Published in final edited form as:
Hepatology. 2009 January ; 49(1): 306–317. doi:10.1002/hep.22603.

Non-alcoholic fatty liver disease and non-alcoholic steatohepatitis:

Selected practical issues in their evaluation and management

Raj Vuppalanchi, MD and **Naga Chalasani, MD**
Division of Gastroenterology and Hepatology, Department of Medicine, Indiana University School of Medicine, Indianapolis, IN

Nonalcoholic fatty liver disease (NAFLD) is one of the most common causes of elevated liver enzymes and chronic liver disease in the Western countries.[1-3] Its incidence in adults and children is rising rapidly due to the ongoing epidemics of obesity and type2 diabetes.[4, 5] It is a multifaceted metabolic disorder and is encountered in clinical practice by a variety of health care specialists ranging from primary care physicians and gastroenterologists to cardiologists, radiologists and gynecologists. It comprises of a spectrum of liver disease ranging from simple steatosis to full blown steatohepatitis that is characterized by steatosis, lobular inflammation, ballooning and fibrosis.[6] Over the last several years, much progress has been made in terms of our understanding of its risk factors, pathogenesis, natural history, non-invasive markers and treatment. This review is tailored towards clinicians caring for patients with NAFLD and it discusses practical issues related to selected aspects of its evaluation and management.

Evaluation of newly suspected NAFLD

Suspected NAFLD represents one of the most common reasons why patients visit gastroenterologists and hepatologists in an ambulatory setting.[1-3] While some patients may have attributable abdominal symptoms and tender hepatomegaly, the majority are asymptomatic and their liver disease identified incidentally on routine blood tests and/or abdominal imaging. Its initial assessment consists of excluding competing and co-existing etiologies and identifying clinically important co-morbidities.

Competing etiologies

The diagnosis of NAFLD requires that there is no history of previous or ongoing significant alcohol consumption. There is no consistent agreement to the definition of significant alcohol consumption but it is generally believed that average alcohol consumption more than 2 drinks per day in women and more than 3 drinks per day in men is necessary to develop alcoholic fatty liver.[7, 8] However, in individuals with metabolic risk factors such as obesity and diabetes, it is possible that alcohol consumed at lower quantities may promote hepatic steatosis. This notion is supported by a population-based study in which Ruhl and Everhart have shown that ≤ 1 alcohol drink per day causes elevated ALT only in the obese but not in normal weight individuals.[9] This study is at odds with recent epidemiological data suggesting that modest wine consumption may reduce the prevalence of NAFLD.[10]

When the alcohol consumption history is insufficient, it becomes difficult to distinguish alcoholic and non-alcoholic forms of fatty liver, especially in those with obesity and associated

Author for Correspondence Naga Chalasani, MD, Professor of Medicine, Indiana University School of Medicine, RG 4100, 1050 Wishard Boulevard, Indianapolis, IN 46202, Tel (317) 278-0414, Fax (317) 278-1949, nchalasa@iupui.edu.

metabolic risk factors. Conventional markers like GGT, MCV and AST/ALT ratio are not useful, and specific serum markers for chronic alcohol abuse are of limited utility.[11] The carbohydrate-deficient transferrin (CDT) is the most widely used and perhaps the most specific serum marker for detecting chronic alcohol abuse.[12] This test evaluates the ratio of desialylated transferrin to total transferrin and it has 81% sensitivity with 98% specificity in detecting chronic alcohol abuse. Unfortunately, this and other tests like the ratio of mitochondrial AST to total AST[13] are not readily available in clinical practice.

More recently, investigators from the Mayo clinic have developed "ALD/NAFLD Index" (ANI) that consisted of five easily available variables: mean corpuscular volume, AST and ALT values, height and weight and gender (http://www.mayoclinic.org/gi-rst/mayomodel10.html).[14] This weighted multivariate model uses logistic regression analysis to generate ANI score, and a score greater than zero incrementally favors ALD whereas a value less than zero favors NAFLD in decrement. For example, ANI of 8.95 would correspond to greater than 99% probability of alcoholic liver disease whereas a value of -5.04 would correspond to greater than 99% probability of NAFLD. As the majority with alcoholic liver disease in this study had high MELD scores, this tool is more likely applicable to patients with decompensated cirrhosis presenting for liver transplant evaluation rather than outpatients with fatty liver.

Elevated serum auto-antibodies are common in patients with NAFLD. Although low titer anti nuclear antibody (ANA) positivity can be seen in up to 33% of patients with NAFLD, ANA positivity in titers greater than 1:320 is generally rare.[15-17] Low titers of anti-smooth muscle and anti-mitochondrial antibodies may also be noted in patients with NAFLD.[18] The presence of these auto-antibodies is generally thought to be an epiphenomenon, although in one study their presence correlated with more severe histological damage.[19, 20] In patients with suspected NAFLD and ANA positivity at titers greater than 1:160 or ASMA positivity at titers greater 1:40, a liver biopsy may be considered to exclude the presence of autoimmune hepatitis.

Mildly increased serum ferritin is not uncommon in patients with NAFLD and it does not necessarily indicate co-existing iron overload.[21] Metabolic syndrome and hyperinsulinemia are known to be associated with increased serum ferritin, and this association may be mediated by the presence of NAFLD.[22] Nonetheless, elevated serum ferritin in a patient with suspect NAFLD should prompt testing for HFE gene mutations. The prevalence of HFE gene mutations in NAFLD patients has been variable depending on the population studied and their relevance remains largely unknown.[23, 24] While the prevalence of HFE gene mutations and their clinical relevance remain unclear,[22-24] homozygote or heterozygote C282Y mutations along with elevated serum ferritin may justify a liver biopsy in patients with suspected NAFLD.

