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Medical and Surgical Treatment Options for Nonalcoholic Steatohepatitis

Kathleen E. Corey, MD, MPH, MMSc and

Liver Center, Gastrointestinal Unit, Massachusetts General Hospital, Harvard Medical School, Boston, MA, kcorey@partners.org

Mary E. Rinella, MD

Department of Gastroenterology and Hepatology, Northwestern University Feinberg School of Medicine, Chicago, IL, mrinella@nm.org

Abstract

Nonalcoholic fatty liver disease (NAFLD) is the most common cause of liver disease in the United States with a growing prevalence worldwide. Nonalcoholic steatohepatitis (NASH), progressive form of NAFLD can lead to the development of cirrhosis, hepatocellular carcinoma (HCC), and the need for liver transplantation. Treatment of NASH may decrease the risk of progressive disease. Treatment for NAFLD should center around weight loss and exercise. Pharmacotherapy with vitamin E and pioglitazone should be considered for those with NASH, especially those with fibrosis. Weight loss surgery is also an effective treatment for NASH in individuals with other indications for surgery. In this review we will discuss the currently available therapies for NASH including lifestyle, pharmacologic and surgical options.

Scope of NAFLD and NASH

Nonalcoholic fatty liver disease (NAFLD) represents a spectrum of hepatic pathology that encompasses simple steatosis, nonalcoholic steatohepatitis (NASH) and NASH cirrhosis. It is estimated that 80 million American adults have NAFLD and 25% will develop the progressive phenotype referred to as NASH.[1] The prevalence of NAFLD is also growing with worldwide estimates of approximately 30%.[2] Some with NASH will develop hepatocellular carcinoma (HCC), cirrhosis or the need for liver transplantation.[3] As a result of the growing prevalence of NAFLD and its potential consequences, there is a pressing need to better understand how to identify those at highest risk for disease progression and liver-related complications in order to target patients for treatment. In this review we will discuss the currently available therapies for NASH including lifestyle, pharmacologic and surgical options. Emerging therapies will be addressed in a separate article.

Who Requires Treatment

Hepatic steatosis is defined by the presence of ≥5% lipid laden hepatocytes on a liver biopsy or ≥10% fatty infiltration of the liver on magnetic resonance imaging (MRI). The presence of hepatic steatosis alone is associated with a low risk for progression to cirrhosis. This is distinct from NASH which is characterized by steatosis accompanied by lobular

inflammation, hepatocyte ballooning and, in a subset of patients, fibrosis. Those with NASH or those with NAFLD and fibrosis are at risk of progressive liver disease.[4-6] Additionally, individuals with steatosis and lobular or portal inflammation not meeting criteria for NASH may be at risk of progressive disease and should be closely monitored for progressive disease including consideration of repeat liver biopsy.[5] As these phenotypes carry a risk of disease progression, treatment for the prevention of liver-related comorbidities should be focused on those individuals with NASH, particularly those with NASH and fibrosis stage ≥2.

Outcomes in NASH Treatment Trials: An Evolving Target

Inflammation and cellular injury pathways such as those leading to oxidative stress drive stellate cell activation. This can result in the accumulation of fibrosis and progression to cirrhosis in some patients. The NAFLD activity score (NAS) is a composite score developed to quantify features of steatohepatitis and assess treatment response in NASH clinical trials.[7] It is composed of steatosis (0-3), lobular inflammation (0-3) and hepatocyte ballooning (0-2) grades and ranges from 0-8.[8] Fibrosis in NASH is staged separately on a scale from 0-4, with stages 3-4 considered advanced fibrosis. The primary outcome in the first generation of pivotal trials for NASH such as Pioglitazone versus Vitamin E versus Placebo for the Treatment of Nondiabetic Patients with Nonalcoholic Steatohepatitis (PIVENS) and Farnesoid X nuclear receptor ligand obeticholic acid for non-cirrhotic, nonalcoholic steatohepatitis (FLINT), was a 2 point improvement in the NAS (at least one of which an improvement in ballooning), with no worsening of fibrosis. Resolution of NASH gives a ‘gestalt’ diagnosis of steatohepatitis, independent of NAS. In these trials, resolution of NASH and improvement in fibrosis were secondary outcomes.

