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Treatment regimens for non-alcoholic fatty liver disease

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Abstract

With the growing epidemic of obesity and diabetes, more attention has been placed on metabolic syndrome and its associated hepatic manifestation, non-alcoholic fatty liver disease (NAFLD). Within the spectrum of clinico-pathologic conditions known as NAFLD, only a minority of patients has the histological features characteristic of non-alcoholic steatohepatitis (NASH), which has the potential to progress to cirrhosis and hepatocellular carcinoma. Therefore, diagnosis and therapy should target patients with NASH. Current treatment recommendations include weight loss and the reversal of other components of metabolic syndrome, but several other treatment modalities are under investigation. To date, no pharmacologic treatment has been reliably shown to be effective for NASH. This article reviews all available treatment modalities, including lifestyle changes, bariatric surgery, weight loss medications, insulin sensitizers, lipid lowering agents, antioxidants, cytoprotective agents, and other novel treatments.

Key words: NAFLD, NASH, treatment.

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Abbreviations:
Non-alcoholic fatty liver disease (NAFLD); Non-alcoholic steatohepatitis (NASH); Tumor necrosis factor (TNF); Thiazolidinedione (TZD); N-Acetyl-cysteine (NAC); Ursodeoxycholic acid (UDCA); Angiotensin receptor blocker (ARB); Homeostatic model assessment (HOMA); Roux-en-Y gastric bypass (RYGB); Laparoscopic adjustable gastric banding (LAGB); Vertical banded gastroplasty (VBG); Peroxisomal proliferator activated receptor (PPAR).

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Introduction, epidemiology, and natural history

Since first described by Ludwig in 1980, non-alcoholic fatty liver disease (NAFLD) has progressed from a poorly understood liver disease to one with more well defined boundaries. NAFLD is one of the most common causes of chronic liver disease in the Western world, and its prevalence is likely to parallel the increasing prevalence of diabetes, obesity, and other components of metabolic syndrome. NAFLD is now accepted as the hepatic component of the metabolic syndrome. NAFLD includes a spectrum of clinicopathologic entities ranging from simple steatosis to non-alcoholic steatohepatitis (NASH), with the possibility of progression to cirrhosis and hepatocellular carcinoma.[1,2] These entities are differentiated by histological features, and have in common the presence of hepatic steatosis and the absence of excessive alcohol consumption.

Estimates of the incidence and prevalence of NAFLD and NASH are limited by the lack of reliable non-invasive screening modalities. For example, a large proportion of patients with NAFLD and NASH may have normal transaminase levels. Sonography can often identify steatosis, but only if it involves 33% or more of the hepatic parenchyma.[3] Sonography is also suboptimal for evaluating obese patients. Proton magnetic resonance spectroscopy is an expensive tool, not suited for large scale population screening.[4] Nonetheless, estimates of the prevalence of NAFLD in the United States range from 3% to 34% in adults and approximately 10% in children.[4,5] Estimates of prevalence in other parts of the world are as high as 36.9%.[6] The prevalence of NAFLD in morbidly obese patients can be as high as 75% to 100%.[7]

Evidence regarding the natural history and progression of NASH indicates that simple steatosis does not typically progress to advanced liver disease. Only a minority of NAFLD patients may have the histologic features consistent with steatohepatitis.[8-12] Liver-related morbidity and mortality occurs exclusively in cases of advanced fibrosis and cirrhosis. Evidence from tertiary medical centers, sequential biopsy series, and population-based studies suggest that 10% to 15% of patients with NASH progress to cirrhosis, putting them at risk for liver-related death.[1,2] Progressive liver disease also occurs more frequently in NAFLD patients with components of

metabolic syndrome such as insulin resistance.[13] Additionally, patients with NAFLD and diabetes mellitus, have more aggressive disease and may be at risk for increased liver-related mortality.[2,13]

