REVIEW ARTICLE

A Review of the Available Remedial Procedures for the Treatment of Fatty Liver Disease

DELARAM ESKANDARI[1], NILOOFAR KHODABANDEHLOO[2], HOSEIN SAMADANIFARD[1], AMIR ZIAEE[3], ALIREZA HEJRATI[4]*

[1]*Department of endocrinology, School of Medicine, Hazrat-e Rasool Hospital, Iran University of Medical Sciences. Tehran, Iran*
[2]*School of Medicine, Hazrat-e Rasool Hospital, Iran University of Medical Sciences. Tehran, Iran*
[3]*Institute of endocrinology and metabolism, Iran University of Medical Sciences. Tehran, Iran*
[4]*Department of Internal Medicine, School of Medicine, Hazrat-e Rasool Hospital, Iran University of Medical Sciences. Tehran, Iran*
Correspondence to Alireza Hejrati, Email: Hejrati.a@iums.ac.ir, Tel: +98 21 64352474, Fax: +98 21 64352475

ABSTRACT

Fatty liver disease (FLD), known as a common cause of chronic liver disease globally, refers to a spectrum of disease-causing lipid accumulation in the liver. There are two types of FLD, including Alcoholic Liver Disease (ALD) and Non-Alcoholic Fatty Liver Disease (NAFLD). The pathological spectra of these two diseases are similar TO a range of conditions from steatosis to cirrhosis and hepatocellular carcinoma. The diagnosis of FLD relays highly on clinical suspicion, laboratory tests, or diagnostic techniques. Despite advancements in understanding the pathophysiology of FLD, targeted therapies for the disease are still absent. Abstinence, nutritional support, and medications such as corticosteroids and pentoxifylline are used for the management of patients with ALD. The treatment modality for patients with NAFLD is mainly based on weight loss and adjutant management using specific agents such as Insulin sensitizers and Anti-oxidants and cytoprotective therapies. The aim of this study is to provide a thorough review of the current therapies and strategies regarding the management of ALD and NAFLD.

Keywords: Fatty liver disease, steatosis, alcoholic liver disease, abstinence, non-alcoholic fatty liver disease

INTRODUCTION

Fatty liver disease (FLD) is a broad term for a spectrum of disease-causing the build-up of triglyceride fats in the liver. Fatty liver is a common condition, and many people with FLD may show no symptoms and experience no adverse effects. However, fatty liver is a progressive disease and, in severe cases, it can cause irritation, inflammation, and fibrosis of the liver, thereby impairing its function.

Generally, there are two types of FLD with different causes, but similar liver injuries. The first one is called Alcoholic Liver Disease (ALD) and relates mostly to the toxicity of alcohol and transforming it into a toxic compound called acetaldehyde by specific enzymes in the liver[1]. ALD is considered as a major cause of cirrhosis, liver cancer, and liver failure in patients which causing a significant rate of mortality and morbidity all around the world. The severity of ALD is affected by the amount and duration of alcohol consumption, as well as other environmental and genetic factors. ALD-related liver injury may be improved by abstinence[2].

The second type is called Non-Alcoholic Fatty Liver Disease (NAFLD), which occurs for reasons other than consuming alcohol. There is a strong association between the NAFLD and the symptoms of insulin resistance as well as between the NAFLD and several metabolic risk factors such as obesity, type 2 diabetes, hypertension, and dyslipidemia[3]. NAFLD is defined as building up the fat in liver parenchyma (hepatic steatosis) due to the reasons other than excessive alcohol consumption[1]. The global prevalence of obesity and metabolic syndrome make the NAFLD as a public health concern all over the world. Presently, it is considered as a major cause of liver transplant in the US[4]. The general prevalence of NAFLD has been reported to be 25%-35% in Western countries and 5%-15% in Asian countries[5]. This rate has been reported 60%-70% in diabetic people and 75%-92% in obese people[6,7]. NAFLD can be further divided into two subgroups of Non-Alcoholic Fatty Liver (NAFL) and Non-Alcoholic Steatohepatitis (NASH). NAFL is characterized by the incidence of hepatic steatosis with minimal or absent lobular inflammation, while NASH is characterized by the presence of hepatocyte injury (ballooning), fibrosis, and diffused lobular inflammation. In other words, if we consider NAFLD as a spectrum, NAFL will be the mildest and, NASH will be on the other end of the spectrum[8]. Despite the considerable advancement in clinical laboratory tests and imaging technologies, liver biopsy has remained as the leading approach for the diagnosis of FLD and provide valuable information regarding grade and stage of the disease[9]. Liver biopsy in the early stages of NAFLD is associated with lower rates of mortality and reduced advancement to cirrhosis. Increased liver enzymes without a definite cause, finding steatosis or fibrosis on imaging or during surgery are some scenarios that may cause a suspected FLD patient to be referred for conducting a liver biopsy[2].

ALD treatment is challenging, and the treatment options have remained unchanged during the last few decades[10]. Even now, abstinence is regarded as the primary treatment of ALD, which is usually supported by steroids and nutrition aids[11,12]. However, there are limited therapeutic options for steroid-unresponsive patients, or those who cannot bear steroid usage. Liver transplantation (LT) is a treatment option for patients with advanced stages of liver disorders such as cirrhosis and alcoholic hepatitis, which are the most severe manifestations of ALD. It has been reported that liver transplantation results in a low relapse rate and comparable prognosis to other etiologies[1].

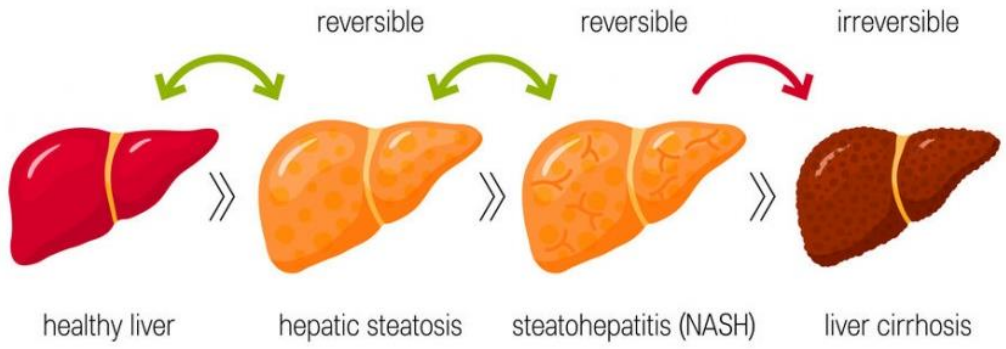
Although there are few treatment options for patients with severe ALD, good evidence exists regarding the benefit of corticosteroids in severe alcoholic hepatitis[13]. The

main therapeutic option for patients with NAFLD is lifestyle modification with a focus on gradual weight loss by nutrition and exercise[14,15]. In addition to surgical intervention, other medications and supplements are also found to play an important role in managing NAFLD. Generally, treatment of NAFLD is based on four pathways, including targeting hepatic fat accumulation, oxidative stress alleviation, using antiobesity medications, and using antifibrotics[16]. However, the safety and adverse effects of these medications in the long-term are not fully understood and require more investigations. According to above mentioned document, this review provides the comprehensive review of the current therapies, and sheds light on the strategies regarding the management of ALD and NAFLD.

