

Treatment of Non-Alcoholic Fatty Liver Disease (NAFLD): A Systematic Review

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ABSTRACT

No treatment has been proven to be effective in nonalcoholic fatty liver disease (NAFLD) and/or steatohepatitis (NASH). Numerous studies have addressed this issue. However conclusive recommendations cannot be drawn solely from the currently available studies. Hence we performed this systematic review to determine which of the available therapeutic modalities are supported by adequate evidence in terms of decreasing the adverse clinical outcomes of interest.

A specific strategy was utilized to perform a computerized literature search in MEDLINE; of which, a total of 375 studies were retrieved. According to current literature, modifying the potential risk factors such as obesity, hyperlipidemia, and poor diabetic control in all patients is considered the treatment of choice. Certain treatments can be recommended under special circumstances and some medications, although used clinically, are not supported by adequate evidence to be recommended for the treatment of NAFLD/NASH.

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is characterized by hepatic histological changes similar to alcohol-induced liver injury, in patients with no or minimal alcohol consumption.

A range of histological changes can be seen. Some patients have accumulations of fat within the hepatocytes without significant inflammation or fibrosis (simple hepatic steatosis) while others have hepatic steatosis with prominent necro-inflammatory changes (steatohepatitis), with or without associated fibrosis.

This latter condition (nonalcoholic steatohepatitis, NASH) may lead to cirrhosis and end stage liver disease in a significant number of patients.¹

Despite its prevalence, no treatment has been proven to be effective in NAFLD/NASH.

A major reason is lack of understanding that is attributed to its pathogenetic mechanisms.

General measures of risk reduction, such as weight loss in obese patients, effective treatment of hyperlipidemia and diabetes mellitus (if present) are usually recommended. Other methods currently in use include:

weight loss drugs (orlistat), physical activity, oral antidiabetic medications (metformin, troglitazone, pioglitazone, and rosiglitazone), cytoprotective agents [taurine, ursodeoxycholic acid (UDCA)], hypolipidemics (clofibrate, gemfibrozil, bezafibrate, atorvastatin, and other HMG-CoA reductase

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inhibitors), several antioxidants, and a combination of different therapies (diet and UDCA, vitamin E and pioglitazone).²⁻⁶

These modalities have primarily been addressed in uncontrolled settings of small sample sizes. Therefore, conclusive recommendations cannot solely be drawn from the currently available studies. Hence we performed this systematic review to determine which of the available therapeutic modalities are supported by adequate evidence in terms of decreasing the adverse clinical outcomes of interest.

MATERIALS AND METHODS

A computerized literature search was performed in MEDLINE (1966 to January 2010).

The search was limited to studies in humans over the age of 19 years old. The search was further limited to “Meta-Analysis”, “Randomized Controlled Trial” and “Clinical trials”. There were no language restrictions for searching. The following search protocol was used in PubMed:

1. Fatty liver OR Liver steatosis OR fatty liver disease OR NASH OR NAFLD
2. “weight reduction” OR “diet” OR “Orlistat” OR “exercise”
3. Statin OR “Hydroxymethylglutaryl-CoA Reductase Inhibitors” OR atorvastatin OR simvastatin OR lovastatin OR fluvastatin
4. “hypolipidemic” OR clofibrate OR gemfibrozil OR bezafibrate OR probucol
5. “antidiabetic” OR metformin OR troglitazone, OR pioglitazone OR rosiglitazone
6. “cytoprotective” OR taurine OR “ursodeoxycholic acid”
7. “antioxidants” OR “vitamin E”
8. treatment OR therapy
9. #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
10. # 1 AND #9
11. (“humans”[MeSH Terms] AND (Clinical Trial [ptyp] OR Meta-Analysis [ptyp] OR Randomized Controlled Trial [ptyp])) AND “adult”[MeSH Terms]”
12. #10 AND # 11

To be included in this systematic review, the studies

needed to be meta-analysis, randomized controlled trials (RCTs) or controlled clinical trials. The studies were included regardless of the number of intervention groups, numbers of patients, publication status, year of publication and language.