Identifying treatment candidates

Treatment of NAFLD requires a consideration of which patients require treatment. Because not all cases progress to advanced liver disease, and because the goal of treatment is to improve liver-related outcomes from a liver standpoint efforts should be focused on patients with steatohepatitis and not simple steatosis. Several approaches have been used to differentiate simple steatosis and steatohepatitis. The clinical presentation of patients with simple steatosis is similar to the presentation in NASH, therefore clinical presentation cannot reliably distinguish between the two. Demographic and clinical parameters such as age, gender, race, body mass index, dyslipidemia, or diabetes cannot reliably differentiate between simple steatosis and steatohepatitis.[1] Steatohepatitis cannot be reliably identified by simple serum tests, or the current generation of serum markers of fibrosis, or combination panels for fibrosis. Several NASH diagnostic biomarker panels have been developed but their accuracy is either limited or yet to be fully validated.[14] The few studies that have examined the diagnostic ability of imaging studies have largely concluded that radiological means are insufficient as well.[15-19] Measuring liver stiffness by transient elastography may accurately predict hepatic fibrosis in patients with hepatitis C; however, the utility of elastography is limited in NASH because obese body habitus greatly limits the accuracy of elastography.[20,21]

Currently, liver biopsy remains the "imperfect gold standard" for diagnosis and staging. Despite the invasiveness, cost, inconvenience, perioperative risk, and the potential for sampling error, no other modality produces the same measure of detail about the presence and severity of fibrosis. Because standardized pathologic protocols for histologic staging of NAFLD have been well delineated, liver biopsy continues to be the most reliable diagnostic and prognostic modality. No reliable recommendations indicate which NAFLD patients should undergo biopsy for diagnoses and staging of NASH, although persistent transaminase elevations or the presence of metabolic syndrome or type 2 diabetes may strengthen the case for biopsy. Weighing the potential risks and benefits of liver biopsy remains in the hands of individual clinicians and patients.

Identifying therapeutic targets

The following discussion of NAFLD and NASH pathogenesis briefly identifies areas potentially amenable to intervention and reviews potential treatment modalities. The pathogenesis of NAFLD and NASH is a complex process involving many pathways. Several factors, including medications, parenteral nutrition, toxins, and certain surgical procedures can lead to the development of fatty liver, sometimes called secondary NAFLD. We focus here on the type of NAFLD typically associated with insulin resistance, which is sometimes referred to as primary NAFLD.[6]

The "multi-hit" hypothesis of NASH development in the setting of insulin resistance includes a hepatic process and one or several non-hepatic processes. The "first hit" is a hepatic process involving increased hepatic macrosteatosis due to increased insulin resistance. Three specific mechanisms are increased de novo hepatic lipogenesis, decreased hepatic oxidation of free fatty acids, and decreased lipid export from the liver. Proposed "second hits" are non-hepatic processes including oxidative stress, apoptosis, and increased pro-inflammatory cytokines. In addition, adipocytes release cytokines such as leptin, resistin, interleukin-6, tumor necrosis factor alpha (TNF-α), and others. For more details on this topic, read-

Table I. Potential targets for therapeutic treatment.

Target	Treatment
Obesity	Weight loss • Diet with or without exercise • Pharmacologic - Orlistat - Sibutramine • Surgical
Insulin resistance	Insulin sensitizing agents • Thiazolidinediones (TZDs) • Metformin
Hyperlipidemia	Lipid lowering agents • Statins • Fibrates • Omega-3 fatty acids
Oxidative stress	Antioxidants • Vitamin E • Other vitamins • Betaine • N-Acetyl-cysteine (NAC)
Increased endotoxin levels	Probiotics • VSL#3 • Oligofructose
Apoptotic pathway	Cytoprotective agents • Ursodeoxycholic acid (UDCA) • Lecithin • Silymarin • Beta-carotene
Pro-inflammatory cytokines	Anti-tumor-necrosis-factor agents • Pentoxifylline
Other	Novel treatments • ACE inhibitors/ARBs • Incretin analogs • Second generation sulfonylureas

ers are referred to recent review articles on the subject.[2] Nevertheless, pathways potentially involved in the pathogenesis of NAFLD are promising targets for therapeutic intervention.