It is important to verify that chronic hepatitis B and hepatitis C have been convincingly excluded, and depending on the clinical scenario, rare disorders such as alpha-1 antitrypsin deficiency and Wilson's disease should also be excluded. Thorough medication history is important as several commonly prescribed medications (e.g., tamoxifen, methotrexate, amiodarone) are noted for their ability to cause hepatic steatosis.[1]

Evaluation for co-morbidities

The patients with NAFLD frequently have many clinically significant co-morbidities (Table 1). Obesity, type2 diabetes and hyperlipidemia are well known to co-exist in patients with NAFLD, and it is important to systematically characterize them. The body mass index and waist circumference should be measured to better characterize the degree (mild, moderate and severe) and the nature (central versus peripheral) of obesity. Type2 diabetes and glucose intolerance are very frequent in patients with NAFLD and they have prognostic significance.[25] In patients without preexisting type2 diabetes, the presence of glucose intolerance and insulin

resistance should be evaluated by obtaining fasting blood glucose and insulin levels and hemoglobin A1c. In non-diabetic patients, insulin resistance should be assessed by calculating HOMA-IR (homeostasis model assessment-insulin resistance) or QUICKI (quantitative insulin-sensitivity check index).[26, 27] Both HOMA-IR and QUICKI are mathematical transformation of fasting blood glucose and insulin levels. In our practice, we calculate HOMA-IR ([fasting insulin (μU/ml) * fasting glucose (mmol/L)]/22.5), and as a general guideline, we consider a HOMA-IR value > 3 to be clinically significant.[28] If not done recently, fasting lipid profile should be obtained as dyslipidemia is nearly universal. Typically, fasting serum triglyceride levels are high along with low HDL values. Recent data suggest that high-sensitivity CRP (hs-CRP) is frequently elevated in patients with NAFLD and should be measured along with fasting lipid profile to assess cardiovascular risk (*vide infra*).[29, 30]

In addition, patients should be systematically explored for the presence of other co-morbidities such as obstructive sleep apnea,[31, 32] hypopituitarism,[33] hypothyroidism,[34] and polycystic ovary syndrome[35-37]. Obstructive sleep apnea (OSA) is commonly present in patients with NAFLD and may contribute to fatigue that sometimes these patients experience.[38] Some studies have suggested causal relationship between OSA and the pathogenesis of NAFLD but these are far from convincing.[39, 40] Previous studies have shown that patients with hypothyroidism and hypopituitarism have increased prevalence of NAFLD.[33, 34] Several studies have shown high prevalence of NAFLD in premenopausal women with polycystic ovary syndrome[35, 37] and one study[36] suggested that such individuals are at higher risk for disease progression.

Identification of NASH in patients with NAFLD

The NAFLD can be categorized into simple steatosis and steatohepatitis (NASH). A well-defined case of NASH histologically exhibits macrovesicular steatosis, lobular inflammation, balloon degeneration of hepatocytes and zone-3 pericellular fibrosis.[41] Undoubtedly, NASH is histologically progressive and can lead to cirrhosis and associated liver dysfunction. Simple steatosis has a relatively benign course but is not totally without histological consequences.[42] For example, investigators from the Cleveland Clinic reported in their initial paper that 4% of patients with simple steatosis developed cirrhosis and 2% had liver-related mortality over a median follow-up of ~ 8 years.[6] The extended follow-up of the same cohort was reported in an abstract form recently and it confirmed that simple steatosis is not entirely benign.[43]

Liver biopsy is the current gold standard to identify steatohepatitis but it is not without controversies and practical difficulties. Several recent studies have highlighted its sampling variability and inter-observer discordance.[44-46] The precise histological definition of NASH is not entirely known and the experts believe that it should be based on pattern recognition rather a composite score of individual components such as steatosis, ballooning and fibrosis.[47] It remains controversial whether ballooning or pericellular fibrosis that should be considered as critical for the histological diagnosis of NASH. The recently described NAFLD Activity Score (NAS) is valuable for quantifying histological changes, especially in clinical trials,[47] but its generalizability and diagnostic utility are unknown.

Over the past several years, there has been significant interest to non-invasively predict liver histology in patients with NAFLD. However, it remains somewhat controversial which histological finding(s) should be targeted for non-invasive assessment. Most studies to date have attempted to predict advanced fibrosis (bridging fibrosis/cirrhosis),[25, 48, 49] but it has been argued that one should attempt to predict steatohepatitis rather than advanced fibrosis.[50] It is our view that future studies should attempt to predict three histological states (simple steatosis, NASH without significant fibrosis and NASH with advanced fibrosis), rather than dichotomous descriptive states.

Aminotransferase values and common imaging tests such as liver ultrasound, computed tomography and magnetic resonance are of limited value in predicting liver histology. Numerous circulating biomarkers and prediction models have been investigated to noninvasively predict hepatic histology in patients with NAFLD (Table 2) and their full discussion is beyond the scope of this review. However, cytokeratin 18 (CK-18) fragments and serum dehydroepiandrosterone (DHEA), two hypothesis-driven circulating biomarkers, deserve further discussion. Based on experimental data that hepatocytes apoptosis may play an important role in the pathogenesis of NAFLD, Wieckowska et al. measured plasma CK-18 fragment levels in 44 consecutive individuals with suspected NAFLD undergoing liver biopsy.[51] CK-18 is a major intermediate filament protein in hepatocytes and it is cleaved by the effector caspases (mainly caspase 3) upon the activation of the apoptosis cascade.[52, 53] Compared to individuals normal histology and those without NASH, patients with definite NASH had significantly higher CK-18 fragment levels.[54] It was suggested that CK-18 fragment levels > 380.2 U/L can predict definite in a very precise fashion.[51] A puzzling and unexplained aspect of this small cross-sectional study is that nearly 25% of patients with suspected NAFLD supposedly had normal hepatic histology on liver biopsy. More recently, Charlton et al. have shown that serum DHEA levels had a consistent and stepwise inverse relationship with the degree of hepatic fibrosis that persisted after adjusting for age.[55] This observation which was initially made on a derivation cohort consisting of 122 patients was subsequently reproduced on a validation cohort consisting of 361 NAFLD patients recruited from two separate academic centers.[55] These provocative preliminary data deserve further study but it may be too optimistic to assume that a single biomarker can reliably predict histology in NAFLD, a condition with relatively complex phenotype and multiple co-morbidities.