Studies with miscellaneous treatment options such as: “Chinese herbs”, “Omega-3 fatty acids”, “N-3 polyunsaturated fatty acids”, “Highly purified eicosapentaenoic acid”, “Pentoxifylline” and “Gynostemma pentaphyllum” were not included in this review. Participants in these studies needed to be at least 18 years old with a definite diagnosis of NASH. The principle outcome measures of biochemical, histological or imaging response needed to be addressed in the primary studies which were selected.

The titles were screened for all relevant studies. Subsequently, abstracts of all relevant studies were studied for inclusion in the review. Full texts of all studies meeting the inclusion criteria were retrieved and appropriate data extracted.

RESULTS

A total of 375 studies were retrieved. Of these, 52 were considered to be relevant upon initial screening. Abstracts of these 52 articles were reviewed and 21 studies (4 meta-analyses and 17 controlled trials) were agreed upon to meet the inclusion criteria. The full texts of all included studies were precisely evaluated and relevant data extracted. Characteristics of excluded studies are shown in Table 1.

Weight loss

Many reports and studies have shown that weight loss and increased physical activity can lead to improvement in liver enzymes, histology, serum insulin levels, and quality of life.²⁰⁻²² Treatments for obesity include a decrease in energy intake or an increase in energy consumption.

Treatments which decrease energy intake are potentially more successful treatment options for weight loss than those which increase energy consumption through exercise. For initial weight loss, treatment should be directed at decreasing

Table 1: The characteristics of excluded studies.

Study	Design	Participants	Intervention(s)	Reason(s) for exclusion
Hyogo et al., 2008 ⁷	Prospective cohort	Patients with biopsy-proven NASH with hyperlipidemia	Atorvastatin	Inappropriate study design No control group
Enjoji et al., 2008 ⁸	Prospective cohort	Non-alcoholic fatty liver disease (NAFLD) and chronic hepatitis C	Telmisartan or Olmesartan	Inappropriate study design No control group Inhomogeneous group
Fernández-Miranda et al., 2008 ⁹	Prospective cohort	biopsy-proven NASH	Fenofibrate	Inappropriate study design No control group
Merat et al., 2008 ¹⁰	Prospective cohort	Biopsy-proven NASH	Probucol	Inappropriate study design No control group
Duseja, 2007 ¹¹	Prospective cohort	Biopsy-proven NASH	Metformin	Inappropriate study design No control group
Zib, 2007 ¹²	RCT	Patients with DM type 2	Pioglitazone	NASH diagnosis was not confirmed in the patients
Wang et al., 2002 ⁵	Prospective Cohort	Patients with DM type 2 and sonographic Dx of NASH	Rosiglitazone	Inappropriate study design No control group
Harrison et al., 2004 ¹³	Prospective Cohort	Obese patients with biopsy- proven NASH	Orlistat	Inappropriate study design No control group
Nair, 2004 ¹⁴	Prospective Cohort	Biopsy-proven NASH	Metformin	Inappropriate study design No control group
Shadid, 2003 ¹⁵	Prospective Cohort	Dx with ultrasound or histology	Pioglitazone	Inappropriate study design No control group
Promrat et al., 2010 ¹⁶	Prospective Cohort	Biopsy-proven NASH	Pioglitazone	Inappropriate study design No control group
Neuschwander-Tetri et al., 2003 ⁶	Prospective Cohort	Biopsy-proven NASH	Rosiglitazone	Inappropriate study design No control group
Sabuncu, 2003 ¹⁷	Prospective Cohort	Obese patients, Dx with ultrasound	Orlistat	Inappropriate study design No control group
Merat et al., 2003 ¹⁸	Prospective Cohort	Biopsy-proven NASH	Probucol	Inappropriate study design No control group
Abdelmalek et al., 2001 ¹⁹	Case series	Diagnosis with imaging	Betaine	Inappropriate study design No control group

food intake and, when possible, increasing energy expenditure. Weight loss may be executed by dieting, with or without the addition of anti-obesity drugs. An average deficit of 500 Kcal/day should result in weight loss of 0.45 kg/week (1lb/week).^{23,24}

One report has suggested that weight loss should not exceed approximately 1.6 kg per week in adults. In this prospective study 41 morbidly obese, non-

alcoholic subjects had liver biopsies performed both before and after a median weight loss of 34 kg. Fatty change significantly improved, however 24% of the patients developed a slight portal inflammation or slight portal fibrosis.