Treatment

Because insulin resistance participates in the pathogenesis of NASH, we first discuss therapies targeting obesity and insulin sensitivity. Several studies examine the effect of weight loss on NASH, either by lifestyle, pharmacologic, or surgical measures. Later we discuss: Lipid Lowering Agents, Antioxidants, Cytoprotective Agents, Anti-TNF Agents, and Novel Treatments.

Weight loss by lifestyle changes

Patients with NAFLD or metabolic syndrome are encouraged to adopt a program of diet and exercise with the goal of weight loss as a first step in their treatment. Many studies have examined the effects of weight loss achieved by diet with or without exercise; however, most enrolled fewer than 50 subjects. A relatively large study by Suzuki and colleagues examined the effect of weight loss due to lifestyle change upon elevated ALT levels.[22] Records from annual employee health checkups showed that 348 men out of 1,546 employees had elevated ALT in the absence of concomitant liver disease. Weight loss of at least 5% was significantly associated with improved ALT levels, and maintaining this 5% weight loss was significantly associated with sustained ALT improvement. However, histologic criteria were not used to diagnose NAFLD and only 6% of the cohort was able to achieve a weight loss of 5% or more; for these reasons, the conclusions may not be applicable to most NAFLD patients. Because lifestyle changes associated with diet and exercise are so difficult to maintain for most patients, attention has turned to other means of achieving sustainable weight loss.

Weight loss by pharmacologic measures

The medications orlistat and sibutramine are used for the treatment of obesity and have been studied for their effects on steatohepatitis. Hussein and colleagues conducted an open-label study in which fourteen patients underwent liver biopsy before and after treatment with six months of orlistat 120 mg tid.[23] At the end of six months, ten patients (70%) had reduced fatty infiltration, and inflammation improved by two grades in 22% and one grade in 50% of patients. Fibrosis improved two grades in three patients (21%) and one grade in seven patients (50%). Improvement was also noted in transaminases levels, total cholesterol, triglycerides, LDLs, and insulin resistance index. Although the size of the cohort was small, the findings include histological data from paired liver biopsies.

In a similar study in ten obese patients with biopsy-proven NASH, Harrison and colleagues found that after six months of orlistat treatment, steatosis improved in some patients.[24] Improvements were also noted in body weight, hemoglobin A1C, and transaminases. The authors noted that improvements in steatosis, fibrosis, and hemoglobin A1C were generally associated with a weight loss of 10% or more. A study by Sabuncu and colleagues noted improvements in insulin resistance (measured by HOMA scores), AST, ALT, GGT and sonographic findings in a six-month open label trial of sibutramine or orlistat in combination with a low calorie diet.[74] Thirteen patients were treated with sibutramine and twelve patients were treated with orlistat. Liver biopsies were not performed.

Weight loss by surgical measures

Most of the work on histological improvement after weight loss relies on patients who have had bariatric surgery. Jejunoileal bypass for treatment of obesity has largely been abandoned due to poor postoperative outcomes. Jejunoileal bypass has been associated with high rates of mortality, more often than not due to liver failure. Biliopancreatic diversion with or without duodenal switch is the only form of bariatric surgery still in use that aims at effecting weight loss through malabsorption of macronutrients. A single observational study involving 104 patients who had liver biopsies at time of initial surgery and at surgical revision showed that overall fibrosis scores were unchanged in the majority of patients but decreased in 11 patients found to have cirrhosis upon initial biopsy.[25]