Alcoholic liver disease (ALD): Alcoholic liver disease (ALD) refers to liver damage due to excessive alcohol consumption and considers as one of the leading causes of chronic liver disease in the world[17]. In addition to ALD, alcohol plays a contributory role in a variety of diseases and disorders such as hemochromatosis, chronic hepatitis, and non-alcoholic fatty liver[1]. Moreover, chronic alcohol intake contributes to the development of many psychiatric and somatic disorders such as fetal alcohol syndrome[18] and alcohol-induced pancreatitis[19]. According to the World Health Organization (WHO), morbidity attributable to alcohol consumption ranks second place only after tobacco in developed countries[20]. Heavy consuming alcohol in the long term exposes the individual to the risk of advanced liver disease including, cirrhosis, alcoholic steatohepatitis, and hepatocellular carcinoma[21]. Alcohol consumption is also regarded as a contributory factor to the development of various cancers (liver, oropharynx, rectum, esophagus, colon, and the female breast cancer)[1], neuropsychiatric disorders[22] and cardiovascular diseases[23]..

Spectrum: The spectrum of liver injury related to ALD can range from simple steatosis to hepatocellular carcinoma (HCC)[24]. (Figure 2). These stages are not necessarily distinct, and it is possible that multiple stages of the disease can be simultaneously present in a given patient.

Figure 2: Stages of liver damage.



Histologically, ALD-related liver injuries can be grouped into four stages.

- *Hepatic steatosis* is macro-vesicular and develops in about 90-95% of heavy alcoholics because of disrupted lipid turnover. The majority of patients with hepatic steatosis are asymptomatic; however anorexia, nausea, and vomiting may sometimes be present. Heavy and regular alcohol consumption may cause the development of hepatic steatosis within two weeks. Typically, complete abstinence can quickly resolve this disorder[25].
- *Alcoholic hepatitis,* also known as steatohepatitis, develops in approximately one-third of patients with steatosis. Patients with steatohepatitis are at higher risk of cirrhosis development than those with simple steatosis. Around half of the patients with steatohepatitis develop advanced fibrosis or cirrhosis. As steatosis, steatohepatitis is also reversible upon abstinence[1,26].
- Cirrhosis develops in 8-20% of chronic alcohol drinkers[27]. In liver cirrhosis, the hepatocytes are highly damaged and leads to the formation of permanent scar tissue. Cirrhosis is not reversible upon abstinence and may coexist with alcoholic hepatitis. Also, there are additinal factors accelerating the evolution of cirrhosis, including patterns of alcohol drinking, obesity, female gender, genetic polymorphisms, and comorbidities such as hepatitis infections and hemochromatosis[24].
- *Hepatocellular carcinoma (HCC),* approximately 3-10% of patients with cirrhosis develop HCC which is the most worrying disorder related to ALD[1,28].

Diagnosis: Patients developing early stages of ALD show little or no symptoms; thus diagnosis relays mostly on clinical suspicion, laboratory tests, or diagnostic techniques[29]. Excess alcohol consumption (more than 40 g/day in men and 20 g/day in women) for several years and the presence of liver abnormalities are two main factors in the diagnosis of ALD[1,13]. Sometimes, patients with early ALD may present with malnutrition, muscle wasting, parotid, and lacrimal gland enlargement, Dupuytren's contractures, and evidence of peripheral neuropathy. In patients with progressed ALD, jaundice, ascites, hepatic encephalopathy, pedal edema, and typical liver-related skin signs such as spider angiomata, gynecomastia, palmar erythema, and smooth tongue may also be visible[30].

Laboratory tests such as γ-glutamyl transferase (GGT), mean corpuscular volume of red blood cells, and aminotransferase can be used to indicate early ALD; however, they lack specificity in patients with cirrhosis[31].

Elevated levels of triglycerides and uric acid are frequently seen in heavy alcohol drinkers[32].

Although there are noninvasive methods such as liver stiffness measurement and serum markers to assess liver fibrosis in ALD patients, none of them can sufficiently validate the presence of ALD. However, these tests are useful to differentiate mild fibrosis from the severe case[33]. A liver biopsy may be used to establish the diagnosis if noninvasive methods fail to obtain a precise result. Moreover, clinical and biochemical indicators cannot accurately validate the severity of the liver disease, and performing a liver biopsy can help in detecting the stage and severity of ALD[34]. Biopsies are performed percutaneously in most of the cases; however depending on the type of disorder or the required measurements, they may be performed through a transjugular route[1].

Treatment: A summary of treatment options for ALD is shown in Table 1.

Table 1: A summary of treatment options for alcoholic liver disease.

Treatment options	Description
Non-pharmacologic therapies	*Alcohol abstinence* can resolve early ALD and improve the survival rate in patients with cirrhotic *Nutrition support* is directly associated with the severity of disease in ALD patients
pharmacologic therapies	*Corticosteroids* the use of corticosteroids resulted in improved survival in these patients *Pentoxifylline (PTX)* is an effective alternative for the treatment of severe alcoholic hepatitis patients who cannot bear steroids *The antioxidant* can compensate for the oxidative stress produced by alcohol
Liver transplantation	Liver transplantation (LT) is usually indicated for patients with advanced alcoholic cirrhosis or those with severe AH who are unresponsive to steroids and have a Lille score greater than 0.56

Abstinence: Alcohol abstinence is considered as the first step towards the management of patients with ALD since the efficacy of medical treatments depends on the abstinence from alcohol[1]. Alcohol abstinence can resolve early ALD and improve survivability in patients with cirrhotic. Thus, it is highly recommended to motivate the patients to stop drinking alcohol and follow the given therapy regime. In this regard, anonymous group meetings can be held for self-control and motivation of alcoholics. Moreover, recognition and treatment of possible psychiatric conditions may help such a patient to maintain abstinence and sobriety[35]. Close cooperation between physicians, addiction specialists, and psychologists can facilitate abstinence in ALD patients.

Pharmaceutical approaches are also available to treat alcohol dependence, which can help to maintain abstinence. The oldest medication used for this purpose is disulfiram but has poor tolerability, and the evidence regarding its efficacy on abstinence is insufficient[13]. Also, due to its possible hepatotoxicity, disulfiram should not be administered in patients with liver disorders. Other drugs such as naltrexone, acamprosate, topiramate, baclofen, acamprosate, and topiramate are also used for improving alcohol dependency, but their efficacy is not verified for ALD treatment[1,13,36-39]. Among these agents, baclofen has been reported to be safe and efficient for the treatment of ALD patients in several clinical trials[40,41]. Metadoxine is another drug that can be used to keep abstinence and decrease craving in heavy alcoholics[35].