Looking forward with the goal of eventual FDA approval for compounds in development, a given drug will likely need to achieve ‘clinically meaningful benefit’. The only histologic feature in the setting of NASH that predicts outcomes is the presence of fibrosis.[4] Since the presence of steatohepatitis likely drives the development and progression of fibrosis, resolution of NASH is also thought to be an important endpoint. No individual feature of the NAS or the NAS itself has been shown to predict outcomes. Thus the focus of clinical trials in the NASH space has shifted towards NASH resolution and fibrosis regression or stabilization. As such, NASH treatment should focus on improvement in radiographic steatosis for pilot studies and for later stage studies on 1) resolution of NASH and/or 2) regression or stabilization of fibrosis.[9]

Treatment Options

Weight Loss

Lifestyle modification is the cornerstone of treatment of all patients with NAFLD, regardless of disease stage. Most patients with NAFLD benefit from weight loss, and a discussion of how to incorporate healthy dietary changes and more exercise is an essential component of treatment.(**Table 1**) Promrat et al., randomized 31 overweight or obese individuals with biopsy-proven NASH to an intensive lifestyle intervention or structured education for 48 weeks.[10] Regardless of treatment group, those who achieved a ≥7% total body weight

(TBW) loss had significant improvement in steatosis, lobular inflammation, hepatocyte ballooning and NAS compared to those who lost <7%. Percent weight lost directly correlated with improvement in NAS. However, no change in fibrosis stage was observed in either group. Harrison et al., found similar outcomes. [11] In this study those who lost ≥5% TBW had a significant improvement in insulin sensitivity and steatosis while those who lost ≥9% TBW improved steatosis, inflammation, ballooning and NAS. The largest prospective trial to date evaluated 293 patients with NASH and the impact of 52 weeks of lifestyle intervention on histology. Paired liver biopsies were available for 261 patients. Among the entire cohort, NASH resolution occurred in 25%, NAS reduction in 47% and fibrosis regression in 19%. Thirty percent of patients were able to achieve a ≥5% total body weight loss and among this group 58% had NASH resolution and 82% had an improvement in NAS. Among those who achieved a ≥10% total body weight reduction 90% experienced resolution of NASH, 100% had a reduction in NAS and 45% had regression of fibrosis.[12] Thus, a minimum of 9-10% TBW loss can not only improve NASH but may result in fibrosis regression in a significant proportion of patients. The major challenge of weight loss remains the ability to maintain weight lost, which has not been addressed in the context of NASH.

Dietary Modification

While weight loss improves NAFLD histology, data regarding the ideal diet for NAFLD is limited. Several studies have demonstrated that low carbohydrate diets reduce intrahepatic triglyceride concentration and improve histologically-defined NAFLD and are superior to low calorie diets with equivalent weight loss.[13-15] A pilot trial of the Mediterranean diet in biopsy-proven NAFLD demonstrated a reduction in hepatic steatosis by magnetic resonance spectroscopy (MRS) when compared to subjects on a low fat, high carbohydrate diet (39% vs. 7% reduction, p=0.01), with no difference in total weight loss between groups. [16] This suggests that dietary macronutrient content may offer additional benefit beyond that of weight loss. Furthermore, the Mediterranean diet is associated with a reduction in the incidence of cardiac events in the general population.[17] This may offer additive benefit to those with NASH, given the high prevalence of cardiovascular disease in these individuals.

Other dietary nutrients, such as fructose, may have a negative effect on patients with NAFLD. Fructose in the diet is primarily derived from high fructose corn syrup and sucrose, both found in a variety of processed foods. Fructose is rapidly taken up by hepatocytes after ingestion and unlike glucose, its conversion to fructose-1-phosphase is not rate limited, leading to ATP depletion, ATP enhanced endoplasmic reticulum stress, mitochondrial dysfunction and potentially hepatic inflammation and injury.[18 19] In addition, fructose consumption does not stimulate satiety as other sugars do. Fructose consumption does not result in insulin secretion mediated rise in leptin levels that is seen with the consumption of other sugars. Thus the failure of fructose to stimulate leptin secretion leads to decreased satiety.[20]

Some data suggest that fructose consumption may be associated with the development of NAFLD and worsening of fibrosis.[21 22] However, it is unknown whether fructose elimination or minimization improves NASH histology. A pilot study in children with NAFLD found that a low fructose diet decreased oxidized low-density lipoprotein levels and

resulted in a trend towards improvement in alanine aminotransferase levels.[23] However, large trials in adults are lacking and thus guidelines do not address fructose consumption. The 2010 United States Dietary Guidelines recognized fructose as an added sugar and recommended limiting total daily added sugars to ≤3 servings per day for <2,000 calorie daily diets and ≤5 servings for ≥2,000 calorie diets. Based on these recommendations and the benefits of a low carbohydrate diet seen in NAFLD, we recommend patients limit added sugar consumption including fructose to <3 servings per day.