There are numerous papers published in the literature describing non-invasive prediction models but the majority of them consisted of small sample size and lacked rigorous external validation. Three recently described models with relatively large sample size and some level of validation have shown encouraging results.[56-58] In a multicenter study consisted of 480 patients in the derivation and 253 in the validation cohorts, Angulo et al.[56] have shown that NAFLD fibrosis score consisting of 6 variables (age, BMI, AST/ALT ratio, hyperglycemia, platelet count and albumin) can reliably predict advanced fibrosis. The formula for the fibrosis score was " $-1.675 + 0.037 \times age\ (years) + 0.094 \times BMI\ (kg/m2) + 1.13 \times impaired\ glucose\ tolerance/diabetes\ (yes=1, no=0) + 0.99 \times AST/ALT\ ratio - 0.013 \times platelets\ (X10^9/l) - 0.66 \times albumin\ (g/dl)$", and a low cutoff point (score < -1.455) signified the absence of advanced fibrosis whereas a high cutoff point (score > 0.676) identified advanced fibrosis. It was concluded that NAFLD fibrosis score can be utilized as a triaging tool for optimizing liver biopsy yield in terms of identifying or excluding advanced fibrosis. More recently, Guha et al.[57] have compared the performance of "Enhanced Liver Fibrosis" (ELF) score to that of the "NAFLD Fibrosis Score" in predicting advanced fibrosis. The ELF is essentially the "Original European Liver Fibrosis" (OELF) test without "age" included in the algorithm. The OELF test, a model consisting of age and three serum markers of matrix turnover (TIMP 1, hyaluronic acid and P3NP), predicted advanced fibrosis in a variety of liver disorders.[59] In this report, the ELF score had excellent ability to predict different levels of fibrosis (any fibrosis, moderate fibrosis, or advanced fibrosis) and when it was combined with the "NAFLD fibrosis score", its ability to predict different levels of fibrosis improved further.[57] Harrison et al. have recently developed BARD score to predict advanced fibrosis in patients with NAFLD[57]. The BARD score is a weighted sum of three easily available variables [BMI > 28 kg/m^2 (1 point), AST/ALT $\geq$ 0.8 (2 points) and diabetes (1 point)] and authors have shown that a score of 2-4 was associated with an odds ratio 17 (95% CI: 9.2-31.9) for predicting advanced fibrosis[57]. These promising models will need to be validated by external investigators before they are recommended for wide clinical use.

One French study tested "Fibrotest" for predicting advanced fibrosis in NAFLD and found encouraging results.[60] "Fibrotest" is a popular serum test for predicting advanced fibrosis in individuals with chronic hepatitis C, but more studies are needed to test its utility in NAFLD. Similarly, liver stiffness measured by transient elastography (FibroScan) may have some role in predicting the degree of fibrosis, but the data are sparse in terms of its utility in NAFLD.[61, 62]

In summary, there has been significant research in developing biomarkers of liver histology in patients with NAFLD, and in fact one editorialist recently opined that the future is around the corner for non-invasive diagnosing progressive NASH.[63] While this may be the case for advanced fibrosis, insufficient attention has been paid to developing markers for non-invasively identifying steatohepatitis in patients with NAFLD. Until more definite data with external validation become available, we will continue to our current practice of recommending liver biopsy to selected patients with suspected NAFLD based on the presence of certain risk factors such as older age, diabetes, severe obesity and metabolic syndrome.

Management of patients with NAFLD

Advice regarding weight loss, exercise and specific diets

The NAFLD is largely a manifestation of obesity and metabolic syndrome and is characterized by excess calorie intake and lack of optimal health-related fitness or physical activity.[64] It is generally believed that weight loss is beneficial for patients with NAFLD, but data are sparse in terms of specifics such as *how*, *how much* and *how rapidly* to lose weight. Furthermore, precise hepatic and extrahepatic benefits of weight loss are not well defined. In a recent review, Bellentani et al.[65] pointed out that there are only four human studies consisting of less than 40 total patients that evaluated the effect of calorie restriction alone, and change in liver enzymes was the primary end point in all but one study. There are 10 published studies consisting of 626 total patients that evaluated the effect of calorie restriction combined with exercise, but liver histology was the primary end point in only four studies (123 patients).[65] This paucity of data makes it difficult to make evidence-based recommendations about dietary modification and exercise to treat NAFLD and NASH.

