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Review Article

A REVIEW OF APPROVED AND CURRENTLY ONGOING TREATMENT STRATEGIES FOR THE TREATMENT OF NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD)

Mohsin Jamil Khan[1*] and Hongyan Ge[2]

[1]*School of Clinical Medicine, Inner Mongolia University for the nationalities, 536 West Huo Lin He Street, Horqin District, Tongliao City, Inner Mongolia, P.R China*

[2]*Department of Internal Medicine (Gastroenterology), Affiliated Hospital of Inner Mongolia University for the Nationalities, Horqin District, Tongliao City, Inner Mongolia, P.R China*

ABSTRACT

Non-alcoholic fatty liver disease (NAFLD), is one of the most common cause of chronic liver diseases in the western countries and it is also an emerging disease in Asia. Non-alcoholic fatty liver disease is a hepatic manifestation of metabolic syndrome with insulin resistance as a main pathogenic mechanism which can progress from simple fatty liver disease to non-alcoholic steatohepatitis (NASH) which in later stages can leads to liver fibrosis and hepatocellular carcinoma and also leads to cardiovascular diseases. There are several pathogenic pathways leads to non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH). Till date there are no approved therapies available for the treatment of non-alcoholic fatty liver disease, but many advances have been made with the discovery of some pharmacological agents which are currently in trails. Several attempts were made with different kind of pharmacological agents among which some of the pharmacological agents show positive results against non-alcoholic fatty liver disease (NAFLD) and NASH. This review paper is aimed to provide a comprehensive review of approved and studied treatment strategies for the treatment of non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH). Both pharmacological and non-pharmacological treatment strategies were reviewed in this paper e.g. life style modifications like diet control and physical activity. Pharmacological agents which reduces oxidative stress, liver fibrosis, inflammation and hepatic fat accumulation were revived in this paper.

Keywords: NAFLD (non-alcoholic fatty liver disease), NASH (nonalcoholic steatohepatitis), cirrhosis, hepatocellular carcinoma, obesity

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is said to be the most common cause of chronic liver disease worldwide which affect 24%-25% of the general population with a highest rate in south America, Middle East, Asia, USA and Europe.[1] NAFLD is a large spectrum of diseases which ranges from simple steatosis to non-alcoholic steatohepatitis (NASH) and can lead to end stage liver disease like cirrhosis and hepatocellular carcinoma and is said to be the leading cause of liver transplantation in the next decades.[2] Non-alcoholic fatty liver disease is said to be very closely associated with metabolic comorbidities such as obesity, dyslipidemia and type 2 diabetes mellitus and can be define as the presence of >5% of the hepatic steatosis with or without the presence of hepatic cellular injury and inflammation.[3] The global prevalence of NAFLD in type 2 diabetes was 55.5 %(95% CI 47.3–63.7), studies from Europe reported a high prevalence with (68.0% [62.1–73.0%]), NASH among type 2 diabetes was reported as 37.3% (95% CI 24.7–50.0%), and advanced fibrosis was reported in NAFLD and type 2 diabetes as17.0% (95% CI 7.2–34.8).[4]Pathogenesis of NAFLD is not clearly understood yet, but recent findings supports a "multiple hit hypothesis" which leads to contribute in the progression of NAFLD through gut microbiome dysbiosis , insulin resistance, obesity, oxidative stress which leads to an imbalance between inflammatory cytokines.[5,6]

Currently the treatments for NAFLD and NASH are limited or there is no FDA-approved treatment available for the disease. Weight loss and physical activity is said to be the traditional treatment of NAFLD which is hard to achieve in extremely morbid patients. Looking into the complex pathogenesis of NAFLD the only targeted and available pharmacological and non-pharmacological treatments were studied. In this review paper we aimed to review the current available pharmacological and non-pharmacological therapies for NAFLD and NASH.