Nutritional support: Nutrition support is an essential step in the treatment of patients with ALD. Most patients with ALD, especially those with advanced ALD, reveal considerable clinical signs of malnutrition, and the severity of the disease has a direct correlation with the degree of malnutrition. Many ALD-related complications are significantly related to protein-calorie malnutrition[42]. Moreover, changes in the profile of vitamins (A, B, D, and E) and minerals (magnesium, selenium, copper, and zinc) in ALD patients have also been reported in several studies[43,44]. Accordingly, recent guidelines have recommended that nutritional support be involved in the treatment of ALD patients. Possible causes for malnutrition in patients with ALD include, but not limited to, the following:

- Poor dietary intake
- Diarrhea and malabsorption
- Nausea and vomiting
- Hypercatabolism
- Effects of cytokines
- poor palatability of foods low in sodium
- lack of appetite due to esophagitis, gastritis malfunction, dysgeusia, or dental problems
- deficits of vitamins (B, A, D, and E) and minerals (magnesium, selenium, copper, and zinc)
- Complications related to liver diseases, such as hepatic encephalopathy and ascites

The result of clinical trials shows that parenteral nutritional therapy provided little benefits for treating ALD patients. However, there is robust evidence on the efficacy of enteral nutritional therapy on the improvement of the nutritional status of patients with ALD, such as anthropometric variables, nitrogen balance, and patients' survival[45,46]. Several studies reported that supplementation with amino acids, leucine, isoleucine, and valine resulted in inadequate protein uptake with no adverse effect on hepatic encephalopathy in patients with cirrhotic who are intolerable to protein[47,48,49]. Current guidelines suggested a daily protein consumption of 1.2-1.5 g/kg and 35-40 kcal per kg of the weight of the body for energy intake in ALD patients. Malnourished ALD patients are more prone to various infections, and thereby, using empiric antibiotic treatment may be recommended[35].

Corticosteroids: The use of corticosteroids for the management of FLD goes back for about 40 years[50]. Various clinical trials investigated the efficacy of corticosteroids in the treatment of ALD patients[51]. Although there are some contradictories in the results of these studies, it could be concluded that overall the use of corticosteroids resulted in improved survival in these patients[53]. Prednisolone is the most studied formulation used in a daily dose of 40 mg for a total duration of 4

weeks. The response to prednisolone is evaluated by monitoring the variations in bilirubin content after one week of therapy. In patients who are unable to take medications orally, intravenous methylprednisolone can be used with a dose of 32 mg per day.

However, about one-half of patients are unresponsive to corticosteroid, and another type of therapies should be considered for these patients[25]. Although using corticosteroids have been found to produce a significant effect on responders, it dose not effect on null responders, and interruption of treatment with corticosteroids is recommended as these patients do not benefit the therapy, and side effects may occur. Lille score can be used to determine the response to corticosteroid therapy, in which a Lille score over 0.45 after one week of treatment initiation indicates that patients are unresponsive to steroids, and treatment should be stopped. In such cases, a survival rate of 25% at six months is estimated. Lille score has recently modified, and patients with a score ≤of 0.16 regarded as complete responders, a score of 0.16-0.56 as partial responders, and a score ≥ of 0.56 as null responders. The survival rate of these three groups at 28 days has been estimated to be 91%, 79%, and 53%, respectively[11].

Additionally, steroids should be avoided in patients suffering active infections, hepatorenal syndrome, hepatitis B virus infection, gastrointestinal bleeding, and active tuberculosis due to the possibility of occurring adverse effects in these patients[54]. Hence, patients are recommended to be screened for any infections before onset and during the treatment with steroids. It has been reported that the survival rate of patients infected after initiation of steroid treatment was two months lower than that of patients with no infection[55].

PTX: Pentoxifylline (PTX) is a phosphodiesterase inhibitor that inhibits pro-inflammatory cytokines like TNF-α. In those patients suffering hepatorenal syndrome or having a contraindication to steroids, PTX is an effective alternative for the treatment of severe alcoholics with hepatitis[56]. The effect of TNF-α on the disease severity in AH patients and the liver injury induced by alcohol has been found in several animal models. The results of studies showed that using PTX in patients with alcoholic steatohepatitis (ASH) has been related to reduced risk of renal injuries in these patients[52]. However, the results regarding the survival benefit of PTX in these patients are inconsistent; although some studies have reported survival superiority of PTX over steroids, many other randomized studies failed to show such a benefit in severe ASH patients[25,53,57]. Moreover, the mortality benefit of PTX may be attributed to its role in reducing the incidence of renal injuries[25,35].

Antioxidants: Alcohol decreases the level of endogenous antioxidants and increases reactive oxygen species, causing oxidative stress, which actively contributes to the pathogenesis of ALD. Most of the antioxidants studied such as lecithin, vitamin C and E, β-carotene, allopurinol, among others, result in no considerable advantages in the treatment of patients with AH[25]. However, there is some evidence regarding improved survival among patients receiving N-acetylcysteine infusion either alone or in combination with corticosteroids[58]. A recent meta-analysis reported that a combination of N-acetylcysteine and prednisolone provided the best 28-days survival benefit with an 85% mortality reduction from AH compared to various pharmacological agents[59]. However, more studies are needed to verify the efficacy of N-acetylcysteine in the treatment of severe AH patients.

Liver transplantation: Liver transplantation (LT) is usually indicated for advanced alcoholic cirrhosis patients who show no sign of significant recovery after three months of alcohol abstinence[60]. Moreover, patients with severe AH who are unresponsive to steroids and have a Lille score greater than 0.56 is suggested to put under LT[61]. Although LT is considered as the only option for such patients, there are concerns regarding this operation among alcoholics such as recidivism, post-op care, and poor compliance. The risk of post-transplantation echo bright is reported to be 10%-50%. The possible factors responsible for recidivism include poor social support, the background of alcohol abuse in the family, and abstinence for six months or less before LT[35].

Transplant programs frequently require patients to avoid alcohol consumption for six months before undergoing LT[62]. The leading causes of this 6-months abstinence are (i) recovery of liver function (sometimes, liver function improves so that there is no longer need to LT), (ii) lower risk of post-transplant recidivism [1]. However, some studies have challenged the 6-months abstinence, argued that this period should be shorter (3 months or less) as some patients may pass away during the waiting period[63].