Patients who developed portal fibrosis had a higher degree of fatty change at entry, a more pronounced reduction of fatty change, and a faster weight loss.

It has been concluded that morbidly obese subjects with a high degree of hepatic fatty change are at risk of developing portal inflammation and fibrosis when undergoing rapid dietary weight reductions.¹⁶ The characteristics and outcomes of the relevant studies are summarized in Table 2.

Table 2: Characteristics of clinical trials which considered weight reduction and/or exercise for treatment of NAFLD/NASH.

Author, Year	Design, Duration	Participant	Intervention, Number	Control, Number	Primary outcome	Significant effect
Promrat and Kleiner, 2010 ¹²	RCT 48 weeks	BMI>25+NAFLD	Intensive life style intervention-20	Structured education-10	NASH Histological Activity Score	Yes
Jounson, 2009* ²⁵	Before-after clinical trial 4 weeks	BMI>29+NAFLD	Aerobic exercise without weight reduction-19	----	Hepatic lipid saturation by proton MR spectroscopy	Yes
Catalano, 2008* ²⁶	Before-after clinical trial 6 months	NAFLD	Moderately hypocaloric/ balanced dietary/lifestyle-50	----	Bright Liver Score, HOMA	Yes
Sreenivasa, 2006* ²⁷	Before-after clinical trial 3 months	NASH	Exercise and dietary modification- 94	----	Serum aminotransferase levels	Yes
Ueno, 1997 ²⁸	Case control 3 months	Obese NASH	Restricted diet and exercise-15	Control 10	Liver histology, serum aminotransferase levels	Yes

*These studied were excluded because of lack of control groups

Vitamin E and other Antioxidants

The observation that vitamin E decreases oxidative stress provides a rationale for its use in NASH diagnosed patients. According to the ‘two-hit’ hypothesis, the first hit involves accumulation of excess fat in the liver cells due to insulin resistance and leads to hepatic steatosis. The second hit concerns oxidative stress that causes lipid peroxidation and activates inflammatory cytokines resulting in NASH.^{29,30}

There are several studies that have researched the use of antioxidants for NAFLD or steatohepatitis.^{18-24, 29-42}

A reduction in aminotransferases with vitamin E was noted in a preliminary report of a controlled trial which compared vitamin E alone to vitamin E with pioglitazone; however, histologic improvement was only seen with combined therapy.⁴²

A prospective, double-blind, randomized, placebo-controlled trial with a total enrollment of 49 patients was performed in 2003. All patients were randomized to receive either vitamins E and C (1000 IU and 1000 mg,

respectively) or placebo daily for six months.

Additionally, all patients were given standard weight-loss counseling and encouraged to follow a low fat diet (<30 fat g/day). There were 45 patients who completed six months of therapy without significant side effects. Vitamin treatment resulted in a statistically significant improvement in fibrosis score.

No changes were noted in inflammation with treatment and no improvement in necroinflammatory activity or ALT was seen with this combination of drug therapy.¹³ Based upon the above experience vitamin E has been used for treatment of NASH by some hepatologists.

However considering the following meta-analyses in addition to more recent concerns related to an increase in mortality with vitamin E, use of this type of drug in the treatment of NASH does not seem to be beneficial. In one meta-analysis published in 2007, treatment with antioxidant supplements showed a significant, though not clinically relevant, amelioration of aspartate aminotransferase levels

but not of alanine aminotransferase (ALT) levels, as compared to placebo or other interventions.

Gammaglutamyl-transpeptidase was decreased, albeit not significantly, in the treatment arm.

Radiological and histological data were too limited to draw any definite conclusions on the effectiveness of these agents.

The authors noted that the results of the randomized trials identified in that review did not provide sufficient evidence on the pros or cons of antioxidant supplements for treating NAFLD or NASH due to the small number of trials, their low methodological quality, the variability in clinical and histological assessment, and the numbers of different antioxidant supplements which were tested.⁴³

Drugs improving insulin resistance

Some controlled clinical trials have shown that insulin sensitizers and gradual weight loss (gastric banding, diet, or physical exercise) appear promising.^{6,21,44} In one Iranian study by Merat et al. it was concluded that metformin did not improve liver enzyme levels in NASH patients.⁴⁵

One systematic review assessed the beneficial and harmful effects of drugs known to improve insulin resistance in NAFLD and/or NASH.