Exercise

Aerobic Training (AT)—Exercise, even in the absence of weight loss, can improve NAFLD. Aerobic exercise decreases aminotransferase levels in subjects with NAFLD.[24] Further, several studies have demonstrated the benefit of aerobic exercise (AE) on radiographic NAFLD.[25-27] Both 30-45 minute cycling sessions or 90 minutes of brisk walking or jogging thrice weekly improved hepatic triglyceride content.

Resistance Training—Resistance training can also improve radiographic NAFLD although its benefit in addition to aerobic exercise is uncertain. Hallsworth et al., studied 19 individuals with NAFLD randomized to resistance training or placebo for 8 weeks.[28] Resistance training resulted in a 13% decrease in radiographic steatosis as well as decreases in lipid oxidation, homeostasis model assessment of insulin resistance and glucose control despite no difference in body weight or visceral adipose tissue.

Aerobic vs. Resistance Training

Limited studies have compared the benefit s of aerobic training (AT) and resistance training (RT) in individuals with NAFLD. [29] Thirty-one subjects were randomized to 2 months of AT consisting of 60 minutes of exercise on a treadmill, stationary bike or elliptical machine thrice weekly. RT involved 3 series of 10 repetitions of 9 different muscle groups with one minute rest periods between exercises. BMI decreased in both groups with no significant change between interventions. Both AT and RT decreased hepatic fat as assessed by MRI with no difference between treatment groups. A second study compared the impact of combining AT and RT on hepatic and visceral fat.[30] 196 individuals with obesity, dyslipidemia and NAFLD were randomized to AT, RT or combined AT/RT for 8 months. AT was equivalent to 12 miles per week at 75% peak oxygen uptake. RT consisted of 3 days per week of 3 sets of 8 exercises. In this study RT improved only subcutaneous fat without impacting liver fat. In contrast, AT resulted in a decrease in liver-spleen ratio and visceral fat with a non-significant decrease in absolute hepatic fat from baseline. No added benefit was seen in the AT/RT over the AT group alone. A meta-analysis by Keating at al., reviewed 16 studies that assessed the impact of exercise defined as either AT or RT on steatosis.[31] Pooled analysis found that exercise was associated with an improvement in steatosis even in the absence of significant weight loss. Overall aerobic training had the most consistent impact on radiographic steatosis and may be the preferred type of exercise for those with NAFLD.

Medications

While numerous medications have been evaluated for the treatment of NASH, only a limited number have been shown to be beneficial. (Table 2) One of the greatest unmet needs in the field is the ability to assess treatment response without the use of repeat liver biopsy. While many with NASH do not have elevated ALT at baseline, an improvement in ALT often correlates with improved histology.[32-34] Furthermore, in those being treated with vitamin E, substantial improvement in NASH histology, to approximately 90%, can be seen in patients who also experience modest weight loss.[32] MRI technology is rapidly advancing and offers another modality through which treatment response could be assessed. Although the detection of NASH (or its resolution) cannot yet be determined non-invasively, MRI is very sensitive to changes in hepatic fat and could be used as a surrogate for response, particularly in early phase clinical trials. MRI- proton-derived fat fraction (PDFF) is a very sensitive technique that can be used to detect such changes as illustrated in the MOZART trial.[35] Furthermore, MR elastography may be used to in the future to detect changes in hepatic stiffness that correlate with a reduction in fibrosis or inflammation once more effective therapies for NASH emerge. Current imaging technology is most accurate to detect advanced fibrosis, however ongoing refinement in such techniques may allow for the assessment of subtle changes or even have the ability to detect NASH.

Vitamin E

Vitamin E is an antioxidant that has been studied extensively in NASH. The pivotal trial of vitamin E use was the PIVENS trial conducted by the Nonalcoholic Steatohepatitis Clinical Research Network (NASH CRN).[36] The PIVENS trial evaluated the efficacy of pioglitazone 30mg daily, vitamin E 800 units daily, or placebo in individuals with biopsy-proven NASH but without diabetes over 96 weeks. The PIVENS trial used the natural form of vitamin E (rrr α-tocopherol) which of the 7 isoforms, has the highest bioavailabilty. Both vitamin E and pioglitazone were associated with an improvement in steatosis and lobular inflammation without an improvement in fibrosis. Vitamin E resulted in higher rates of improvement in NASH compared to placebo (43% vs. 19%, P=0.001). In a pooled analysis from the PIVENS and Farnesoid X nuclear receptor ligand obeticholic acid for non-cirrhotic, non-alcoholic steatohepatitis (FLINT) trial the potential efficacy of vitamin E was explored. In the FLINT trial diabetic patients were included. Furthermore, patients on vitamin E were allowed to enter the trial if they continued to have active NASH despite being on a stable dose of vitamin E for 6 months. In this pooled post-hoc analysis, those on vitamin E had histologic improvements regardless of diabetic status and in those receiving placebo, compared to subjects not on vitamin E throughout the study, those on vitamin E had more histologic improvement, regardless of diabetic status. While data on vitamin E in diabetic subjects is limited, these data suggest that vitamin E is likely to be efficacious in diabetic patients as well.[37] (Figure 1)