Roux-en-Y gastric bypass (RYGB), gastroplasty, and laparoscopic adjustable gastric banding (LAGB) are presently the most common surgeries for weight loss. At least five small studies have examined the effect of RYGB on NASH patients.[26-30] Paired liver biopsies during and after RYGB were performed in a total of 108 patients. No worsening of liver disease was reported. All five studies reported varied measures of histological improvement, with NASH resolving in up to 89%.[29] Gastroplasty techniques, such as vertical banded gastroplasty (VBG) with or without gastric sleeve are not used as commonly as RYGB or LAGB. RYGB tends to yield better results, although the adjustable features of LAGB are attractive. At least four studies have examined the effect of gastroplasty on NAFLD.[31-34] Improved steatosis was reported in all four studies, but the reports regarding inflammation and fibrosis are mixed. Reports on patients with paired liver biopsies with LAGB are limited. Two published studies by Dixon and coworkers showed improved steatosis after LAGB.[35,36] Features of fibrosis improved in most patients. One study showed that of 23 patients with NASH upon initial biopsy, only four showed findings of NASH on subsequent biopsy.[35] The

other study showed that 30 of 60 patients had NASH findings upon initial biopsy, whereas only 6 showed these findings upon subsequent biopsy.[36] In a review of 19 studies on the histological effects of gastric bypass on NAFLD, Verna and Berk reported that bariatric surgery usually improves steatosis,[37] but the evidence for improvement in NASH features was less uniform. These authors also noted occasional reports of regressed cirrhosis.

On the other hand, some authors are still concerned that, the risk of liver disease progression due to rapid weight loss within the first few postoperative months makes the role of bariatric surgery in the treatment of NAFLD and NASH unclear. Nevertheless, further study of this issue requires trials with larger numbers of paired biopsies, clearer indications, follow-up liver biopsies, and clearer histological endpoints.

Insulin sensitizing agents

Among the insulin sensitizing agents used for the treatment of NASH, thiazolidinediones (TZDs) have been studied the most and have shown the most favorable results. TZDs such as pioglitazone and rosiglitazone act as peroxisomal proliferator activated receptor-γ (PPAR-γ) agonists. Studies have also been conducted with troglitazone, which has since been withdrawn from the market due to issues of hepatotoxicity.[38] TZDs increase fatty acid oxidation and decrease fatty acid production within the liver. Insulin sensitivity is improved both peripherally and within the liver. Several studies on the effects of TZDs on NAFLD and NASH report favorable results,[39-46] including improved transaminases and steatosis. A large, recently published study by Aithal and colleagues randomized 74 nondiabetic, biopsy-proven NASH patients to receive pioglitazone 30 mg qd or placebo with standard diet and exercise for 12 months.[39] Sixty-one patients (30 placebo, 31 pioglitazone) had follow-up biopsies, and pioglitazone treated patients showed significant improvements in hepatocellular injury, Mallory bodies, and fibrosis. Improved necroinflammation is a common finding in such studies, with the exception of a 48-week placebo-controlled trial of rosiglitazone by Ratziu and colleagues.[40] The effect of TZDs on fibrosis is variable, improving in some, unchanged in others, but not worsening.

The favorable results observed with TZDs requires prospective, randomized, controlled trials before these agents can be routinely recommended. Side effects must also be kept in mind, as mild weight gain and lower extremity edema have been reported.[39] The recent controversy over the possibility of increased cardiac risk with use of rosiglitazone also must be taken into consideration.

Several studies have examined the utility of metformin in the management of NAFLD and NASH. Metformin's mechanisms of action include decreasing hepatic gluconeogenesis, increasing peripheral and hepatic insulin sensitivity, slowing intestinal glucose absorption, and reducing serum lipid levels and hepatic fatty acid oxidation. At least seven trials have examined the effect of metformin upon NAFLD and NASH.[47-53] Only the trials by Uygun et al., and Bugianesi et al., were randomized controlled trials[48,51]. The study by Uygun et al, randomized 36 patients to either caloric restriction alone or caloric restriction plus metformin.[48] Significant improvement in transaminases, insulin, and C-peptide levels were noted in the metformin group, and although more improvement in necroinflammatory activity was noted in the metformin group, the difference was not statistically significant. Bugianesi and colleagues randomized 55 patients to receive metformin 2000 mg daily for 12 months, 28 patients to receive vitamin E 800 IU daily, and 27 patients to diet alone.[51] Due to concerns raised by the ethics committee, only 17 patients treated with metformin underwent biopsy at the end of treatment, but significant decreases in steatosis, necroinflammation, and fibrosis were reported. Several studies have reported improved inflammation but not much improvement in fibrosis. Again, the strength of these conclusions about metformin's efficacy is limited by the lack of adequately powered, randomized, placebo controlled trials with histological data from paired biopsies.