Only three randomized clinical trials were included. Two of the trials had unclear allocation concealment and none were blinded regarding outcome assessment.

In two trials, metformin was associated with a significantly higher normalization of serum ALT versus vitamin E, and improvement of liver echographic response was seen. Additionally, an improvement of fatty infiltration was observed in a limited number of patients who underwent liver biopsies.⁴⁶⁻⁴⁹ In the single pioglitazone trial, a statistically significant improvement of NASH histology was demonstrated.⁴⁶

Despite the limitations of this systematic review which included the considerable heterogeneity among these trials with respect to inclusion criteria, sample size, type of experimental interventions, type of control interventions, duration of

interventions, and methods of outcome assessment, the authors found a favorable response to Metformin treatment in patients with NAFLD and/or steatohepatitis. In both Metformin trials,^{47,48}

Treatment was associated with higher rates of biochemical response. Indeed, in these trials, ALT activity significantly decreased in the Metformin treatment groups and a higher proportion of patients reached ALT normalization when compared to the control groups, who were treated either with vitamin E or with a weight reducing prescriptive diet.

In addition, in a limited number of patients who underwent liver biopsies, an improvement of fatty infiltration was observed, though it was not statistically significant. Finally, in a trial by Uygun et al., a significantly higher decrease in the mean grade of steatosis as seen by upper abdominal ultrasonography was reported in Metformin-treated patients.⁴⁷

Conversely, in the one pioglitazone trial, a statistically significant improvement in NASH histology was demonstrated, although similar percentages of aminotransferase normalizations were recorded in the treatment group and in the control group.⁴³

Another study which has been published since the abovementioned systematic review included 55 patients with diagnoses of impaired glucose tolerance or type 2 diabetes and NASH, who were randomly assigned to a hypocaloric diet plus Pioglitazone (45mg daily) or placebo for six months.

Pioglitazone was associated with significant declines in serum aminotransferase levels, increased hepatic insulin sensitivity, and improvement in histology. One patient who received Pioglitazone developed fatigue and mild lower-extremity edema; otherwise treatment was well-tolerated.⁴⁶

Probucol

Probucol is a lipid-lowering agent with strong antioxidant properties. A double-blind randomized controlled study to evaluate the effects of probucol in NASH was designed by Merat et al. in Iran. There were 30 cases of biopsy-proven NASH included.

Subjects were randomly allocated to either the treatment group or to the control group by a 2:1 ratio. The treatment group was given 500 mg of probucol daily for six months, and the control group, an identically appearing placebo.

The decrease in ALT level in the treatment group as compared to the control group was significant at the $p < 0.005$ level (95% confidence interval: 20.2-93.7 IU). Both AST and ALT levels dropped to normal in nine cases of the treatment group (50%) but in none of the control group ($p = 0.01$).

The authors concluded that probucol appeared to be significantly effective in decreasing ALT levels in patients with NASH.¹⁸

The safety of probucol has been previously determined with an open labeled study by this group.⁴⁶ In a paper by Merat et al. the effect on liver histology was assessed. The authors concluded that probucol also significantly reduces the histology grade of steatohepatitis after one year of treatment.¹⁰

Betaine

Betaine is a normal component of the metabolic cycle of methionine, which has a protective effect against steatosis in animal models.²³

Ten adult patients with NASH were enrolled in an open-label study which received an oral solution of betaine anhydrous (cystadane) which was divided into two daily doses for a 12 months period. A significant improvement in serum levels of aspartate aminotransferase ($p = 0.02$) occurred during treatment.

Additionally, a marked improvement in the degree of steatosis, necroinflammatory grade, and stage of fibrosis was noted after one year of treatment with betaine.³¹ In the subsequent randomized controlled trial, administration of betaine for 12 months was associated with nonsignificant improvement in liver steatosis.^{49,50}

Ursodeoxycholic acid (UDCA)

A pilot study was conducted to evaluate the safety and estimate the efficacy of ursodeoxycholic acid (UDCA) and clofibrate in the treatment of NASH. From forty biopsy-proven NASH patients, twenty-four patients received 13 to 15 mg/kg/d of UDCA

for 12 months and sixteen patients with hypertriglyceridemia were placed on clofibrate, 2 g/day for 12 months.