DISCUSSION

Pharmacological therapy:

Vitamin E:

Vitamin E is a fat soluble vitamin having an antioxidant activity and play a major role in lipid peroxidation in the disease process of NAFLD and NASH.[7] Animal model studies shows a very positive results in NASH by administering 0.5g/kg of vitamin E for three weeks human trails still needs to be evaluated.[8] A Randomized, double-blind, double-dummy, placebo-controlled clinical trial was conducted at 10 university clinical research centers in 173 with biopsy-confirmed NAFLD and a daily dose of 800 IU of vitamin E (58 patients), 1000 mg of metformin (57 patients), or placebo (58 patients) was given for 96 weeks. The primary outcomes of the trial were to assess that wither vitamin E and metformin can reduce alanine aminotransferase (ALT) and liver histology, but the end results of this trial failed to do so, there was no significant reduction in ALT neither in liver histology when it was compared to placebo group. In short vitamin E and metformin was not superior to placebo. [9] A meta-analysis by Miller et al of 9 out of 11 randomized control trails was studies for the dose-response relationship with all-cause mortality. This study suggested an increase in all cause-

mortality with high dose of vitamin E (≥400 IU/day). The trails were small and all the patient were having chronic diseases, thus a high dose of vitamin E (> or =400 IU/d) may increase all-cause mortality and should be avoided. [10] An analysis of randomized clinical control trials was carried out with vitamin E as a treatment of non-alcoholic fatty liver disease (NAFLD) to assess all-cause mortality in the patients with NAFLD. Selected trials were 57 (n = 57). Sample sizes range from 28 to 39,876 (median = 423), yielding 246,371 subjects and 29,295 all-cause deaths. Duration of supplementation for the 57 trials range from one to 10.1 years (median = 2.6 years). The end results of this meta-analysis show that there is no relation between doses related all-cause mortality as high as up to 5500 IU/day.[11] On another hand we cannot ignore the significant side effects of chronic vitamin E use as a treatment option for non-alcoholic fatty disease (NAFLD). A meta-analysis of clinical trials revealed that, vitamin E increased the risk for hemorrhagic stroke by 22% and reduced the risk of ischemic stroke by 10%. [12] Another concern about chronic or prolong use of vitamin E is an increased risk of prostate cancer, however the risk of prostate cancer is still unclear as different studies have given mixed results. [13,14] Thus more studies are needed to evaluate the risk of prostate cancer with high dose of vitamin E administration in a patient with NAFLD.

Ursodeoxycholic acid:

Ursodeoxycholic acid (a bile acid) was tried as a treatment option for NAFLD and NASH in 1548 randomized control trails during 2004-2018 of which 85% shows beneficial effects on reducing serum transaminases and improving liver histology and 15% does not shows any beneficial effects.[15] An animal study on Wastar rates was carried out by Gheibi et al, NAFLD was induced and their liver profile was elevated a combine therapy of ursodeoxycholic acid and curcumin was given at 14 and 28 consecutive days significant changes in liver profile was observed, serum triglycerides were reduced and no changes were seen on serum LDL-C.[16] A clinical trial by Oliveira et al, was carried out with the combination of ursodeoxycholic acid and metformin, evaluating results shows an improvement in steatosis degree, hepatocyte blooming and serum alanine aminotransferase (ALT) no modification was seen in liver fibrosis.[17] Ursodeoxycholic acid was compared with a Chinese herbal extract Fructus akebia extract (FAE) in NAFLD by Jin et al, in a randomize control trial where ursodeoxycholic acid alone fails to treat NAFLD while in combination with Fructus akebia extract (FAE) shows effective therapeutic effects by decreasing liver enzymes and reduces hepatic fat accumulation.[18]

Pentoxifylline (PTX):

The imbalance between inflammatory cytokines such as TNF-α may lead to hepatocyte injury.[19] Five randomized control trails of 147 patients were analyzed by Du et al, where NAFLD and NASH patient were treated with pentoxifylline (PTX) where they found a significant reduction in total body weight (p=0.04), alanine aminotransferase (P < 0.00001), aspartate transaminase (P=0.0006), glucose (P = 0.0008) and tumor necrosis factor-α (P = 0.007), but did not significantly affect blood triglyceride profile and total cholesterol.[20] A randomized placebo-control trial by Zein et al, was carried out on 55 biopsy proven NASH patients where patients received pentoxifyllin (PTX) three times a day for the duration of 1 year, they found that PTX

significantly improved steatosis (mean change in score -0.9 versus -0.04 with placebo < 0.001) and lobular inflammation (median change -1 versus 0 with placebo, P = 0.02).[21] Another Study by Zein et al, shows a significant reduction of oxidized fatty acids which might limit the progression of NASH and NAFLD and improve histological features of the disease.[22] Pentoxyphyllin (PTX) was well tolerated by all patients except having a minor side effect with nausea and this side effect was improved with dose reduction.[21,23]