Lipid lowering agents

Interest in the use of antihyperlipidemic agents for NAFLD stems from the role of dyslipidemia in metabolic syndrome and its association with NAFLD. Fatty acid metabolism abnormalities are likely to contribute to the development of NAFLD. Statins competitively inhibit hepatic hydroxymethyl-glutaryl coenzyme A (HMG-CoA) reductase, thereby decreasing cholesterol production and reducing serum cholesterol. The use of statins in patients with chronic liver disease has raised concerns about the potential for of hepatotoxicity, but most agree that the incidence of significant hepatotoxicity is exceedingly rare and statin use in the setting of compensated liver disease is essentially safe.[54-56]

Only a few studies have examined the efficacy of statins for NAFLD treatment. A pilot study by Rallidis and colleagues examined pravastatin use in four NASH patients for six months; they found improvement in inflammation in three patients and improvement in steatosis in one patient.[57] Ekstedt and colleagues retrospectively reviewed initial and follow-up liver biopsies of 68 NAFLD patients, 17 of whom began treatment with statins at some point after the initial biopsy.[58] The time between biopsies ranged from 10.3 to 16.3 years. Although patients treated with statins showed greater body mass index (BMI) and insulin resistance at initial and follow-up biopsies compared to patients without statins, greater improvements in

hepatic steatosis were noted in the patients treated with statins. The study also reported that only four of the 17 patients treated with statins showed progression of their fibrosis stage on follow-up biopsy. These findings are preliminary and the number, size, and design of the studies are suboptimal. No conclusions can yet be drawn about the efficacy of metformin for NAFLD treatment.

There is some suggestion that fibrates, such as clofibrate, gemfibrozil, and fenofibrate may have some benefit in NAFLD treatment. A 12-month pilot study comparing 24 NASH patients treated with ursodeoxycholic acid (UDCA) to 16 biopsy-proven NASH patients treated with clofibrate noted significant improvement in ALT, GGT, and histologic amounts of steatosis with UDCA. Significant improvements in alkaline phosphatase levels were only noted with Clofibrate.[59] A four-week study showed that gemfibrozil improved ALT levels, but histological data was not obtained.[60] Because pioglitazone, a PPAR-γ agonist with weak PPAR-α activity, has shown some benefit in NAFLD treatment, it is possible that fenofibrate may have some benefit as well, due to its PPAR-α activity; this however has not been evaluated in any trials.[61]

Antioxidants

Oxidative stress is considered a major contributor as the "second hit" in the pathogenesis of NAFLD and NASH, justifying the study of several antioxidants in NAFLD treatment. Many of these studies have examined the effects of vitamin E. Alpha-tocopherol, the form of vitamin E that is preferentially metabolized in humans, inhibits transforming growth factor beta1, which is thought to contribute to fibrosis progression; six of the nine studies reviewed showed improved transaminases.[44,62-66] However, only three of the studies examined histological changes. Hasegawa's one-year study of open-label vitamin E in 10 patients with NAFLD and 12 patients with NASH reported improvement in transaminases and histological findings in the NASH cohort.[63] Kugelmas' pilot study of diet and aerobic exercise with or without vitamin E in 16 patients showed no additional benefit with vitamin E.[64] A small pilot study by Sanyal and colleagues showed that vitamin E alone was not as effective as vitamin E with pioglitazone. Significant improvements in steatosis, ballooning and pericellular fibrosis were noted on the follow-up biopsies of the 10 patients treated with vitamin E and pioglitazone.[45] A placebo-controlled double-blind study by Harrison and colleagues randomized 49 patients with biopsy-proven NASH to receive either vitamin E 1,000 IU qd and vitamin C 1,000 mg qd or placebo for 6 months. On follow-up biopsy, a statistically significant improvement was noted in fibrosis score, although inflammation grade remained unchanged.[68] So far, these data are of mixed quality; the study sizes are small and the results range from heterogeneous to conflicting. A large randomized, multicenter, double-blinded, placebo-controlled trial of pioglitazone and Vitamine E is currently in progress by investigators from NASH Network.[69] These researchers have enrolled 247 patients who will receive pioglitazone 30 mg qd, vitamin E 800 IU qd or placebo for 96 weeks. The primary outcome, improvement according to defined histological criteria, will be based on paired liver biopsies. The results are expected to shed more light on the efficacy of treatment with vitamin E.