It is generally recommended that overweight and obese patients with NAFLD lose 7-10% of their body weight by dietary modification and exercise over the course of 6-12 months. This is based on short-term studies showing that gradual weight loss of this magnitude improves insulin resistance and hepatic histology.[3, 66] Our recommendations to enhance patient compliance with lifestyle modifications are shown in Table 3. Scientific evidence is lacking to make precise recommendations specific to modifying macronutrient composition, but it appears sensible to recommend low glycemic food with decreased saturated and trans-fat intake but increased mono and polyunsaturated fatty acid intake.[67] Evolving data suggest diets consisting of high fructose should be avoided by these patients.[68] Due to lack of safety and efficacy data, popular weight-loss diets such as Atkins, Ornish and South Beach diets should not be recommended.[67] In our clinical practice, we recommend diminished portions of balanced diet (consisting of low glycemic and low fat diet and increased portions of fruits and vegetables) and 5-7 sessions per week of moderate aerobic exercise with each session lasting for 30-45 minutes. However, such prescriptive recommendations made in a clinic setting are rarely effective both short term or long term.[65]

Orlistat, a reversible inhibitor of gastric and pancreatic lipase, may be effective in promoting limited weight loss in selected patients, but side effects such as diarrhea and bloating make it less desirable. In a randomized study, Harrison et al. have shown that orlistat does not cause weight loss or histological improvement above and beyond that is accomplished with calorie restriction alone.[69] Rimonabant (endocannabinoid receptor 1 antagonist) is approved in Europe

for promoting weight loss, and it may have favorable anti-steatotic and anti-fibrotic properties.[70-74] Large clinical trials are underway with this and other similar compounds in NASH but their results will not become available for at least several years.

Advice regarding bariatric surgery

As many patients with NAFLD have severe obesity, it often comes up in clinical practice whether bariatric surgery in suitable in this patient population. Jejunoileal bypass was widely popular in mid-1950s to mid-1970s for the surgical treatment of obesity but due to disastrous hepatic and extrahepatic consequences it is now totally abandoned.[75-77] Over the last decade, an increasing number of foregut bariatric surgery procedures are being performed to treat obesity and its complications, and its short and long term benefits are becoming well established.[78-80] The commonly performed foregut bariatric surgery procedures include roux-en-Y gastric bypass (most common), adjustable gastric banding, gastroplasty and sleeve gastrectomy.[81, 82] To date, there have been no studies that evaluated foregut bariatric surgery to specifically treat NAFLD but many published papers described its favorable effect of hepatic histology when performed for other indications and thus introducing selection bias .[78-80] In general, liver histology improves significantly following foregut bariatric surgery with very minimal risk of worsening.[83, 84] In a recent meta-analysis consisting of 15 studies and 766 paired liver biopsies, Mummadi et al.[84] have shown that all components of NAFLD show significant improvement following foregut bariatric surgery. Pooled proportion of patients with improvement or resolution in steatosis was 93% (95% CI: 84-98%), with improvement or resolution of steatohepatitis was 82% (95% CI: 64 - 95%), with improvement in fibrosis when assessed using needle biopsies was 73% (95% CI: 65 - 81%). We speculate that liver disease is unlikely to worsen in association with rapid and profound weight loss unless there are additional risks such as bacterial overgrowth (e.g., jejunoileal bypass) or nutrient depletion (e.g., kwashiorkor). This forms the basis for our view that very long roux limb (i.e., > 150 cms) should be avoided in patients with advanced fibrosis. Compensated cirrhosis is not a contraindication for foregut bariatric surgery provided it is performed by an experienced surgeon and clinically evident portal hypertension is absent (no esophageal or abdominal varices). There are reports that cirrhosis may reverse following bariatric surgery.[85, 86]

In our practice, we recommend foregut bariatric surgery as a therapeutic possibility for the severely obese NAFLD patients with advanced fibrosis who failed to lose weight despite repeated nutritional counseling. In those with cirrhosis, we exclude clinical portal hypertension by performing abdominal imaging and upper endoscopy. Bariatric surgery may be particular attractive for carefully selected patients with Child's A cirrhosis not only because it may stabilize or improve the liver disease but it also may enhance their future suitability for liver transplantation.

Role of insulin sensitizers

As insulin resistance is nearly universal in patients with NASH, it is not surprising that many studies tested insulin sensitizers as its treatment. However, a large number of them are proof-of concept studies with small number of patients without rigorous study design, making it difficult to make definite recommendations. Biguanides (metformin) and thiazolidinediones (pioglitazone and rosiglitazone) are the two classes of insulin sensitizers studied in humans.

Metformin—Although its exact mechanism of action is not entirely clear, its therapeutic benefit as an anti-diabetic agent and insulin sensitizer is well recognized. Its anti-diabetic action is likely related to decreased hepatic gluconeogenesis, decreased glucose absorption and increased insulin sensitivity by facilitating glucose uptake and utilization.[86, 87] In addition, its stimulatory effect on AMP activated protein kinase or modulation of hepatic TNFα expression may be benefit favorably.[88]89 A summary of studies evaluating metformin to treat NASH is

shown in Table 4. A recent meta-analysis published in Cochrane database showed that metformin leads to normalization of serum aminotransferases in a significantly greater proportion of patients compared to dietary modification (OR: 2.83, 95% CI: 1.27 - 6.31and improved steatosis by imaging (OR: 5.25, 95% CI: 1.09 - 25.21).[90] The total number of patients treated with metformin in controlled studies is admittedly small and its favorable effect on hepatic histology may not be robust, but we favor its use in non-diabetic patients with NASH because of its safety profile. As most non-diabetic patients with NASH have glucose intolerance, it has the added benefit of lowering the risk of developing frank diabetes.[91] As metformin has not been studied to treat NASH in diabetic individuals, its role in diabetic population is not known. An ongoing, multicenter study comparing metformin to vitamin E or placebo in pediatric patients with NASH (TONIC; NCT00063635) should provide more insight into metformin's role in treating NASH.