The potential risk of adverse events with treatment with vitamin E has been raised in several studies. The Selenium and Vitamin E Cancer Prevention Trial (SELECT) followed 35,533 men over 7 years randomized to placebo, selenium, vitamin E 400 units or vitamin E plus selenium. Vitamin E use was associated with an increased risk of prostate cancer (HR 1.17, 95% CI 1.004-1.36).[38] However, the Physicians' Health Study II followed 14,641

randomized to placebo or vitamin E for 8 years and found no difference in prostate cancer risk by treatment group.[39]

Two meta-analyses have suggested that vitamin E use may increase all-cause mortality at doses >1000 units daily. [40 41] However, these studies were limited by the inclusion of heterogeneous studies and of patients with chronic disease that may have confounded results. However, as risks may exist, vitamin E use is recommended only for biopsy-proven NASH where benefit may outweigh adverse events. As vitamin E has not been well-studied in individuals with NASH and diabetes it is not recommended for this population.

Pioglitazone

Pioglitazone is a thiazolidinedione (TZD) developed for the treatment of insulin resistance. Belfort et al. evaluated pioglitazone 45 mg daily in those with NASH and diabetes mellitus or insulin resistance.[42] Pioglitazone resulted in a significant improvement in NAS when compared to placebo (73% vs. 24%, P<0.0001). In addition, a non-significant trend toward improvement in fibrosis stage was seen in the pioglitazone group. Pioglitazone was associated with a significant weight gain compared to placebo (mean 2.5kg). Aithal et al., also evaluated pioglitazone 30 mg for 12 months in individuals with NASH.[43] Pioglitazone improved overall inflammation and fibrosis, although steatosis was unchanged.

In the PIVENS trial, pioglitazone resulted in the resolution of NASH in 47% compared to only 21% in the placebo arm (P=0.0001) but did not meet the primary endpoint of a ≥2 point decrease in NAS without progression of fibrosis. However, the outcome may have been the result of disproportionate misclassification of hepatocyte ballooning in the group that received pioglitazone. Post hoc analysis revealed that when the misclassification of ballooning was taken into account, pioglitazone met the primary endpoint.[36] A meta-analysis of the impact of pioglitazone on NASH demonstrated a significant improvement in steatosis and inflammation.[44] Thus, pioglitazone 30-45mg daily is recommended for the treatment of NASH. While small studies included diabetics, the majority of data for pioglitazone is in non-diabetics and the long term safety and efficacy among diabetic patients with NASH is unknown.[45] (Figure 1)

Pioglitazone use can result in significant weight gain (up to 4.7kg in PIVENS trial) and this often persists after stopping the drug.[46] In a meta-analysis of 19 trials (16,390 patients) with T2DM, pioglitazone was associated with more congestive heart failure (CHF) (2.3%) compared to the control group (1.8%) ($P = .002$), however there was no effect on mortality. [47 48] In other studies of diabetic patients, those receiving pioglitazone had an increased risk of CHF but a decrease in all-cause mortality.[49-51] For patients with CHF started on pioglitazone, careful monitoring for signs of CHF should be performed and pioglitazone should be rapidly discontinued if such symptoms arise.[45]

Pentoxifylline

Pentoxifylline (PTX) has been show to improve histologic steatosis and ballooning, possibly via a reduction in lipid oxidation.[52 53] Thirty patients with biopsy-proven NASH were treated with 1200 mg of PTX for 12 months. Steatosis and hepatocyte ballooning improved in the PTX group from baseline while no change was seen in the placebo group over the

study duration. However, the changes in histology were not significantly different between treatment groups. A second study evaluated PTX in 55 adults with biopsy-proven NASH for 12 months and used the primary endpoint of a ≥2 point decrease in NAS.[54] The primary endpoint was achieved in significantly more patients in the PTX than placebo arms (38.5% vs. 13.8%m P=0.036). These small studies suggest that PTX may have benefit in NASH and has a very good safety profile. However, until more definitive data are available, its impact on NASH remains elusive. (Figure 1)