Other antioxidants such as betaine and N-acetyl-cysteine (NAC) have also been studied for their purported antifibrotic effects.[72-75] Betaine, a metabolite of choline, increases S-adenosyl-L-methionine (SAM) levels, which contributes to cellular membrane integrity and protects against fatty infiltration in animal models.[70,71] Abdelmalek and colleagues examined the effects of betaine anhydrous for oral solution bid for 1 year in 10 patients with biopsy proven NASH.[72] Seven patients completed the study, and although statistically significant improvements were noted in transaminases levels, the improvement in the amount of steatosis, histological inflammation and fibrosis were not statistically significant. In a subsequent study by the same investigators, betaine was not shown to be efficacious (personal communication with Dr. Abdelmalek 2008).

Gulbahar and colleagues conducted a small study on the effects of NAC in 11 patients and reported improvements in transaminases, but no histological data was obtained.[74] NAC shows some benefit in a variety of liver conditions, reports of its use in NASH treatment are scarce and preliminary.

Some researchers have surmised that endotoxins produced by gut flora may also contribute to oxidative stress in the liver, and that alterations in that flora may have beneficial effect upon the liver. Most of the support comes from results in animal models.[76,77] Only two small open label studies have been conducted with probiotics in patients with NAFLD.[78,79] A study by Loguercio and colleagues showed that VSL#3 is well-tolerated in patients with NAFLD, alcoholic cirrhosis, and chronic hepatitis C.[79] Various serum markers of hepatic damage showed improvement after 120 days of treatment, but no biopsies were performed. Oligofructose, an indigestible insulin-type fructan, decreases hepatic uptake of triacylglycerol in rats.[80] An eight-week double-blind crossover pilot study by Daubioul et al. randomized seven patients with biopsy-proven NASH to receive either oligofructose or maltodextrine, which served as a placebo.[81] Insulin levels improved after four weeks of therapy and transaminases improved after eight weeks.

Cytoprotective agents

Several studies have examined the effects of ursodeoxycholic acid (UDCA) in NAFLD and NASH pa-

tients. UDCA is a naturally occurring bile acid believed to have cytoprotective and immunomodulator properties and may decrease apoptosis.[82] UDCA has long been used in the treatment of primary sclerosing cholangitis and primary biliary cirrhosis, and its adverse effect profile is generally benign. Initial pilot studies showed improvements in transaminases and steatosis;[83-85] however, these results were not confirmed in a large randomized placebo-controlled trial by Lindor and colleagues.[86] One hundred sixty-six biopsy-proven NASH patients were randomized to receive either UDCA at 13-15 mg/kg daily for two years; 126 patients completed the two year study and 107 follow-up biopsies were performed. Histological improvement was not significantly different between the two groups. Other studies have also reported that UDCA monotherapy is no better than placebo.[87,88] A six-week, double-blind, placebo-controlled trial by Mendez-Sanchez and colleagues randomized 14 obese women to receive UDCA 1200 mg qd and 13 to receive placebo.[87] All patients were also placed on a 1200-calorie diet. UDCA and dietary restriction were not superior to dietary restriction alone. These results with cytoprotective agents have been disappointing, but UDCA may have some benefit when used in combination with other agents such as vitamin E.[89] Studies are also underway to determine whether higher dosages of UDCA are as safe and might be more efficacious. UDCA's benign side effect profile suggests that further study of its use as an adjunct in NASH treatment should be conducted. The potential benefits of other cytoprotective agents such as lecithin, silymarin, beta-carotene, and metadoxine might also be examined.