Elafibranor:

PPAR-α helps in increasing beta-oxidation which in response leads to decrease in steatosis and inflammation while it leads to increase in insulin sensitivity. Reduction in inflammation and fat accumulation was seen in animal model study. [24] A study by Ratziu et al, shows a hepatoprotective effect of Elafibrinor by resolving NASH without worsening liver fibrosis with the dose of (120 mg/d for 1 year). During the course of the treatment Elafibrinor did not shows any side effects. A randomized control trail (RCT) was carried out in NASH patients, Elafibrinor was administered 80mg or 120mg daily which shows a significant reduction in inflammation and NASH resolution by the dose of 120mg/day in treatment group.[25] An ongoing study on the therapeutic effects of Elafibrinor by Westerouen Van Meeteren, shows a significant effects of the drug in the resolution of NASH by two key drivers of NASH progression, insulin resistance and serum lipid normalization. The safety profile is said to be favorable but an increase in serum creatinine occurs reversely. [26]

Statins (as a lipid-lowering agents):

Statins are used as a lipid lowering agents which carries an anti-oxidant and anti-inflammatory properties. [27,28] a small pilot study with atorvastatin treatment shows a significant effect on serum aminotransferases and reduction in lipid profile in patient with NAFLD.[29] This study does not show any significant effect on histological features of the disease. Another open label study shows a good therapeutic effect of atorvastatin in biopsy proven NASH.[30] Another randomized control trail was carried out with the combination of atorvastatin and anti-oxidants like vitamin E and C which reduces the risk of steatosis by 71% with the duration of 4 year treatment in NAFLD patients.[31] A clinical trial by Park et al, was carried out in the patient with NAFLD a total number of 45 patients were treated with Ezetimibe for 24 months and significant results were obtained as a reduction in triglycerides and total cholesterol, low-density lipoprotein cholesterol (LDL-Ch), oxidative-LDL, and improvement in liver histology was seen.[32] A 24-week randomized, double-blind, placebo-controlled trial with oral ezetimibe 10 mg daily (n = 25) vs. placebo (n = 25), by Lin et al, was carried to examine a relationship between MRI-derived proton-density fat-fraction (PDFF), total liver volume (TLV), total liver fat index (TLFI), vs. histology in a NASH trial. The MRI-PDFF and TLV was strongly related with TLFI. A decrease in steatosis were seen by improvement of hepatomegaly.[33] A study involving animal rat model with type 2 diabetes mellitus (T2DM) treated with Valsartan (15mg/kg/day), for four months shows a significant reduction in hepatic fibrosis and steatosis.[34] A large number of placebo-controlled and randomized control trials are needed to investigate the therapeutic effects of lipid lowering agents in the patients with NASH and NAFLD.

Aramchol (A fatty acid-bile acid conjugate):

Stearoyl-CoA desaturase 1 (SCD1) is an enzyme which is involved in the biosynthesis of triglycerides. Aramchol leads to inhibit SCD1 which leads to fatty acid oxidation and thus decrease NASH and fibrosis in mice model.[35] A randomized, double-blind, placebo-controlled trial of 60 patients of NAFLD with 6 patients of NASH confirm by biopsy was carried out by Safadi, in Israel where the study shows a significant reduction in liver fat. The results were demonstrated as, liver fat decrease by 12.57% ± 22.14% in patients given 300 mg/day Aramchol, while Aramchol did not shows any significant effect on serum alanine aminotransferase (ALT) which is an indicator of hepatocyte injury.[36] A phase-2 one year study (a randomized control trail) shows a significant effect of Aramchol with the dose of 400mg-600mg, when compared with placebo 600mg/day of Aramchol was able to show a positive therapeutic effect by reducing hepatic fat accumulation, hepatocyte blooming and decreasing the degree of NASH.[37] A decrease in serum aminotransferases were also noted studies or still underway to evaluate the therapeutic effects of Aramchol in NAFLD and NASH.[38]