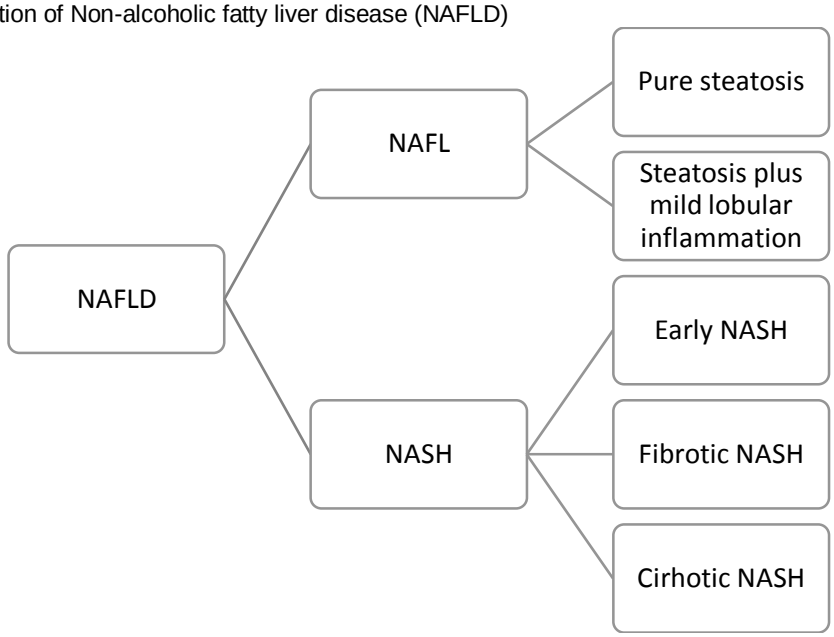
Although post-LT morbidity and mortality in patients with ALD are almost the same with that of non-ALD patients, the mortality causes after transplantation differ for ALD patients[64]. The most common conditions in patients receiving LT for ALD include cardiovascular complications, de novo malignancies, skin cancer, and lymphoproliferative disorder[60,65]. Cigarette smoking has shown to directly relate with most of these conditions, demonstrating that these patients should be monitored for tobacco use before and after LT. Liver-transplanted patients usually present with a variety of comorbidities such as malnutrition, vitamin and mineral deficiencies, muscle wasting, neural system abnormalities, among others[66]. Hence, a multidisciplinary approach is needed for the best caring for ALD patients after LT.

Non- Alcoholic fatty liver disease (NAFLD): Non-alcoholic fatty liver disease (NAFLD) is regarded as the leading cause of chronic liver disease all over the world. It is reported that up to 25% of the world population is affected by NAFLD, while this rate is about 34 percent in the US[5]. NAFLD is defined as deposition and accumulation of adipose tissue inside the liver for the reasons other than excessive alcohol intake[15,67]. Terminologically, NAFLD is further divided into two subgroups of non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH). In NAFL, liver steatosis is present, but there is no evidence of hepatocyte injury, while NASH is characterized as a necro-inflammatory process, causing damage to liver cells[68].

Current trends in the dietary and sedentary lifestyle cause a growing prevalence of NAFLD worldwide. NAFLD is associated with the symptoms of insulin resistance and several metabolic risk factors, including obesity, type 2 diabetes, hypertension, and dyslipidemia[69,70]. Moreover, it is currently the second most common reason for liver transplantation (LT)[71,72]

Spectrum: NAFLD is a heterogeneous disease, representing a spectrum of disorders ranging from simple liver steatosis to more aggressive forms such as non-alcoholic steatohepatitis and cirrhosis[73]/. NAFLD is generally classified into the non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH). NAFL is described by pure steatosis or steatosis in association with mild lobular inflammation in at least 5% of hepatocytes. Steatosis less than 5% is clinically insignificant[74,75]. On the other hand, NASH is characterized by the presence of steatosis, inflammation, and ballooning at a liver biopsy of NAFLD patients (Figure 3).

Figure 3. Classification of Non-alcoholic fatty liver disease (NAFLD)



Diagnosis: NAFLD usually remains asymptomatic until liver decompensation occurs. So it is often diagnosed incidentally during investigation of other complications in the liver[4,76]. An abnormal liver test or the presence of insulin resistance, obesity, or metabolic risk factors may be an indication to further investigation for the possible liver disease[77]. Detection of abnormalities in the result of laboratory exams could indicate the presence of NAFLD. For example, a slight increase in the levels of alanine transaminase (ALT) and serum aspartate transaminase (AST) may be observed in the case of NAFLD[78] but they are poor markers for prediction of advanced fibrosis in NAFLD patients[15,79]. Furthermore, it is reported that the level of serum ferritin is elevated, and titers of autoimmune antibodies are decreased in the patients with NAFLD. Other standard variables in NAFLD patients include age, BMI, the ratio of AST to ALT, and glucose tolerance impairment[80].

Abdominal ultrasound (US) is considered as the first examination option in the diagnosis of liver steatosis in patients suspected for NAFLD. Despite broad availability and low cost of the US, its sensitivity is low, especially in obese patients with a BMI greater than 40 kg/m^2 [8]. US scan can depict an echo bright liver in NAFLD patients developing at least 30% steatosis[81]. Magnetic resonance imaging (MRI) is an accurate technique to assess hepatic steatosis, having a sensitivity to detect liver fat as low as 5%-10%. However, its clinical use is still limited, due to the reasons such as limited availability, high costs, and time-consuming execution[82]. Ultrasonography-based transient elastography (TE) is another promising tool in the assessment of liver fat content with fairly good sensitivity[83]. Despite advantages such as low cost and rapid execution, however, its clinical use needs to be further defined. Currently, liver biopsy has remained the leading approach for the diagnosis of FLD and provides valuable information regarding the grade and stage of the disease[9].

Treatment: A summary of treatment options for NAFLD is shown in Table 2.

Table 2: A summary of treatment options for patients with non-alcoholic fatty liver disease.

Treatment options	**Description**
Non-pharmacologic therapies	*Lifestyle modification* relays on weight loss through a healthy diet and physical activity
pharmacologic therapies	*Insulin sensitizers* can improve insulin resistance by enhancing insulin sensitivity *lipid-lowering agents* can improve obesity and metabolic syndrome both of which are main factors contributing to NAFLD *Ursodeoxycholic acid (UCDA)* is found to produce desirable outcomes when used as a combined therapy with another medication regime *Vitamin E* has an anti-oxidant property and is able to reduce oxidative stress markers and improve liver test functions in patients with NASH *Pentoxifylline (PTX)* has antioxidant, anti-fibrotic, and anti-inflammatory properties and can improve the histological parameters in NAFLD patients *Incretin analogs* lead to improved glycaemic profile, increased insulin sensitivity, and weight loss.
Liver transplantation	Liver transplantation may be considered for NAFLD patients with end-stage decompensated liver disease

Lifestyle changes: Lifestyle modification is focused on weight loss through a healthy diet and proper physical activity and remains as a keystone element in the treatment of NAFLD patients. Weight loss benefits in the treatment of NAFLD have shown in various studies[15,35,84,85]. It has been shown that a weight loss of 3%-5% is associated with reduced steatosis, while 5%-7% weight loss can resolve NASH. Weight loss of more than 10% may also help improving hepatic fibrosis. Guidelines have specified a weight loss of 7%-10% as the target of lifestyle interventions.

