat dyslipidemia in patients with NAFLD and NASH, but they should not be used specifically to treat NASH, pending evidence from randomized controlled trials.
- Abstinence from alcohol
- Diet and weight loss

No specific dietary restrictions are needed in patients with simple alcoholic steatosis. Patients with alcoholic fatty liver may have deficiencies of vitamins, minerals, and trace elements. Adequate replacement of these deficiencies should be a part of management. Protein-calorie malnutrition is a common finding in patients with alcoholic liver disease (ALD) and is associated with the major complications observed with cirrhosis. Consequently, it is vital to recognize and understand the significance of malnutrition in these patients.

A low-fat American Diabetes Association (ADA) diet is recommended, and a weight loss goal of 1-2 pounds per week is suggested. Diets associated with improvement include those restricted in rapidly absorbed carbohydrates and those with a high protein-to-calorie ratio. Weight loss should be gradual, moderate, and controlled. [12]

NAFLD can be prevented in most patients by taking the following measures:

- Eating appropriate portions
- Eating healthy choices
- Exercising regularly

Treatment of the underlying disease

Patients with celiac sprue who follow a gluten-free diet can experience reversal of fatty liver disease. Patients with growth hormone deficiency who receive growth hormone can experience reversal of NASH.

Exercise

Multiple human studies have shown that exercise added to diet appears to improve the results and increase insulin sensitivity by increasing muscle mass. Exercise that includes both cardiovascular fitness and weight training should improve NASH. Cardiovascular fitness often results in weight loss. Weight training will increase the muscle mass and improve insulin sensitivity. Combining these two activities helps relieve the underlying derangements of NASH.

Pharmacologic therapy

A number of studies have been initiated to evaluate the therapeutic roles of lipid-lowering agents and insulin sensitizers in the management of fatty liver. Specifically, thiazolidinediones (eg, pioglitazone and rosiglitazone), metformin, gemfibrozil, and atorvastatin have all been found to yield laboratory and histologic improvement in small uncontrolled trials.

Thiazolidinediones have been shown to decrease inflammation in the liver in both humans and rats, with the effects lasting only as long as the medication is being delivered. This class of medication results in improved insulin sensitivity and universal weight gain (which has been shown to involve an increase in whole-body fat rather than total-body water).

Rosiglitazone is an antidiabetic agent (thiazolidinedione derivative) that improves glycemic control by improving insulin sensitivity. It is sold both as a single-ingredient product under the brand name Avandia and as combination products under the brand names Avandamet (rosiglitazone with metformin) and Avandaryl (rosiglitazone with glimepiride).

Patients currently taking rosiglitazone and benefiting from the drug may continue if they choose to do so. Rosiglitazone is available to new patients only if they are unable to achieve glucose control on other medications and are unable to take pioglitazone, the only other thiazolidinedione.

Gemfibrozil has resulted in biochemical improvement, but histologic data are lacking. Ezetimibe was studied in a Japanese population in conjunction with lifestyle changes and yielded improved results on follow-up liver biopsy.

Pentoxifylline has received much attention in both animal models and human trials, but published results have been conflicting.

Orlistat has led to histologic and biochemical improvement in patients who used the drug for several months.

Vitamin E and ursodeoxycholic acid (ursodiol) have brought about improvements in specific populations.

Research data suggest a possible link between obstructive sleep apnea and NAFLD/NASH. Studies have been initiated to determine whether treatment of obstructive sleep apnea results in alleviation of fatty liver disease

All patients with chronic liver disease are at risk for liver disease progression.

Patients should be educated to avoid alcohol and other hepatotoxic substances. If patients have a liver insult from another liver problem, they may have longer recovery times than patients without fatty liver disease would.

Patients with fatty liver disease should be seen regularly by a primary care physician, who may be

able to detect disease progression through physical examination findings (eg, spider telangiectasia, palmar erythema, or splenomegaly), laboratory findings (eg, decreasing platelets, elevated bilirubin, or decreasing albumin), patient complaints (eg, encephalopathy, ascites, or fatigue), or incidental imaging study findings (eg, cirrhotic liver, splenomegaly, varices, or ascites).

Provide follow-up care for patients in an outpatient facility. In patients with alcoholic steatosis, determination of blood alcohol at every outpatient visit often is helpful in determining patient's compliance with abstinence.Patients who have NASH cirrhosis should be screened for **gastroesophageal varices as well as hepatocellular carcinoma.**

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