Thiazolidinediones (TZD)

TZDs are a novel class of oral anti-diabetic medications that improve insulin resistance by acting as selective PPAR-γ agonists.[92, 93] Troglitazone, the first generation TZD, has been withdrawn from the market due to its hepatotoxicity[94] whereas rosiglitazone and pioglitazone are the second generation TZDs that are currently available for clinical use.[93, 95] They redistribute fat from muscle and liver to adipose tissue and thereby improving peripheral (skeletal muscle) and hepatic insulin sensitivity.[93] In addition, they increase circulating levels of adiponectin which is produced exclusively by the adipose tissue and has insulin sensitizing properties.[96]

There has been significant interest in evaluating TZDs to treat NASH, and to our knowledge, eight studies have been published either as full length papers or solely as an abstract to date.[97-104] Troglitazone was tested in one study[97] whereas rosiglitazone in 2[98, 103] and pioglitazone in 5 studies.[99-102, 104] Four were randomized controlled studies with 213 total enrolled patients with histologically proven NASH.[101-104] Selected characteristics and outcomes of three studies that randomized at least 50 patients are shown in Table 5. In general, TZDs improve hepatic histology in patients with NASH although their favorable effect on steatosis is more striking than on other histological variables such as inflammation, ballooning or fibrosis. Their favorable effect on liver histology and liver biochemistries disappears upon their discontinuation, suggesting that long term treatment is needed to maintain their therapeutic benefits[105]. This is potentially a significant issue as recent studies questioned the long term safety of TZDs (especially rosiglitazone)[106]. As majority of the participants in these studies were non-diabetic, it is not clear if TZDs are equally effective in diabetics with NASH. In fact, the presence of diabetes was a negative predictor of response to rosiglitazone in one study.[103] Furthermore, Ratziu et al. recently raised the possibility that TZDs alone without lifestyle modification may not be as effective.[103] Overall, there are more questions than answers about the role of TZDs in patients with NASH and the ongoing large US multicenter study (PIVENS; NCT00063622) may provide some additional insight.

Promising agents

There is intense research into developing suitable treatment for NASH and a list of compounds that are being tested to treat NASH in humans is shown in Table 6. Oral endocannabinoid receptor (CB1 receptor) antagonists are of potential benefit due to multiple potential favorable effects (on body weight, fibrogenesis and de novo lipogenesis) and large multicenter studies are underway. Neuropsychiatric side-effects are concern, but if proven effective, they may have a role at least in a select group of patients without underlying neuropsychiatric co-morbidities. The CB-1 receptor antagonist studies in humans have just begun and their results will not be available for few years. Based on promising animal data[107] and its ability to promote

weight loss[108], we have initiated an open-label study of exenatide in 2006, but its recruitment has been hampered due to its injectable route of administration and potential GI side effects.

Cardiovascular disease in NAFLD

The cardiovascular morbidity and mortality is perhaps one of the most important aspects of NAFLD and NASH, and our knowledge of their association is evolving rapidly.[109-112] The patients with NAFLD have very high prevalence of cardiovascular risk factors and atherosclerosis and high incidence of cardiovascular morbidity and mortality.[43, 113, 114] Over the last decade, numerous studies have demonstrated that patients with NAFLD are enriched with classic cardiovascular risk factors such as obesity, insulin resistance and type2 diabetes, dyslipidemia, and the metabolic syndrome.[115-117] Cross-sectional studies consisting of control groups have shown increased prevalence of endothelial dysfunction, [118] elevated levels of ox-LDL,[119] Framingham coronary risk scores [109, 119] in NAFLD patients. Cross-sectional studies have also shown increased prevalence of premature atheroma formation,[120] carotid artery intima media thickness (surrogate for atherosclerosis),[121, 122] vulnerable coronary plaques, [123] increased mediastinal fat and abnormal left ventricular energy metabolism.[124] Recently it has been suggested that NAFLD poses cardiovascular risk above and beyond that is conferred by the presence of the metabolic syndrome.[43, 113, 114, 125] In a nested case-control, prospective study, Targher et al. have shown that NAFLD in diabetic individuals is associated with moderately increased risk of incident cardiovascular disease even after adjusting for classic risk factors, glycemic control and the metabolic syndrome.[125] Most importantly, several longitudinal studies have shown that cardiovascular disease is much more common than liver disease as a cause of death in patients with NAFLD.[43, 113, 114] In a longitudinal study consisting of 420 Olmsted county residents with NAFLD, Adams et al.[113] have shown that ischemic heart disease accounts of 25% of deaths, compared to liver disease accounting for 13% of deaths. By linking the NHANES III to Linked Mortality Files, Ong et al.[114] have shown that cardiovascular disease is the most common cause of death and it exceeds that of liver disease among 817 individuals with suspected NAFLD in comparison to 10,468 persons without liver disease. More recently, Rafiq et al.[43] have reported extended follow-up of an expanded NAFLD cohort that has been described previously. The mortality rate over an 11.1 year median follow-up (longest f/u 28.5 years) was 45% and the most common cause of death was coronary artery disease. All these data provide unequivocal evidence that coronary artery disease is a serious threat to patients with NAFLD. Therefore, it has become our practice to emphasize the significance of cardiovascular disease to patients with NAFLD and their primary care providers.

Statins remain a cornerstone for managing dyslipidemia and coronary artery disease. Despite initial concerns, several recent studies have shown that statins can be safely used in patients with underlying liver disease.[126-129] Studies have not been conducted to specifically show that statins diminish cardiovascular morbidity and mortality in patients with NAFLD but there are no suspected reasons why they would be any less effective. Minor fluctuations in aminotransferases upon initiating statin therapy are not uncommon but serious hepatotoxicity is quite rare[126] and even when happens, it is almost universally reversible upon prompt recognition and withdrawal of the offending agent.[127]

In summary, when a patient with suspected NAFLD seen in the clinic it is important to carefully evaluate for competing etiologies and clinically important co-morbidities. Many advances have been made in terms of non-invasive biomarkers for predicting advanced fibrosis but insufficient attention has been paid to predicting steatohepatitis. Sustained weight loss can be effective to treat NASH but it is difficult to achieve. Foregut bariatric surgery can be quite effective in improving hepatic histology in selected patients without liver failure or significant portal hypertension. TZDs have shown promise but recent studies raised doubts about their long term

safety. Large multicenter studies of CB1 receptor antagonists are underway but their results will not be available for several years. Several recommendations made in this review are not entirely evidence-based and thus should be cautiously accepted while we await more data and practice guidelines by the consensus of the experts. There is an ongoing effort to develop a multi-society (AASLD ACG, ACP and AGA) consensus practice guideline for managing patients with NAFLD and this would clearly identify the level of evidence available for different recommendations.