Weight loss is mainly achieved through dietary modification and physical activity. A carbohydrate-rich diet has a pivotal role in obesity, insulin resistance; hence dietary change can play a fundamental role in the management of NAFLD. In this regard, a diet consisting of low, low carbohydrate, and low-calorie foods are suggested for these patients. Commonly it is recommended to limit caloric intake by approximately 500 to 1000 kcal per day in such patients[80]. Accordingly, sugar consumption should be restricted, and foods rich in fructose should be avoided in these patients. Moreover, omega-3 fatty acid-rich foods should be considered in the diet of such patients, since it improves the lipid profile through accelerating the oxidation and decreasing the synthesis of fatty acid[86]. Fish and fish oil, soybeans, and walnuts are rich in omega-3 fatty acid, and it is recommended to be included in dietary. Weight loss is also associated with the improvement of cardiovascular risk profile. However, rapid weight loss has been found to worsen steatohepatitis and increase the risk of gallstones and liver failure[35]. Hence, the attention should be paid on the timing of weight loss, so that it happens gradually but consistent over 6 to 12 months[87].

Natural weight loss is best achieved by following a healthy diet and moderate exercise program. Moderate intensity exercises such as aerobic and fast walking for 30-45 min/d can result in the improvement of histological and biochemical characteristics of NAFLD patients[88]. A recent retrospective study of 169 obese men participating in a 3-months weight loss program, including dietary modification and aerobics, found that 250 minutes moderate to severe exercise per week reduces lipid peroxidation and increases adiponectin levels compared with those with less activity[89].

Although lifestyle intervention is a very effective treatment for NAFLD patients, its implementation can be difficult, and this approach suffers from the lack of adherence and time incompatibility[90]. There are certain pharmacological agents such as Sibutramine and Orlistat that have also been used for reducing weight in obese patients. Orlistat inhibits lipase, causing fewer fat absorption in the liver. Sibutramine acts as a serotonin and noradrenaline reuptake inhibitor, which suppresses appetite. It is shown that these agents reduce the levels of serum transaminase and hepatic steatosis. However, their use has been associated with the risk of cardiac-related mortality[91].

Pharmacological treatment:

Insulin sensitizers: As mentioned previously, NAFLD is strongly related to obesity and metabolic syndrome, both of which cause resistance to insulin. Thus, agents able to enhance insulin sensitivity (known as insulin sensitizers) have been investigated in the management of NAFLD.

Metformin: Metformin is a hypoglycaemic agent that is widely used in the treatment of type 2 diabetes. Metformin can decrease hepatic gluconeogenesis, lipogenesis, and glucose reabsorption from the gut and increase the oxidation of free fatty acids, thus causing hepatic and peripheral insulin resistance[92].The efficacy of metformin as a monotherapy for the management of NAFLD is debatable; however, it could be involved as a part of combination therapy[35].

Thiazolidinedione: Thiazolidinediones (TZDs) are peroxisome proliferator-activated receptor-gamma agonist with the ability to enhance insulin sensitivity via effect on plasma adiponectin, which is shown to have anti-fibrotic and anti-inflammatory features[35]. Therefore, TZDs target multiple factors contributed to NAFLD pathogenesis including high resistance to insulin, low levels of adiponectin, and elevated pro-inflammatory cytokines. Troglitazone was a first-generation member of TZDs, although its use was stopped due to hepatotoxicity[75]. However, second-generation TZDs including pioglitazone and rosiglitazone are not hepatotoxic, and their use has been shown to be associated with improvement in insulin sensitivity, hepatic steatosis, aminotransferases, inflammation, and ballooning in patients with NASH and prediabetes[75]. Patients may require long-term therapy with TZDs; however it[95], congestive heart failure, anemia, peripheral edema, and osteoporosis[35]. Moreover, it has been found that the TZDs cannot provide desired results without nutrition and lifestyle changes.

Lipid-lowering agents: The use of agents able to lower lipid absorption could be advantageous in the management of NAFLD patients because obesity and metabolic syndrome are two main factors contributing to NAFLD. Statins and fibrates are used to manage hyperlipidemic patients who are at high risk of developing cardiovascular disorders; however, there are inadequate data regarding the direct benefit of these agents in NAFLD patients. The use of Ezetimibe in a mouse model of NAFLD has produced promising results, but human studies are required to confirm its efficacy in man[35].

Ursodeoxycholic acid (UCDA): UCDA is a hydrophilic bile acid, having cytoprotective characteristics[96]. The results of the efficacy of UCDA in the treatment of NAFLD are a contradiction. Some studies reported that UCDA improves the level of liver enzymes and hepatic steatosis in these patients[35] and some others failed to find significant improvements with using UDCA alone[97]. UDCA is typically used as an adjuvant to another medication regime for NAFLD patients.

Vitamin E: Vitamin E is a fat-soluble vitamin with antioxidant features, and its application has been evaluated in the management of patients with NASH[8]. Various clinical trials have shown that vitamin E has been associated with a reduction in oxidative stress markers and an improvement in liver test functions in patients with NASH[98,99] The efficacy of vitamin E is seemed to enhanced when combined with other agents. For example, it has been shown that a combination of UDCA and Vitamin E improve the histology of NAFLD, and a combination of vitamin E and pioglitazone result in more histological improvement compared to vitamin E alone[35]. However, there are concerns about the safety of vitamin E when it is

used in the long term and at high doses (more than 400 IU per day)[95]

PTX: Pentoxifylline (PTX) is a TNFα inhibitor with antioxidant, anti-fibrotic, and anti-inflammatory properties[96]. Some trials have reported that using PTX has improved the histological parameters in NAFLD patients[100] However, more studies are required to confirm the role of PTX in NAFLD treatment.

Incretin analogs: Incretins are neuroendocrine hormones in the gut, produced in response to food uptake and are capable of limiting glucagon release, incite glucose-dependent insulin release, and delay gastric emptying. The use of incretins in patients with diabetes mellitus has been associated with an improved glycaemic profile, increased sensitivity to insulin, and reduced weight[80]

Glucagonlike peptide 1 (GLP-1) is a type of incretin hormone with a short half-life of about 1-2 minutes, which is quickly broken down by the enzyme dipeptidyl peptidase 4 (DPP-4). GLP-1 has a variety of functions and can decrease the level of blood glucose, prolong gastric emptying, and stimulate insulin secretion. It can also promote weight loss in obese patients with NAFLD[35] GLP-1 receptor agonists such as Exenatide and Liraglutide[101] and DPP-4 inhibitors such as Saxagliptin

CONCLUSION

Fatty liver disease (FLD) is an expression to refer to a range of conditions caused by building up excess fat in the liver. Two types of FLD include Alcoholic Liver Disease (ALD) and Non-Alcoholic Fatty Liver Disease (NAFLD), both of which have similar spectra from steatosis to cirrhosis and hepatocellular carcinoma. The diagnosis of FLD relays highly on clinical suspicion, laboratory tests, or diagnostic techniques. Despite the advancements in the pathophysiology of FLD, no effective therapy has been identified for the management of this disease. The treatment options for patients with ALD are widely relaid on abstinence, nutritional aid, and medications such as corticosteroids and PTX. NAFLD treatment are mainly focused on weight loss and adjutant management using certain agents such as insulin sensitizers, antioxidants, and cytoprotective therapies. Liver transplantation is indicated for patients suffering severe ASH who are not responding to medical treatment. However, given the multiple pathways contributed to the pathogenesis of FLD, a combination therapy using numerous targets may produce more satisfying results than using a single therapeutic agent.