Statins and Omega-3- Fatty Acids

HMG-CoA reductase inhibitor or "statin" use is safe for the treatment of dyslipidemia in individuals with NAFLD and statin use reduces the risk of CVD-related mortality in NAFLD, the leading cause of death in this group.[55 56] [55 57-59] Patients with indications for statin use should remain on statins even in the setting of NAFLD. However, the impact of statin use of NASH histology remains unknown. A cohort study evaluated 17 NAFLD patients treated with a statin for 10.3-16.3 years.[60] Statin use was associated with a reduction in histologic steatosis but did not impact inflammation, ballooning or fibrosis stage. A randomized controlled trial evaluated 10 patients randomized to 12 months of simvastatin or placebo and fond no difference in liver histology by treatment group.[61]

While statins do not clearly impact NAFLD histology, they may decrease the risk of NAFLD development. The St. Francis Heart Study evaluated the impact of atorvastatin 20mg daily combined with vitamin E 1000 IU and vitamin C 1 gram compared to placebo. 444 individuals had baseline and follow-up CT scans with liver/spleen ratios to assess for steatosis. Treatment with atorvastatin, vitamin E and C for a mean duration of 3.6 years was associated with a decreased prevalence of NAFLD at follow-up compared to placebo (70% vs. 34%, OR 0.29).[62] While the intervention group demonstrated a decrease in NAFLD, atorvastatin alone was not evaluated and so the impact of atorvastatin alone cannot be separated from that of vitamin E and C. Statins at this time are not recommended for the treatment or prevention of NASH. However, NAFLD patients with dyslipidemia, increased CVD risk or CVD should be managed with statins based on current guidelines without concern for increased hepatotoxicity compared to baseline population.[63]

Omega-3-fatty acids may improve radiographic steatosis at doses of 2-6 grams daily.[64-66] A recent study evaluated the impact of Omega-3-fatty acids on MR spectroscopy (MRS). The Wessex Evaluation of Fatty Liver and Cardiovascular markers in NAFLD with Omacor therapy (WELCOME) study evaluated the impact of 15-18 months of treatment with docosahexanoic acid (DHA) and eicosapentaenpoic acid (EPA) on liver fat as assessed by MRS and biomarkers of hepatic fibrosis.[67] While there was a trend toward decreased liver fat in the DHA+EPA group there was no significant difference from placebo. However, there was significant evidence of contamination in the placebo group as assessed by erythrocyte DHA and EPA enrichment, indicating that many in the placebo group were taking omega-3 fatty acids. On regression analysis, DHA enrichment was associated with decreased liver fat percentage without improvement in markers of fibrosis indicating the DHA use may reduce radiographic steatosis. However, n-3 poylunsaturated fatty acids have not been shown to improve NASH histology.[68 69] Sanyal et al., evaluated the impact of ethyl-

eicosapentanoic acid (EPA-E), a synthetic polyunsaturated fatty acid.[70] Two hundred forty-three subjects were randomized to placebo, low dose or high dose EPA-E for 12 months. EPA-E did not significantly impact steatosis, inflammation, ballooning or fibrosis. This study was limited by a 25% drop out rate and a high placebo response rate and thus may have been unable to fully assess the impact of EPA-E on NASH histology. Nonetheless, at this time omega-3-fatty acids are not recommended for treatment of NASH but are safe to use in those with NAFLD for the treatment of hypertriglyceridemia.

Endoscopic and Surgical Therapies

Limited data exist on the impact of endoscopic devices for weight loss and the treatment of NASH. Gastric balloon placement and the duodenal-jejunal bypass liner have been associated with weight loss and improvements in ALT and AST levels.[71 72] Lee et al. evaluated the impact of intra-gastric balloon compared to placebo on liver histology.[73] Eighteen patients were randomized to either intra-gastric balloon placement plus diet and exercise or diet and exercise alone for 6 months. Patients who underwent balloon placement experienced a significant decrease in BMI compared to placebo (1.52 vs 0.8, P=0.0008) and had a significant improvement in NAS when compared to control patients (2 vs. 4, P=0.03). While these results are promising, longer follow-up in larger cohorts in needed to determine the impact of endoscopic weight loss devices on NASH and fibrosis resolution.