In the UDCA group, the decreases in mean serum levels of alkaline phosphatase, ALT, and gamma-glutamyl transpeptidase (GGT) as well as the histological grade of steatosis were significant.

Among the patients treated with clofibrate, no change from baseline was found in the mentioned factors, with the exception of alkaline phosphatase which decreased significantly from baseline after 12 months of treatment.⁵¹

Numerous other studies with different designs were performed after this study for the assessment of beneficial and harmful effects of bile acids for patients with NASH.

The last study, a meta-analysis was published in 2007, in which all randomized clinical trials that evaluated any bile acids versus no intervention, placebo, or other interventions in patients with NAFLD were included. Four clinical trials that randomized a total of 279 patients were found. Only one was considered a low-bias risk trial.

No significant differences were found regarding mortality or improvement in liver function tests after treatment with UDCA. Data on the radiological and histological responses were too scant to draw definite conclusions. Adverse events were non-specific and considered to be of no major clinical relevance.⁵²

Probiotics

Probiotics have been proposed as a treatment option for patients with NAFLD and non-alcoholic steatohepatitis because of their balancing role on the flora of the gut that may act as a potential source of hepatotoxic oxidative injury.⁵³

To evaluate the beneficial and harmful effects of probiotics for NAFLD/ NASH a systematic review was conducted in 2006; no randomized clinical trials were identified.

Preliminary data from two pilot non-randomized studies suggest that probiotics may be well tolerated, may improve conventional liver function tests, and may decrease markers of lipid peroxidation.⁵⁴⁻⁵⁶

Statins

Two small pilot studies had shown improvement of liver enzyme activities with Atorvastatin.⁵⁷⁻⁶⁰ Furthermore, Pravastatin (20 mg daily for six months) normalized liver enzymes and improved hepatic inflammation in five patients with non-alcoholic steatohepatitis.⁵⁹⁻⁶⁰ Statins were also safe when administered to subjects with elevated baseline transaminases.^{61,62}

A randomized clinical trial was performed by Nelson et al. in 2008, in which sixteen biopsy proven NASH patients were randomized to receive either Simvastatin or placebo for 12 months. No statistically significant improvement in serum aminotransferases, hepatic steatosis, necroinflammatory activity or stage of fibrosis within or between groups was seen.⁶³

In another randomized trial the effect of a multifaceted approach on NAFLD in subjects with the metabolic syndrome and both biochemical and ultrasonographic evidence of NAFLD was evaluated. Patients received lifestyle advice and treatment for hypertension (mainly inhibitors of the renin-angiotensin system), impaired fasting glucose (metformin), obesity (orlistat) and dyslipidemia. Subsequently, patients were randomly allocated to receive either atorvastatin 20 mg/day, micronized fenofibrate 200 mg/day or both drugs for 12 months.

At the end of treatment, 67% of patients on atorvastatin (as well as 42% on fenofibrate and 70% on combination treatment) no longer had both biochemical plus ultrasonographic evidence of NAFLD.

In addition, 11% of subjects in the atorvastatin group had an echogenic liver at the end of the study but normal transaminases.⁶⁴

Angiotensin II receptor blockers

Angiotensin II is involved in the pathogenesis of hepatic fibrosis and enhances iron deposition and insulin resistance.²³ The therapeutic efficacy of the angiotensin II receptor antagonist, losartan, was studied in patients with NASH. A total of 7 patients with both NASH and hypertension were treated with losartan (50 mg/d) for 48 weeks.

Treatment with losartan resulted in a significant decrease in blood markers of hepatic fibrosis, plasma TGF-beta1 and serum ferritin concentration concurrently with an improvement in serum aminotransferase levels.

Histological assessment showed improvement of hepatic necroinflammation in five patients, reduction of hepatic fibrosis in four patients, and disappearance of iron deposition in two patients.

No side effects of treatment were noted at any time during the study. This study has raised the possibility that an angiotensin II receptor antagonist may be therapeutically efficacious for NASH.^{23,65}

A decrease in serum aminotransferase levels within this subgroup of drugs was reported in patients with confirmed metabolic syndrome and NASH.⁶⁶

Orlistat

Orlistat is a gastrointestinal lipase inhibitor used in the treatment of obesity and type 2 diabetes mellitus.¹³ Correlation between improvement of liver histology and degree of weight reduction with Orlistat was reported in a non-controlled study.⁶⁷ Two RCT were evaluated in this review.^{10,59}

In one study, 52 biopsy proven NASH patients were randomized to receive either orlistat (120 mg, three times daily for six months) or placebo.