REFERENCES

1. Stickel F, Datz C, Hampe J, Bataller R. Pathophysiology and management of alcoholic liver disease. Gut and Liver 2017; 11: 173-88.
2. Mostafa M, Abdelkader A, Evans JJ, et al. Fatty liver disease: A practical approach. Arch Pathol Lab Med. 2019; 341: 1-9.
3. Chang E, Park CY, Park SW. Role of thiazolidinediones, insulin sensitizers, in nonalcoholic fatty liver disease. J Diabetes Investig, 2013; 4(6): 517-524.
4. Patel V, Sanyal AJ, Sterling R. Clinical presentation and patient evaluation in nonalcoholic fatty liver disease. Clin Liver Dis. 2016; 20(2):277–292.
5. Younossi ZM, Koenig AB, Abdelatif D, et al. Global epidemiology of nonalcoholic fatty liver disease-Metaanalytic assessment of prevalence, incidence, and outcomes. Hepatology 2016; 64: 73-84.
6. Ballestri S, Zona S, Targher G, Romagnoli D, et al. Nonalcoholic fatty liver disease is associated with an almost twofold increased risk of incident type 2 diabetes and metabolic syndrome. J Gastroenterol Hepatol 2016; 31: 936-944.
7. Lonardo A, Ballestri S, Guaraldi G, Nascimbeni F, et al. Fatty liver is associated with an increased risk of diabetes and cardiovascular disease - Evidence from three different disease models: NAFLD, HCV and HIV. World J Gastroenterol 2016; 22: 9674-9693.
8. Leoni S, Tovoli F, Napoli L, et al. Current guidelines for the management of non-alcoholic fatty liver disease: a systematic review with comparative analysis. World J. Gastroenterol. 2018; 24(30):3361-3373.
9. Sanyal AJ, Brunt EM, Kleiner DE, et al. Endpoints and clinical trial design for nonalcoholic steatohepatitis. Hepatology. 2011;54(1):344–353.
10. Rowell RJ, Anstee QM. An overview of the genetics, mechanisms and management of NAFLD and ALD. Clin Med (Lond) 2015; 6: s77-s82.
11. Mathurin P, O'Grady J, Carithers RL, et al. Corticosteroids improve short-term survival in patients with severe alcoholic hepatitis: meta-analysis of individual patient data. Gut. 2011; 60: 255-260.
12. Fialla AD, Israelsen M, Hamberg O, et al. Nutritional therapy in cirrhosis or alcoholic hepatitis: a systematic review and meta-analysis. Liver Int. 2015; 35: 2072-2078.
13. Pal P, Ray S. Alcoholic liver disease: A comprehensive review. EMJ. 2016; 85-93.
14. Musso G, Gambino R, Cassader M, Pagano G. A meta-analysis of randomized trials for the treatment of nonalcoholic fatty liver disease. Hepatology 2010; 52: 79-104.
15. Chalasani N, Younossi Z, Lavine JE , et al. The diagnosis and management of non-alcoholic fatty liver disease: Practice guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association. Am J Gastroenterol 2012; 107: 811-826.
16. Rotman Y, Sanyal AJ. Current and upcoming pharmacotherapy for non-alcoholic fatty liver disease. Gut 2017; 66: 180-190.
17. Yoon Y-H, Chen CM. Surveillance Report #105. Liver cirrhosis mortality in the United States: national, state, and regional trends, 2000–2013. 2017. Available at https://pubs.niaaa.nih.gov/publications/surveillance105/Cirr13.htm.
18. Popova S, Lange S, Shield K, et al. Comorbidity of fetal alcohol spectrum disorder: a systematic review and meta-analysis. Lancet 2016;387:978-987.
19. Yadav D, Lowenfels AB. The epidemiology of pancreatitis and pancreatic cancer. Gastroenterology 2013;144:1252-1261.
20. World Health Organization. WHO mortality database: raw data files. Geneva: World Health Organization, 2015.
21. Askgaard G, Gronbaek M, Kjaer MS et al. Alcohol drinking pattern and risk of alcoholic liver cirrhosis: a prospective cohort study. J Hepatol 2015;62:1061–7.
22. Foulds JA, Adamson SJ, Boden JM, et al. Depression in patients with alcohol use disorders: systematic review and meta-analysis of outcomes for independent and substance induced disorders. J Affect Disord. 2015;185:47-59.
23. Fernández-Solà J. Cardiovascular risks and benefits of moderate and heavy alcohol consumption. Nat Rev Cardiol 2015;12:576-587.
24. Gao B, Bataller R. Alcoholic liver disease: pathogenesis and new therapeutic targets. Gastroenterol. 2011;141(5): 1572-85.