No randomized controlled trials have been conducted to directly evaluate the impact of weight loss surgery specifically on NASH. However, several prospective cohorts have demonstrated significant improvement in NASH histology after surgery. Taitano et al. evaluated the impact of Roux-en-Y gastric bypass (RYGB) and adjustable gastric band (AGB) on NASH histology.[74] Serial biopsies were assessed on 160 patients who underwent RYGB (92%) and AGB (8%) and repeated after a mean of 31 months. In this group steatosis resolved in 75% of individuals and NASH resolution occurred in 90%. In addition, stage 2 fibrosis improved in 59% and stage 3 in 29%. Subgroup analysis by type of procedure was not performed due to the small percentage of AGBs. These findings have been replicated in other cohorts demonstrating that decreases in GGT and AST are predictive of improved histology.[75] A meta-analysis from 2008 included 15 studies evaluating the impact of weight loss surgery (predominantly RYGB) on NASH.[76] Improvement in steatohepatitis occurred in 81.3% (95% CI 61.9%-94.9%), complete NASH resolution in 69.5% (95% CI 42.4%-90.8%) and improvement in fibrosis in 65.5% (95% CI 38.2%-88.1%).

A prospective study by Mattar et al., followed 70 patients who underwent weight loss surgery with liver biopsy at the time of surgery and repeated a mean of 15 months post-op[77]. Forty-one patients underwent RYGB, 29 had ‘restrictive procedures” (sleeve gastrectomy, SG 23, AGB 6). Restrictive procedures were associated with less frequent improvement in steatosis (66% vs. 93%, P=0.004) and a trend in less frequent fibrosis improvement (28% vs. 44%, P=0.11) However, no direct comparison was made between SG and RYGB alone and the inclusion in the restrictive group of those who underwent AGB may obscure the benefits of SG.

Lassailly et al., evaluated the impact of weight loss surgery in the form of RYGB and laparoscopic gastric banding on NASH histology. 109 individuals with biopsy-proven NASH had repeat liver biopsies 12 months after surgery. Among this cohort NASH resolution occurred in 85% and fibrosis was reduced in 33.8%. Persistent NASH was associated with gastric banding and less weight loss than those with NASH resolution. This study demonstrates the benefit of RYGB for NASH and fibrosis after one year. Long term studies are needed to determine the long-term impact of RYGB on NASH histology and to compare the value of RYGB and sleeve gastrectomy for the treatment of NASH.

The impact of weight loss surgery on NAFLD likely extends beyond weight loss alone. (Figure 1) Changes in circulating hormones that occur immediately after surgery likely improve NAFLD. Glucagon-like peptide-1 (GLP-1) is secreted by L cells in the distal small intestine. It is hypothesized ("hind-gut hypothesis") that nutrient delivery to L cells leads to the secretion of GLP-1 which in turn promotes insulin secretion and suppresses glucagon secretion, improving glucose metabolism.[78] The foregut hypothesis suggests that duodenal and proximal jejunal exclusion prevent secretion of hormones/signals that may, in response to nutrient delivery, lead to insulin resistance and diabetes and could also impact NAFLD development and progression. Weight loss surgery also impacts the intestinal microbiota and this alteration in microbiota may increase energy expenditure (EE) and contribute to the weight loss induced by surgery.[79 80] Furthermore, increases in bile acids seen after surgery, may stimulate fibroblast growth factor 19 (FGF19) secretion which can decrease gluconeogenesis while increasing glycogen synthesis and EE and contribute to diabetes remission after surgery.[81] These mechanisms that alter EE and glucose metabolism likely also promote NAFLD resolution after surgery.

Conclusion

Patients with histologically defined NASH, in particular those with fibrosis, should be targeted for therapy. While not yet proven, effective treatment is likely to decrease the risk of disease progression to cirrhosis or potentially the development of complications such as HCC. Current therapy should focus on weight reduction, aerobic exercise and for specific patients, vitamin E or pioglitazone. For individuals with NASH other indications for weight loss surgery, bariatric surgery should be considered. Emerging therapies will vastly broaden the therapeutic landscape and hopefully offer effective therapy that can alter the natural history of the disease.

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Key Findings/Implications

Lifestyle modification including weight loss and exercise are the cornerstones of therapy for NASH.

Individuals with NASH, especially those with fibrosis, should be considered for treatment with vitamin E or pioglitazone.

Weight loss surgery may benefit those with NASH and should be considered in those who meet indications for surgery.