Acknowledgements

This work in part was supported by PHS grant K24 DK072101 (to N.C.). Dr. Chalasani has served as a paid consultant to Atherogenics, Pfizer, Takeda, Advanced Life Sciences, Karo-Bio, Metabasis and Eli-Lilly over the past 12-months. He has agreements to conduct clinical trials related to fatty liver disease with Debiovision, Sanofi-Aventis, Pfizer and Gilead.

Abbreviations

NAFLD, Non-alcoholic fatty liver disease; NASH, Nonalcoholic steatohepatitis; NAS, NAFLD Activity Score; HOMA-IR, Homeostatic Model Assessment - Insulin Resistance; TZD, Thiazolidinediones; ELF, Enhanced Liver Fibrosis Score.

References

1. Angulo P. Nonalcoholic fatty liver disease. N Engl J Med 2002;346:1221–31. [PubMed: 11961152]
2. Clark JM, Brancati FL, Diehl AM. The prevalence and etiology of elevated aminotransferase levels in the United States. Am J Gastroenterol 2003;98:960–7. [PubMed: 12809815]
3. Torres DM, Harrison SA. Diagnosis and therapy of nonalcoholic steatohepatitis. Gastroenterology 2008;134:1682–98. [PubMed: 18471547]
4. Fraser A, Longnecker MP, Lawlor DA. Prevalence of elevated alanine aminotrasferase among US adolescents and associated factors: NHANES 1999-2004. Gastroenterology 2007;133:1814–20. [PubMed: 18054554]
5. Charlton M. Nonalcoholic fatty liver disease: a review of current understanding and future impact. Clin Gastroenterol Hepatol 2004;2:1048–58. [PubMed: 15625647]
6. Matteoni CA, Younossi ZM, Gramlich T, Boparai N, Liu YC, McCullough AJ. Nonalcoholic fatty liver disease: a spectrum of clinical and pathological severity. Gastroenterology 1999;116:1413–9. [PubMed: 10348825]
7. McCullough AJ, O'Connor JF. Alcoholic liver disease: proposed recommendations for the American College of Gastroenterology. Am J Gastroenterol 1998;93:2022–36. [PubMed: 9820369]
8. Coates RA, Halliday ML, Rankin JG, Feinman SV, Fisher MM. Risk of fatty infiltration or cirrhosis of the liver in relation to ethanol consumption: a case-control study. Clin invest Med 1986;9:26–32. [PubMed: 3955918]
9. Ruhl CE, Everhart JE. Joint effects of body weight and alcohol on elevated serum alanine aminotransferase in the United States population. Clin Gastroenterol Hepatol 2005;3:1260–8. [PubMed: 16361053]
10. Dunn W, Xu R, Schwimmer JB. Modest wine drinking and decreased prevalence of suspected nonalcoholic fatty liver disease. Hepatology 2008;47:1947–54. [PubMed: 18454505]
11. Conigrave KM, Degenhardt LJ, Whitfield JB, Saunders JB, Helander A, Tabakoff B. CDT, GGT, and AST as markers of alcohol use: the WHO/ISBRA collaborative project. Alcohol Clin Exp Res 2002;26:332–9. [PubMed: 11923585]
12. Anton RF, Dominick C, Bigelow M, Westby C. Comparison of Bio-Rad %CDT TIA and CDTect as laboratory markers of heavy alcohol use and their relationships with gamma-glutamyltransferase. Clin Chem 2001;47:1769–75. [PubMed: 11568085]

13. Nalpas B, Vassault A, Poupon RE, Pol S, Berthelot P. An overview of serum mitochondrial aspartate aminotransferase (mAST) activity as a marker of chronic alcohol abuse. Alcohol Alcohol Suppl 1991;1:455–7. [PubMed: 1845577]

14. Dunn W, Angulo P, Sanderson S, Jamil LH, Stadheim L, Rosen C, Malinchoc M, Kamath PS, Shah VH. Utility of a new model to diagnose an alcohol basis for steatohepatitis. Gastroenterology 2006;131:1057–63. [PubMed: 17030176]

15. Cotler SJ, Kanji K, Keshavarzian A, Jensen DM, Jakate S. Prevalence and significance of autoantibodies in patients with non-alcoholic steatohepatitis. J Clin Gastroenterol 2004;38:801–4. [PubMed: 15365409]

16. Cho DH, Choi MS, Kim DH, Kim DY, Shim SG, Lee JH, Koh KC, Paik SW, Yoo BC, Rhee JC. A prospective study on the prevalence and clinical significance of autoantibodies in patients with suspected nonalcoholic fatty liver disease. Korean J Hepatol 2005;11:261–7. [PubMed: 16177552]

17. Yatsuji S, Hashimoto E, Kaneda H, Taniai M, Tokushige K, Shiratori K. Diagnosing autoimmune hepatitis in nonalcoholic fatty liver disease: is the International Autoimmune Hepatitis Group scoring system useful? J Gastroenterol 2005;40:1103–8.