25. Singal AK, Bataller R, Ahn J, et al. ACG Clinical Guideline: Alcoholic Liver Disease. Am J Gastroenterol. 2018;113(2):175–194.
26. Ma C, Brunt EM. Histopathologic evaluation of liver biopsy for cirrhosis. Adv Anat Pathol. 2012;19(4):220-30.
27. Bruha R, Dvorak K, Petrtyl J. Alcoholic liver disease. World J Hepatol. 2012;4(3):81-90.
28. Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. Hepatology. 2011;53(3):1020-2.
29. European Association for the Study of Liver. EASL clinical practical guidelines: management of alcoholic liver disease. J Hepatol 2012;57:399-420.
30. Wiegand J, Kühne M, Pradat P, et al. Different patterns of decompensation in patients with alcoholic vs non-alcoholic liver cirrhosis. Aliment Pharmacol Ther. 2012;35(12):1443–50.
31. Singal AK , Chaha KS , Rasheed K et al. Liver transplantation in alcoholic liver disease current status and controversies. World J Gastroenterol 2013;19:5953–63.
32. Tu HP, Tung YC, Tsai WC, et al. Alcoholrelated diseases and alcohol dependence syndrome is associated with increased gout risk: a nationwide populationbased cohort study. Joint Bone Spine. 2017; 84(2): 189-196
33. Lombardi R, Buzzetti E, Roccarina D, Tsochatzis EA. Non-invasive assessment of liver fibrosis in patients with alcoholic liver disease. World J Gastroenterol 2015;21:11044-11052.
34. O'Shea RS, Dasarathy S, McCullough AJ. Alcoholic liver disease. Hepatology, 2010;51: 307-328.
35. Singh S, Osna NA, Kharbanda KK. Treatment options for alcoholic and non-alcoholic fatty liver disease: A review. World J Gastroenterol 2017; 23(36): 6549-6570.
36. Mason BJ, Lehert P. Acamprosate for alcohol dependence: a sexspecific meta-analysis based on individual patient data. Alcohol Clin Exp Res 2012; 36: 497-508.
37. Addolorato G, Mirijello A, Leggio L, et al. Management of alcohol dependence in patients with liver disease. CNS Drugs 2013; 27: 287-299.
38. Haass-Koffler CL, Leggio L, Kenna GA. Pharmacological approaches to reducing craving in patients with alcohol use disorders. CNS Drugs 2014; 28: 343-360.
39. Vuittonet CL, Halse M, Leggio L, et al. Pharmacotherapy for alcoholic patients with alcoholic liver disease. Am J Health Syst Pharm 2014; 71: 1265-1276.
40. Leggio L, Ferrulli A, Zambon A, et al. Baclofen promotes alcohol abstinence in alcohol dependent cirrhotic patients with hepatitis C virus (HCV) infection. Addict Behav 2012;37:561-564.
41. Barrault C, Lison H, Roudot-Thoraval F, et al. One year effectiveness of Baclofen treatment in 100 alcohol-dependent patients. J Hepatol 2015;62(Suppl 2): S758–S759. (1-[107])
42. Huisman EJ, Trip EJ , Siersema PD, et al. Protein energy malnutrition predicts complications in liver cirrhosis. Eur J Gastroenterol Hepatol 2011; 23: 982-989.
43. Fragasso A, Mannarella C, Ciancio A, et al. Holotranscobalamin is a useful marker of vitamin B12 deficiency in alcoholics. ScientificWorldJournal 2012; 128-182.
44. Rossi RE, Conte D, Massironi S. Diagnosis and treatment of nutritional deficiencies in alcoholic liver disease: Overview of available evidence and open issues. Dig Liver Dis 2015; 47: 819-825.
45. Moreno C, Langlet P, Hittelet A, et al. Enteral nutrition with or without N-acetylcysteine in the treatment of severe acute alcoholic hepatitis: a randomized multicenter controlled trial. J Hepatol 2010; 53 : 1117 – 22.
46. Moreno C, Deltenre P, Senterre C, et al. Intensive enteral nutrition is ineffective for patients with severe alcoholic hepatitis treated with corticosteroids. Gastroenterology 2016;150:903–910 e8.
47. Englesbe MJ1, Patel SP, He K. et al. Sarcopenia and mortality after liver transplantation. J Am Coll Surg. 2010;211(2):271-8.
48. Singal AK. Charlton MR. Nutrition in alcoholic liver disease. Clin Liver Dis. 2012;16(4):805-26.
49. Cheung K, Lee SS, Raman M. Prevalence and mechanisms of malnutrition in patients with advanced liver disease, and nutrition management strategies. Clin Gastroenterol Hepatol. 2012;10(2):117-25.
50. Stickel F, Seitz HK. Update on the management of alcoholic steatohepatitis. J Gastrointestin Liver Dis 2013;22:189-197.
51. Forrest E, Mellor J, Stanton L, et al. Steroids or pentoxifylline for alcoholic hepatitis (STOPAH): study protocol for a randomised controlled trial. Trials 2013; 14: 262.
52. Mathurin P, Louvet A, Duhamel A, et al. Prednisolone with vs without pentoxifylline and survival of patients with severe alcoholic hepatitis: a randomized clinical trial. JAMA 2013; 310: 1033-1041 .
53. Thursz MR, Richardson P, Allison M et al. Prednisolone or pentoxifylline for alcoholic hepatitis. N Engl J Med 2015;372:1619–28.
54. Singal AK , Walia I , Singal A et al. Corticosteroids and pentoxifylline for the treatment of alcoholic hepatitis: current status. World J Hepatol 2011;3:205–10.
55. Buch S, Stickel F, Trépo E, et al. A genome-wide association study confirms PNPLA3 and identifies TM6SF2 and MBOAT7 as risk loci for alcohol-related cirrhosis. Nat Genet 2015;47:1443-1448.
56. Sidhu SS, Goyal O, Singla M. et al. Pentoxifylline in severe alcoholic hepatitis: a prospective, randomised trial. J Assoc Physicians India. 2012;60:20-2.
57. Im GY, Lucey MR. Practical concerns and controversies in the management of alcoholic hepatitis. Gastroenterol Hepatol (N Y) 2016; 12: 478-489. (7-[79])
58. Nguyen-Khac E, Thevenot T, Piquet MA et al. Glucocorticoids plus N-acetylcysteine in severe alcoholic hepatitis. N Engl J Med 2011;365: 1781–9.
59. Singh S, Murad MH, Chandar AK et al. Comparative effectiveness of pharmacological interventions for severe alcoholic hepatitis: a systematic review and network meta-analysis. Gastroenterology 2015;149:958–70.
60. Burra P, Senzolo M, Adam R, et al. Liver transplantation for alcoholic liver disease in Europe: a study from the ELTR (European Liver Transplant Registry). Am J Transplant 2010;10:138-148.
61. Testino G, Sumberaz A, Borro P. Comment to "liver transplantation for patients with alcoholic liver disease: an open question". Dig Liver Dis 2013; 45: 80-81.
62. Testino G, Burra P, Bonino F, et al. Acute alcoholic hepatitis, end stage alcoholic liver disease and liver transplantation: an Italian position statement. World J Gastroenterol 2014; 20: 14642-14651.
63. Mathurin P, Moreno C, Samuel D, et al. Early liver transplantation for severe alcoholic hepatitis. N Engl J Med 2011; 365: 1790-1800.
64. Singal AK, Guturu P, Hmoud B, et al. Evolving frequency and outcomes of liver transplantation based on etiology of liver disease. Transplantation 2013;95:755-760.
65. Singal AK, Hmoud BS, Guturu P, Kuo YF. Outcome after liver transplantation for cirrhosis due to alcohol and hepatitis C: comparison to alcoholic cirrhosis and hepatitis C cirrhosis. J Clin Gastroenterol 2013;47:727-733
66. Lucey MR. Liver transplantation for alcoholic liver disease. Nat Rev Gastroenterol Hepatol 2014;11:300-307.
67. Sayiner M, Koenig A, Henry L, Younossi ZM. Epidemiology of Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis n the United States and the Rest of the World. Clin Liver Dis 2016; 20: 205-214.