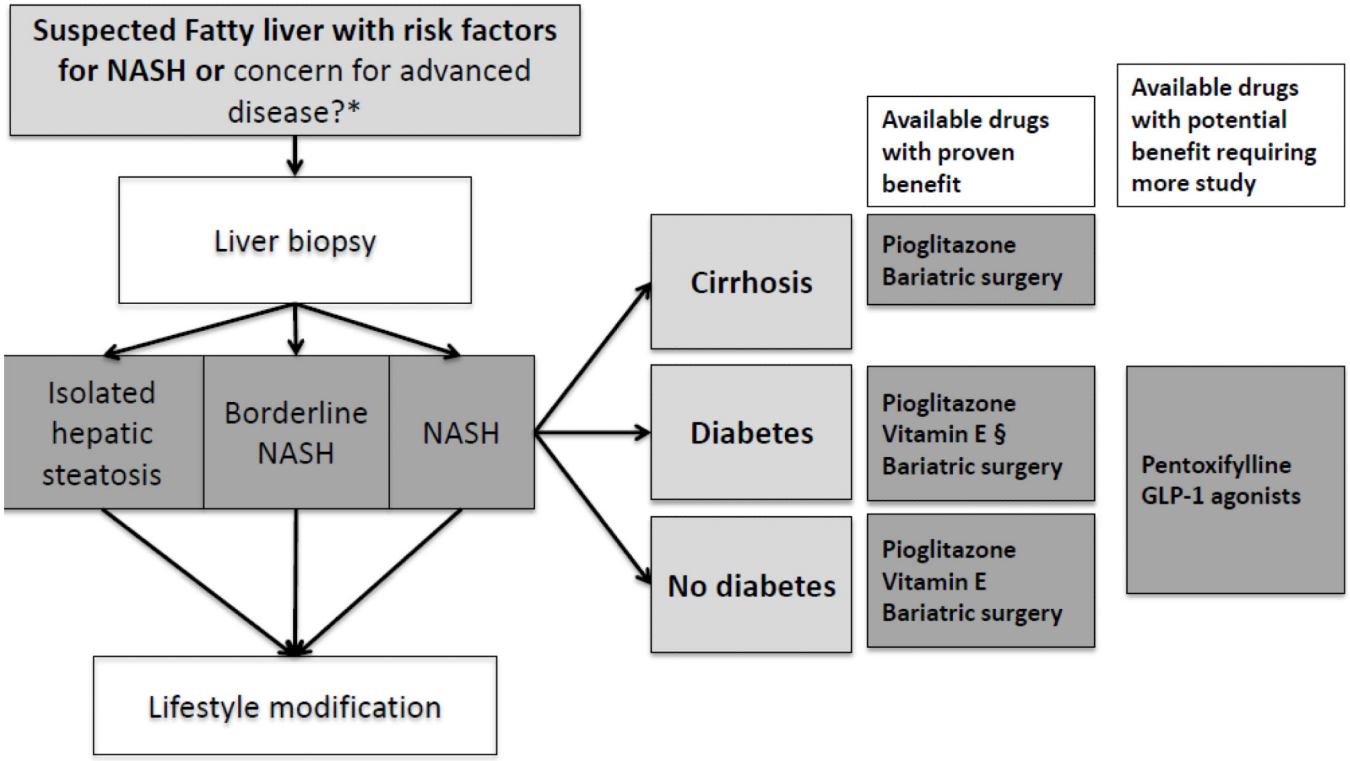

Figure 1. Algorithm for management based on histologically characterized NAFLD using available agents

Patients with isolated hepatic steatosis have a low risk of progression over time. Those with 'borderline' histology characterized by steatosis with inflammation but no cellular ballooning not meeting criteria for NASH, are less well understood and repeat biopsy 3-5 years later should be considered. Patients with NASH should be encouraged to adopt lifestyle change, however in addition may benefit from pharmacological therapy. Therapeutic options listed here only include those currently available. There are no FDA approved drugs specifically for NASH.