Anti-TNF agents

Other potential components targeting the "second hit" in the pathogenesis of NAFLD include those agents improving necrosis, inflammation, and fibrogenesis caused by a number of pro-inflammatory adipocytokines, including tumor necrosis factor alpha (TNF-α).[90] Pentoxifylline, a xanthine derivative that affects blood viscosity, is currently approved for the treatment of claudication. It has also been shown to inhibit TNF-α.[91] Two small open-label trials have examined the safety and efficacy of pentoxifylline in NASH patients. These initial trials show improvement in transaminases after 12 months of open-label pentoxifylline, with 18 patients in a trial by Satapathy and colleagues and 20 patients in a trial by Adams and colleagues.[92,93] Satapathy and colleagues obtained histological evidence of improvement in 2007, in a trial treating 9 patients with biopsy-proven NASH with pentoxifylline 400 mg tid for 12 months.[94] Significant transaminase improvement was again noted. Upon follow-up liver biopsy, improvement in steatosis and lobular inflammation was noted in 55% of patients, decreased stages according to Brunt's criteria was noted in 67% of patients, and fibrosis improved in four out of the six patients with fibrosis at baseline. Further investigation with larger, well-designed clinical trials would be helpful.

Other novel treatments

Attempts to find other safe and efficacious treatments for NAFLD and NASH include investigations of the angiotensin receptor blockers (ARB) telmisartan and irbesartan. The insulin sensitizing properties of these agents results from stimulation of PPARγ.[95] In a study by Yokohama et al., seven patients with NASH and hypertension were treated with 50 mg daily of the ARB losartan for 48 weeks.[96] Significant improvements were noted in the levels of transforming growth factor beta1, serum markers of hepatic fibrosis, and ferritin. Five patients showed decreased necroinflammation upon follow-up biopsy and four patients showed decreased fibrosis.

Preliminary studies with animal models and case reports in humans show that incretin analogs may also be of benefit in NAFLD treatment. Incretin analogues, such as exenatide and sitagliptin, increase glucose-dependant insulin secretion, decrease inappropriate glucagon secretion, and increase satiety by delaying gastric emptying.[97,98]

Second generation sulfonylureas, such as repaglinide and nateglinide, have also been considered as possible NAFLD treatment options. Ten diabetic patients with biopsy-proven NASH were randomized by Morita and colleagues to receive nateglinide 270 mg daily with diet and exercise or diet and exercise alone for 20 weeks.[99] In the nateglinide group, improvements were noted in postprandial glucose, hemoglobin A1C, glucose tolerance test results, liver function tests, and imaging and histological findings of NAFLD. Suffice it to say, these and other possible treatment options require further study and validation.

Conclusion

Despite more than a decade of research and clinical trials, no single intervention has been proven effective for the treatment of NAFLD and NASH in all important outcomes. While some promising results are seen with certain types of bariatric surgery and medications such as TZDs and vitamin E, these results have not been validated with larger, well-designed studies. With most of the trials that have been conducted to date, conclusions have been limited by methodological flaws such as the lack of randomization, small sample size, and failure to address multiple pathogenic pathways. Additionally, because NAFLD and NASH are chronic in nature, as with other components of metabolic syndrome, long-term treatment is likely to be required. This poses a methodological dilemma for clinical trials of shorter duration. As it stands today, no single medication can be

recommended for routine use in clinical practice. For now, clinicians may focus on treating the comorbid conditions associated with metabolic syndrome and reversing factors that predispose patients for NAFLD and NASH. In the absence of clearly superior treatments, NAFLD and NASH patients may appropriately be referred to clinical trials.

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