Thiazolidinediones (TZDs):

Thiazolidinediones (TZDs) also known as Glitazones are the group of insulin sensitizers which is used as a treatment of T2DM (type 2 diabetes mellitus). It has hyperglycemic, hypoglycemic and hypolipidemic activity. [39] a review of clinical trials by Tacelli et al, shows a significant effect on patients BMI (body mass index), serum transaminase and cholesterol levels. Where these studies fails to show a positive effects on liver histology.[40] A study of 18 clinical trials were studied by Blazina et al, were antidiabetic drugs were tried as a treatment option for NAFLD and NASH, results shows an improvement in liver function and liver fat but weight gain was noted in patients treated with pioglitazone thus larger studies are needed to evaluate the role of pioglitazone in NAFLD and NASH.[41] Another trial with pioglitazone improve hepatic steatosis and lobular inflammation but did not shows any significant effect on fibrosis score.[42]Therapeutic effects and adverse effects should be discussed with each patient before starting therapy with pioglitazone. Although pioglitazone may be helpful to improve liver function but it fails to improve liver fibrosis. Thus, pioglitazone should not be used in NAFLD and NASH unless the disease is biopsy proven.

Angiotensin Receptor Blockers (ARBs) :

Angiotensin receptor blockers are used to treat hypertension. Angiotensin-2 is said to be helpful in liver fibrosis by activating transforming growth factor-β (TGF-β) and Toll-like receptor-4 (TLR-4) signaling pathway.[43] An uncontrolled trial demonstrated an improvement in serum aminotransferases and liver histology.[44] An open-label trial with the combination of Rosiglitazone and Losartan shows positive effects on liver histology.[45] An animal rat model study with T2DM (type 2 diabetes mellitus) shows a significant reduction in liver fibrosis and also shows a decrease expression of TNF-α with the combination of angiotensin Receptor Blockers and valsartan 15mg/kg/day for the duration of four months.[34] Further studies are needed to evaluate the therapeutic effects of angiotensin receptor blockers in the patients with NAFLD and NASH.

Vitamin D:

Vitamin D also called as cholecalciferol (vitamin D3) which is a precursor of hormones and plays an important role in calcium and phosphate metabolism.[46] Recent studies have shown a relationship between hypovitaminosis D and NAFLD.[47] A systemic review of randomized control trails was taken out by Hariri et al, where they found hypovitaminosis D is closely associated with the severity of NAFLD.[48] The exact mechanism of action of vitamin D in reducing liver fibrosis is still unknown but recent studies has revealed that, Vitamin D has its anti-fibrotic effect on hepatic stellate cells through vitamin D receptor mediated specific signal transduction pathways which inhibits the expression of pro-fibro genic gene.[49] While an ongoing trail by Ebrahimpour-Koujan et al, are going to investigate the anti-fibrogenic activity of vitamin D supplementation, serum level of vitamin D receptor (VDR) and fibrogenic micro RNAs (MIR) will be investigated in the study.[50] A double blind randomized placebo controlled trial on 109 patients with oral vitamin D demonstrated therapeutic effects on serum biochemical markers (i.e. ALT: 72.±17.6 to 54.5±14.5 IU/L p=0.04; AST: 68±14.5 to 46.± 10.5 p =0.002) serum CRP 3.25±0.68 to 2.28±0.44 mg/L p =0.06 and increase in serum adiponectin 8.56 ±1.12 to 10.44±2.35 mg/L p =0.03 as compared with placebo group, while it fails to show effects on body weight, patient BMI (body mass index) and lipid profile.[51] A double-blinded, randomized, placebo-controlled pilot study with oral vitamin D for 48 weeks shows a significant changes on serum alanine aminotransferase (ALT) in a histologically proven NASH patients. And a significant decrease was also observed in cytokeratin-18 fragments when compared to placebo group, while this study does not provide any histopathological characteristics of the disease.[52] A Double-Blind Randomized Controlled Clinical Trial study of 73 patients by Amiri et al, shows no significant effects on anthropometric measures of both control and treatment groups, but they found significant changes in the biochemical parameters of NAFLD, as AST level was decrease in treatment group treated with vitamin D (-4.2 ± 4.3 μmol/L, P < 0.001), but it shows increase in placebo group (12.6 ± 6.1 μmol/L, P = 0.02) after treated for 12 weeks.[53]Where Sakpal et al, had carried out a randomized controlled trial on patients of NAFLD which was diagnosed by ultrasonography (USG) combined therapy with vitamin D (injectable) 600000 units and standard medical treatment (SMT) was given to treatment group (n=51) and standard medical treatment (SMT) only was given to control group (n=30), after 6 months of treatment serum ALT (alanine aminotransferase) was significantly decrease as compared to control group (ALT [87 ± 48 and 59 ± 32 IU/mL, P < 0.001] vs [64 ± 35 and 62 ± 24 IU/mL, P = 0.70]), this study also shows a significant effects on serum adiponectin levels.[54] Vitamin D is a new emerging pharmacological agent in the treatment of NAFLD and NASH. Till date we have a few numbers of randomized control trials on therapeutic effects of vitamin D in NAFLD and NASH which gives an idea of further evaluating vitamin D as treatment option for NAFLD and NASH.