18. Loria P, Lonardo A, Leonardi F, Fontana C, Carulli L, Verrone AM, Borsatti A, Bertolotti M, Cassani F, Bagni A, Muratori P, Ganazzi D, Bianchi FB, Carulli N. Non-organ-specific autoantibodies in nonalcoholic fatty liver disease: prevalence and correlates. Dig Dis Sci 2003;48:2173–81. [PubMed: 14705824]

19. Niwa H, Sasaki M, Haratake J, Kasai T, Katayanagi K, Kurumaya H, Masuda S, Minato H, Zen Y, Uchiyama A, Miwa A, Saito K, Sudo Y, Nakanuma Y. Clinicopathological significance of antinuclear antibodies in non-alcoholic steatohepatitis. Hepatol Res 2007;37:923–31. [PubMed: 17610500]

20. Adams LA, Lindor KD, Angulo P. The prevalence of autoantibodies and autoimmune hepatitis in patients with nonalcoholic Fatty liver disease. Am J Gastroenterol 2004;99:1316–20. [PubMed: 15233671]

21. Bacon BR, Farahvash MJ, Janney CG, Neuschwander-Tetri BA. Nonalcoholic steatohepatitis: an expanded clinical entity. Gastroenterology 1994;107:1103–9. [PubMed: 7523217]

22. Fargion S, Mattioli M, Fracanzani AL, Sampietro M, Tavazzi D, Fociani P, Taioli E, Valenti L, Fiorelli G. Hyperferritinemia, iron overload, and multiple metabolic alterations identify patients at risk for nonalcoholic steatohepatitis. Am J Gastroenterol 2001;96:2448–55. [PubMed: 11513189]

23. Lin TJ, Lin CL, Wang CS, Liu SO, Liao LY. Prevalence of HFE mutations and relation to serum iron status in patients with chronic hepatitis C and patients with nonalcoholic fatty liver disease in Taiwan. World J Gastroenterol 2005;11:3905–8. [PubMed: 15991291]

24. Chitturi S, Weltman M, Farrell GC, McDonald D, Kench J, Liddle C, Samarasinghe D, Lin R, Abeygunasekera S, George J. HFE mutations, hepatic iron, and fibrosis: ethnic-specific association of NASH with C282Y but not with fibrotic severity. Hepatology 2002;36:142–9. [PubMed: 12085358]

25. Angulo P, Keach JC, Batts KP, Lindor KD. Independent predictors of liver fibrosis in patients with nonalcoholic steatohepatitis. Hepatology 1999;30:1356–62. [PubMed: 10573511]

26. Bonora E, Targher G, Alberiche M, Bonadonna RC, Saggiani F, Zenere MB, Monauni T, Muggeo M. Homeostasis model assessment closely mirrors the glucose clamp technique in the assessment of insulin sensitivity: studies in subjects with various degrees of glucose tolerance and insulin sensitivity. Diabetes Care 2000;23:57–63. [PubMed: 10857969]

27. Muniyappa R, Lee S, Chen H, Quon MJ. Current approaches for assessing insulin sensitivity and resistance in vivo: advantages, limitations, and appropriate usage. Am J Physiol Endocrinol Metab 2008;294:E15–26. [PubMed: 17957034]

28. Stern SE, Williams K, Ferrannini E, DeFronzo RA, Bogardus C, Stern MP. Identification of individuals with insulin resistance using routine clinical measurements. Diabetes 2005;54:333–9. [PubMed: 15677489]

29. Yoneda M, Mawatari H, Fujita K, Iida H, Yonemitsu K, Kato S, Takahashi H, Kirikoshi H, Inamori M, Nozaki Y, Abe Y, Kubota K, Saito S, Iwasaki T, Terauchi Y, Togo S, Maeyama S, Nakajima A. High-sensitivity C-reactive protein is an independent clinical feature of nonalcoholic steatohepatitis

(NASH) and also of the severity of fibrosis in NASH. J Gastroenterol 2007;42:573–82. [PubMed: 17653654]