68. Kanwar P, Kowdley KV. The Metabolic Syndrome and Its Influence on Nonalcoholic Steatohepatitis. Clin Liver Dis 2016; 20: 225-243
69. Calzadilla Bertot L, Adams LA. The Natural Course of Non-Alcoholic Fatty Liver Disease. Int J Mol Sci 2016; 17(5): E774
70. Chang E, Park CY, Park SW. Role of thiazolidinediones, insulin sensitizers, in non-alcoholic fatty liver disease. J Diabetes Investig. 2013;4(6):517–524.
71. Patel V, Sanyal AJ, Sterling R. Clinical Presentation and Patient Evaluation in Nonalcoholic Fatty Liver Disease. Clin Liver Dis 2016; 20: 277-292
72. Wong RJ, Aguilar M, Cheung R, et al. Nonalcoholic steatohepatitis is the second leading etiology of liver disease among adults awaiting liver transplantation in the United States[J]. Gastroenterology, 2015; 148(3): 547–555.
73. De Minicis S, Day C, Svegliati-Baroni G. From NAFLD to NASH and HCC: pathogenetic mechanisms and therapeutic insights. Curr Pharm Des 2013; 19: 5239-5249.
74. Benedict M, Zhang X. Non-alcoholic fatty liver disease: An expanded review. World J Hepatol 2017; 9(16): 715-732.
75. Lindenmeyer CC, McCullough AJ. The natural history of nonalcoholic fatty liver disease - an evolving view. Clin Liver Dis. 2018; 22(1): 11–21.
76. Armstrong MJ, Houlihan DD, Bentham L, et al. Presence and severity of non-alcoholic fatty liver disease in a large prospective primary care cohort. J Hepatol, 2012; 56(1): 234-40.
77. Wong VW, Chu WC, Wong GL, et al. Prevalence of non-alcoholic fatty liver disease and advanced fibrosis in Hong Kong Chinese: a population study using proton-magnetic resonance spectroscopy and transient elastography. Gut, 2012; 61(3): 409-15.
78. Dyson JK, Anstee QM, McPherson S. Non-alcoholic fatty liver disease: a practical approach to diagnosis and staging. Frontline Gastroenterol, 2014; 5(3): 211-218
79. Verma S, Jensen D, Hart J, Mohanty SR. Predictive value of ALT levels for non-alcoholic steatohepatitis (NASH) and advanced fibrosis in non-alcoholic fatty liver disease (NAFLD). Liver Int, 2013; 33(9): 1398-405.
80. Than NN, Newsome PN. A concise review of non-alcoholic fatty liver disease. Atherosclerosis. 2015; 239(1):192-202.
81. Brea A, Puzo J. Puzo, Non-alcoholic fatty liver disease and cardiovascular risk. Int J Cardiol, 2013. 167(4): 1109-17.
82. Banerjee R, Pavlides M, Tunnicliffe EM, Piechnik SK. et al., Multiparametric magnetic resonance for the non-invasive diagnosis of liver disease. J Hepatol, 2014. 60(1): 69-77.
83. Kwok R, Choi KC, Wong GL, et al. Screening diabetic patients for non-alcoholic fatty liver disease with controlled attenuation parameter and liver stiffness measurements: a prospective cohort study. Gut 2016; 65: 1359-1368 .
84. Haufe S, Engeli S, Kast P, et al. Randomized comparison of reduced fat and reduced carbohydrate hypocaloric diets on intrahepatic fat in overweight and obese human subjects. Hepatology 2011; 53: 1504-1514 .
85. Asrih M, Jornayvaz FR. Diets and nonalcoholic fatty liver disease: the good and the bad. Clin Nutr 2014; 33: 186-190 .
86. Simopoulos AP. Dietary omega-3 fatty acid deficiency and high fructose intake in the development of metabolic syndrome, brain metabolic abnormalities, and non-alcoholic fatty liver disease. Nutrients 2013; 5: 2901-2923.
87. Martín V, González-Casas R, Mendoza-Jiménez-Ridruejo J, García-Buey L. Pathogenesis, diagnosis and treatment of non-alcoholic fatty liver disease. Rev Esp Enferm Dig, 2013; 105: 409-420.
88. Promrat K, Kleiner DE, Niemeier HM, et al. Randomized controlled trial testing the effects of weight loss on nonalcoholic steatohepatitis. Hepatology, 2010; 51(1): 121-9.
89. Oh S, Shida T, Yamagishi K, et al. Moderate to vigorous physical activity volume is an important factor formanaging non-alcoholic fatty liver disease: a retrospective study. Hepatology, 2015; 61(4): 1205-15.
90. Hannah WN Jr, Harrison SA. Lifestyle and Dietary Interventions in the Management of Nonalcoholic Fatty Liver Disease. Dig Dis Sci 2016; 61: 1365-1374.
91. James WP, Caterson ID, Coutinho W, et al. Effect of sibutramine on cardiovascular outcomes in overweight and obese subjects. N Engl J Med, 2010; 363(10): 905-17
92. Coughlan KA, Valentine RJ, Ruderman NB, Saha AK. AMPK activation: a therapeutic target for type 2 diabetes?. Diabetes Metab Syndr Obes. 2014;7:241–253.
93. Cusi K, Orsak B, Bril F, et al. Long-Term Pioglitazone Treatment for Patients With Nonalcoholic Steatohepatitis and Prediabetes or Type 2 Diabetes Mellitus: A Randomized Trial. Ann Intern Med 2016; 165: 305-315.
94. Yau H, Rivera K, Lomonaco R, Cusi K. The future of thiazolidinedione therapy in the management of type 2 diabetes mellitus. Curr Diab Rep 2013; 13: 329-341.
95. Abner EL, Schmitt FA, Mendiondo MS, et al. Vitamin E and all-cause mortality: a meta-analysis. Curr Aging Sci 2011; 4: 158-170.
96. Dowman J, Armstrong M, Tomlinson JW, Newsome PN. Current therapeutic strategies in non-alcoholic fatty liver disease. Diabetes Obes Metab, 2011; 13(8): 692-702.
97. Leuschner UF, Lindenthal B, Herrmann G, et al. High-dose ursodeoxycholic acid therapy for nonalcoholic steatohepatitis: a double-blind, randomized, placebo-controlled trial. Hepatology, 2010; 52(2): 472-9.
98. Lavine JE, Schwimmer JB, Van Natta ML, et al. Effect of vitamin E or metformin for treatment of nonalcoholic fatty liver disease in children and adolescents: the TONIC randomized controlled trial. JAMA. 2011;305(16):1659–1668.
99. Williamson RM, Price JF, Glancy S, et al. Prevalence of and risk factors for hepatic steatosis and nonalcoholic Fatty liver disease in people with type 2 diabetes: the Edinburgh Type 2 Diabetes Study. Diabetes Care, 2011; 34(5): 1139-44.
100. Zeng T, Zhang CL, Zhao XL, Xie KQ. Pentoxifylline for the treatment of nonalcoholic fatty liver disease: a metaanalysis of randomized double-blind, placebo-controlled studies. Eur J Gastroenterol Hepatol, 2014; 26(6): 646-53.
101. Blaslov K, Bulum T, Zibar K, Duvnjak L. Incretin based therapies: a novel treatment approach for non-alcoholic fatty liver disease. World J Gastroenterol. 2014;20(23):7356–7365.
102. Fukuhara T, Hyogo H, Ochi H, et al. Efficacy and safety of sitagliptin for the treatment of nonalcoholic fatty liver disease with type 2 diabetes mellitus. Hepatogastroenterology, 2014; 61(130): 323-8.