All patients participated in an identical behavioral weight loss program. At the end of the study, serum glucose and insulin levels were significantly higher in the orlistat group, which also presented a higher degree of fibrosis. Serum ALT levels decreased significantly in both groups, with an almost two-fold reduction in the orlistat group. There was a statistically significant reversal of fatty liver as seen by ultrasound in only the orlistat group.⁶⁸

In another randomized clinical trial, 50 overweight subjects (body mass index of ≥ 27 with biopsy proven NASH) were randomized to receive a 1,400 Kcal/day diet plus vitamin E (800 IU) daily with or without orlistat (120 mg three times daily) for 36 weeks. Both groups had similarly improved serum aminotransferases, hepatic steatosis, necroinflammation, ballooning, and NAFLD activity scores.

Stratified according to weight loss instead of treatment group, a loss of $\geq 5\%$ body weight which was compared to $< 5\%$ body weight correlated with an improvement in insulin sensitivity and steatosis.

Comparing subjects who lost $\geq 9\%$ body weight to those that did not, an improved insulin sensitivity, adiponectin, steatosis, ballooning, inflammation and NAFLD activity score were seen.

Thus the authors concluded that orlistat did not enhance weight loss or improve liver enzymes, measures of insulin resistance, and histopathology.

However, subjects who lost $\geq 5\%$ of their body weight over a 9 month period improved insulin resistance and steatosis, and those subjects who lost $\geq 9\%$ also achieved improved hepatic histologic changes.¹⁰

Surgery

Recent reports indicate that weight loss induced by bariatric procedures could have beneficial effects in NASH.^{69,70} Table 3 summarizes the level of available evidence and grade of recommendations (according to Oxford classification).

Table 3: The level of available evidence and grade of recommendations for treatment of NAFLD.

Intervention	Outcome(s)	Level of Evidence	Recommendation Grade
Weight reduction- exercise	Histology-biochemistry	1	A
Vitamin E	Biochemistry	2	B*
Metformin (In diabetic patients)	Biochemistry	2	B
Pioglitazone	Histology-biochemistry	1	A
Probuocol	Biochemistry	2	B
Betaine	Histology-biochemistry	4	C
Ursodeoxycholic acid	Biochemistry	2	B**
Probiotics	Biochemistry	3	C
Statins (In metabolic syndrome)	Imaging-biochemistry	1	A***
Angiotensin II receptor blockers (in metabolic syndrome)	Histology-biochemistry	3	C****
Orlistat (in obese patients)	Histology-biochemistry	2	B*****

* One systematic review of poor quality RCTs did not provide evidence on the pros or cons of antioxidant supplements, including vitamin E in NAFLD or NASH.⁵⁶

** In a systematic review, no significant differences were found regarding mortality or improvement in liver function tests observed after treatment with UDCA.⁵²

***There was no benefit in patients without metabolic syndrome and in the histological features of the NASH with statins.⁶³

**** Histological improvement was seen only with telmisartan, perhaps because of its specific PPAR-gamma ligand effect.⁶⁴

***** Weight reduction was more important than orlistat use, when the beneficial effects of orlistat were studied.¹⁰

DISCUSSION

Attempts should be made to modify potential risk factors such as obesity, hyperlipidemia, and poor diabetic control in all patients with NAFLD/NASH. These attempts must be serious and persistent. Extensive counseling may help in this regard.

Considering the available data, pioglitazone seems to be a reasonable option for treatment of NASH particularly in patients with type 2 diabetes mellitus or impaired glucose tolerance.

However the cardiovascular benefit-risk ratio of

this drug should be considered. Some treatments can be recommended under special circumstances, such as statins, in patients diagnosed with metabolic syndrome.

Other medications such as UDCA or vitamin E, although in clinical use, are not supported by adequate evidence to be recommended for treatment of NAFLD/NASH, according to the current literature.

CONFLICT OF INTEREST

None declared.

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