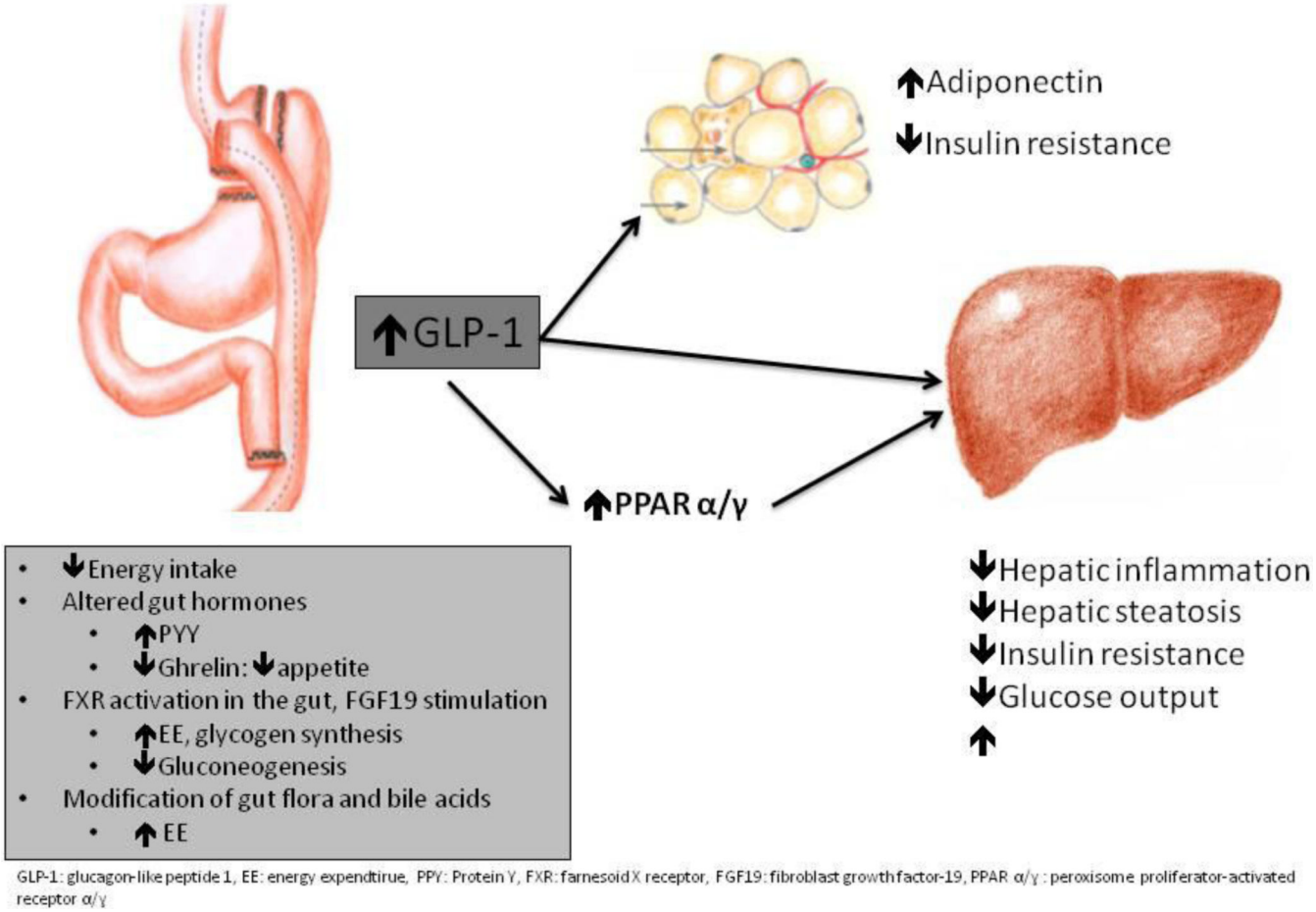

Figure 2.
Potential Impacts of Roux-en-Y Gastric Bypass on Nonalcoholic Fatty Liver Disease.

Table 1

Lifestyle Modifications for NAFLD

	Recommendations	**Impact**
Weight loss	>=7% total body weight loss	Decreases steatosis, inflammation, ballooning and NAFLD Activity Score
Diet	Mediterranean Diet	Decreases radiographic steatosis
	Limit carbohydrate consumption	Decreases radiographic steatosis
	Limit fructose consumption	Associated with reduced risk of NAFLD development, unknown impact on existing NAFLD Decreases radiographic steatosis
Lifestyle	90-120 minutes aerobic exercise weekly	Decreases radiographic steatosis
	Strength training	Decreases radiographic steatosis

Table 2

Pharmacotherapy for NAFLD

Treatment	Dose	Population	Outcomes
Recommended Treatments			
Vitamin E	800 units daily	NASH without DM	Improvement in steatosis and inflammation
Pioglitazone	30-45 mg daily	NASH with DM	Improvement in steatosis and inflammation
Investigational Treatments			
Omega-3 fatty acids	2-6 grams daily	NASH with and without DM	Improvement in radiographic steatosis, 3 RCTs ongoing
Pentoxifylline	1200mg daily	NASH	Improvement in steatosis, ballooning from baseline, not compared to placebo
Treatments Without Benefit			
Metformin	500-2000 mg daily	NASH without DM or DM w/o insulin	No benefit
Ursodiol	10-35 mg/kg	All NASH	No benefit
Orlistat	120mg thrice daily	NASH	No benefit