Non-pharmacological treatments of NAFLD and NASH:

Diet control and physical activity:

Diet control (taking low calorie diet) and physical activity (physical exercise) is the first line treatment of non-alcoholic fatty liver disease. [55] A weight loss by 3% to 10% is needed to reduce hepatic fat accumulation, liver inflammation and liver fibrosis in patients with NAFLD and NASH.[56,57]

Effect of low calorie and Mediterranean diet on patients with NAFLD and NASH:

Taking low calorie diet with or without decrease in the body weight is said to be an effective diet control program.[58] A short term study with the duration of 2-4 weeks shows that a high fat diet and low carbohydrate diet leads to increase in intrahepatic triglyceride as compared with low fat diet.[59] An isocaloric low carbohydrate diet with high fat and protein as 24% leads to decrease in lipogenesis which leads to an increase in fatty acid oxidation and reduces hepatic fat content over the treatment duration of 2 weeks.[60] Where short term studies have demonstrated that dietary intake of plant and animal protein 30% with carbohydrate and fat as 30% of the diet leads to reduction in hepatic fat by 36-48% by 6 weeks of duration.[61] In weight stable patients with type 2 diabetes mellitus a protein rich diet as protein contents 30 % and carbohydrate contents as 30% and fat contents as 40% of the total diet leads to significant reduction in hepatic fat accumulation in 6 weeks of treatment.[62] It can be seen that taking a hypocaloric diet for a longer duration (3-6 months) leads to the reduction of body weight and also reduces hepatic fat contents and intrahepatic triglycerides.[63]

Mediterranean diet is one of best choice in a patient with NAFLD and cardiovascular diseases (CVDs) which mainly contains nuts, olive oil, fruits and vegetables, legumes, whole grain and protein rich meat like fish.[64] Which is very closely related to reduce cardiovascular risk and is counted as a very good adjacent for the patients suffering with NAFLD.[65] A randomized study by Abenavoli et al, was carried on overweight 50 Caucasian patients whose BMI (body mass index) was greater than 25 kg/m2 with Mediterranean diet from June 2015 to June 2016 where Mediterranean diet shows a significant effect on weight, BMI, waist circumference ($p = 0.0001$) and a significant decrease in TG ($p = 0.0001$), total cholesterol ($p = 0.0001$) and LDL-C ($p = 0.005$) and ALT ($p = 0.007$).[66] Where a randomized clinical control trial with Mediterranean diet was carried out on 63 NAFLD patients by Katsagoni et al, they have found a significant improvement in serum ALT (Alanine aminotransferase) and liver stiffness as, ALT<40 U/l ($P=0.03$) and 50 % reduction of ALT levels ($P=0.009$)) and liver stiffness ($P=0.004$) suggesting a positive effect of Mediterranean diet in patients with NAFLD.[67]

Physical activity (Physical exercise) in patients with NAFLD and NASH:

Physical exercise is being hypothesized that it has an improving effect on NAFLD through improving peripheral insulin resistance, reduces excess delivery of free fatty acids to the liver. Exercise leads to an increase fatty acid oxidation and decrease fatty acid synthesis.[68] A trial study was carried out by Keating et al, on 48 NAFLD patients with aerobic exercise with the duration of 8 weeks, low to moderate intensity exercise and high volume aerobic exercise was given to the participants magnetic resonance imaging (MRI) was done before and after the exercise where it shows significant changes in liver fat but the study did not show any significant effects on the biochemical parameters of NAFLD, as the biochemical parameters were not evaluated in the study and weight loss was observed in the participants which was not clinically significant.[69] While a clinical trial study by Gelli et al, was carried out on 46 adult NAFLD patients with physical activity combined with Mediterranean diet for the duration of 6 months the end results of the study shows a clinically significant

effects on body weight, BMI (body mass index), ALT (Alanine aminotransferase), AST (Aspartate aminotransferase), HDL (high density lipoprotein), LDL (low density lipoprotein), TCHO (total cholesterol), GGT (Gama-glutamyle transferase) by clinically significant p value as ($P < 0.01$) , thus the study further strengthen the hypothesis that Mediterranean diet and physically active life style can reduce the risk of fatty liver and related diseases.[70] Looking into the intensity of exercise a high intensity exercise shows more effective results then low intensity exercise. A clinical trial by Abdelbasset et al, on 32 (21 men and 11 women) obese, diabetic patients age 45-60 years with NAFLD was carried out for the duration of 8 weeks, the end result of the trial shows a significant reduction in visceral lipids, glycohemoglobin and plasma glucose ($P <.05$), while the above mentioned parameters did not shows any changes in control group ($P >.05$), this study demonstrated the significance of high intensity exercise in obese, diabetic, NAFLD patients with significant clinical outcomes.[71] Another clinical trial investigating the effects of moderate and vigorous-moderate exercise in the patients with NAFLD, where this study demonstrated an equal effects of moderate and vigorous-moderate exercise for the duration of 6-12 months. Both of the exercises shows clinically significant reduction in intrahepatic triglyceride content, the study demonstrated that the changes in intrahepatic triglyceride content is due to weight loss.[72] A comparison was made between aerobic and intensive exercise by Franco I et al, where they provide a program of moderate aerobic exercise (group 1) lasting for 30 minutes (5 days per week) and intensive muscle stretch program (group 2) lasting for 60 minutes (3 days per week), after the comparison of both groups they found that an aerobic exercise is more realistic in the early prevention of NAFLD and other several chronic diseases.[73]

CONCLUSION

There is no FDA approved pharmacological treatment available for the treatment of NAFLD and NASH. Current treatment strategies for the treatment of NAFLD and NASH is diet control (taking low fat and low-calorie diet) and physical activity (physical exercises) which include aerobic, non-aerobic, high intensity and low intensity exercises. Weight loss in patients with NAFLD is closely associated with altering the biochemical components of the disease i.e. serum Alanine aminotransferase (ALT) and Aspartate aminotransferase (AST) and other components of metabolic syndrome like triglycerides and total cholesterol. The traditional therapy for NAFLD and NASH aims to reduce body weight by 10% of the total body weight which is difficult to attain in some diseases such as coronary artery diseases (CAD) and neurological diseases where a patient may not be able to carry out physical activity. Thus, newer pharmacological agents are need to be investigated during the course of NAFLD and NASH which should not only focuses on improving serum amino transferases but should also focus on treating an advance disease with liver fibrosis. Large number of randomized control trials are needed to be carried out with large number of patients. Looking at the new and complex pathogenic pathways of NAFLD and NASH new pharmacological agents should be tried and which may lead to new therapies in the near future.

Vitamin E, pentoxifylline (PTX), Thiazolidinediones (glitazones) and vitamin D has shown a promising result on liver biochemistry but fails to reduce liver fibrosis score.

Other pharmacological agents reviewed in this paper shows efficacy in resolving NAFLD and NASH and they are further needed to be investigated with greater number of clinical trials and greater number of patients. Future research is needed to understand the complex pathogenesis of the disease and the progression of the disease from simple fatty liver to NASH and fibrosis which will give a way to treat this extremely prevalent and progressing disease worldwide with success and with effective clinical outcomes.

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