30. Targher G, Bertolini L, Rodella S, Lippi G, Franchini M, Zoppini G, Muggeo M, Day CP. NASH predicts plasma inflammatory biomarkers independently of visceral fat in men. Obesity (Silver Spring) 2008;16:1394–9. [PubMed: 18369343]
31. Singh H, Pollock R, Uhanova J, Kryger M, Hawkins K, Minuk GY. Symptoms of obstructive sleep apnea in patients with nonalcoholic fatty liver disease. Dig Dis Sci 2005;50:2338–43. [PubMed: 16416185]
32. Kallwitz ER, Herdegen J, Madura J, Jakate S, Cotler SJ. Liver enzymes and histology in obese patients with obstructive sleep apnea. J Clin Gastroenterol 2007;41:918–21. [PubMed: 18090161]
33. Adams LA, Feldstein A, Lindor KD, Angulo P. Nonalcoholic fatty liver disease among patients with hypothalamic and pituitary dysfunction. Hepatology 2004;39:909–14. [PubMed: 15057893]
34. Liangpunsakul S, Chalasani N. Is hypothyroidism a risk factor for non-alcoholic steatohepatitis? J Clin Gastroenterol 2003;37:340–3. [PubMed: 14506393]
35. Cerda C, Perez-Ayuso RM, Riquelme A, Soza A, Villaseca P, Sir-Petermann T, Espinoza M, Pizarro M, Solis N, Miquel JF, Arrese M. Nonalcoholic fatty liver disease in women with polycystic ovary syndrome. J Hepatol 2007;47:412–7. [PubMed: 17560682]
36. Setji TL, Holland ND, Sanders LL, Pereira KC, Diehl AM, Brown AJ. Nonalcoholic steatohepatitis and nonalcoholic Fatty liver disease in young women with polycystic ovary syndrome. J Clin Endocrinol Metab 2006;91:1741–7. [PubMed: 16492691]
37. Gambarin-Gelwan M, Kinkhabwala SV, Schiano TD, Bodian C, Yeh HC, Futterweit W. Prevalence of nonalcoholic fatty liver disease in women with polycystic ovary syndrome. Clin Gastroenterol Hepatol 2007;5:496–501. [PubMed: 17287148]
38. Newton JL, Jones DE, Henderson E, Kane L, Wilton K, Burt AD, Day CP. Fatigue in non-alcoholic fatty liver disease (NAFLD) is significant and associates with inactivity and excessive daytime sleepiness but not with liver disease severity or insulin resistance. Gut 2008;57:807–13. [PubMed: 18270241]
39. Kheirandish-Gozal L, Sans Capdevila O, Kheirandish E, Gozal D. Elevated serum aminotransferase levels in children at risk for obstructive sleep apnea. Chest 2008;133:92–9. [PubMed: 18187742]
40. Tanne F, Gagnadoux F, Chazouilleres O, Fleury B, Wendum D, Lasnier E, Lebeau B, Poupon R, Serfaty L. Chronic liver injury during obstructive sleep apnea. Hepatology 2005;41:1290–6. [PubMed: 15915459]
41. Brunt EM. Pathology of nonalcoholic steatohepatitis. Hepatol Res 2005;33:68–71. [PubMed: 16214395]
42. de Alwis NM, Day CP. Non-alcoholic fatty liver disease: the mist gradually clears. J Hepatol 2008;48 (Suppl 1):S104–12. [PubMed: 18304679]
43. Rafiq N, Bai C, Fand Y, Srishord mk, McCullough AJ, Younossi ZM. Over twenty five years of follow up for a Non-Alcoholic Fatty Liver Disease Cohort. Gastroenterology 2008;134:A754–A754.
44. Ratziu V, charlotte F, Heurtier A, Gombert S, Giral P, Bruckert E, Grimaldi A, Capron F, Poynard T. Sampling variability of liver biopsy in nonalcoholic fatty liver disease. Gastroenterology 2005;128:1898–906. [PubMed: 15940625]
45. Merriman RB, Ferrell LD, Patti MG, Weston SR, Pabst MS, Aouizerat BE, Bass NM. Correlation of paired liver biopsies in morbidly obese patients with suspected nonalcoholic fatty liver disease. Hepatology 2006;44:874–80. [PubMed: 17006934]
46. Vuppalanchi R, Unalp A, Natta MV, Cummings O, Wass J, Tonascia J, Chalasani N. Increased diagnostic yield from liver biopsy in suspected NAFLD using multiple cores and mutiple readings. Gastroenterology 2007;132:A809.
47. Kleiner DE, Brunt EM, Van Natta M, Behling C, Contos MJ, Cummings OW, Ferrell LD, Liu YC, Torbenson MS, Unalp-Arida A, Yeh M, McCullough AJ, Sanyal AJ. Design and validation of a histological scoring system for nonalcoholic fatty liver disease. Hepatology 2005;41:1313–21. [PubMed: 15915461]
48. Alazmi WM, Regev A, Molina EG, Schiff ER. Predictors of cirrhosis in Hispanic patients with nonalcoholic steatohepatitis. Dig Dis Sci 2006;51:1725–9. [PubMed: 16958001]

49. Kang H, Greenson JK, Omo JT, Chao C, Peterman D, Anderson L, Foess-Wood L, Sherbondy MA, Conjeevaram HS. Metabolic syndrome is associated with greater histologic severity, higher carbohydrate, and lower fat diet in patients with NAFLD. Am J Gastroenterol 2006;101:2247–53. [PubMed: 17032189]
50. Wilson S, Chalasani N. Noninvasive markers of advanced histology in nonalcoholic fatty liver disease: are we there yet? Gastroenterology 2007;133:1377–8. [PubMed: 17919509]discussion 1378-9
51. Wieckowska A, Zein NN, Yerian LM, Lopez AR, McCullough AJ, Feldstein AE. In vivo assessment of liver cell apoptosis as a novel biomarker of disease severity in nonalcoholic fatty liver disease. Hepatology 2006;44:27–33. [PubMed: 16799979]
52. Leers MP, Kolgen W, Bjoklund V, Bergman T, Tribbick G, Persson B, Bjorklund P, Ramaekers FC, Bjorklund B, Nap M, Jornvall H, Schutte B. Immunocytochemical detection and mapping of a cytokeratin 18 neo-epitope exposed during early apoptosis. J Pathol 1999;187:567–72. [PubMed: 10398123]
53. Yilmaz Y, Dolar E, Ulukaya E, Akgoz S, Keskin M, Kiyici M, Aker S, Yilmaztepe A, Gurel S, Gulten M, Nak SG. Soluble forms of extracellular cytokeratin 18 may differentiate simple steatosis from nonalcoholic steatohepatitis. World J Gastroenterol 2007;13:837–44. [PubMed: 17352011]
54. Feldstein AE, Canbay A, Angulo P, Taniai M, Burgart LJ, Lindor KD, Gores GJ. Hepatocyte apoptosis and fas expression are prominent features of human nonalcoholic steatohepatitis. Gastroenterology 2003;125:437–43. [PubMed: 12891546]
55. Charlton M, Angulo P, Chalasani N, Merriman R, Viker K, charatcharoenwitthaya P, Sanderson S, Gawrieh S, Krishnan A, Lindor K. Low circulating levels of dehydroepiandrosterone in histologically advanced nonalcoholic fatty liver disease. Hepatology 2008;47:484–92. [PubMed: 18220286]
56. Angulo P, Hui JM, Marchesini G, Bugianesi E, George J, Farrell GC, Enders F, Saksena S, Burt AD, Bida JP, Lindor K, Sanderson SO, Lenzi M, Adams LA, Kench J, Therneau TM, Day CP. The NAFLD fibrosis score: a noninvasive system that identifies liver fibrosis in patients with NAFLD. Hepatology 2007;45:846–54. [PubMed: 17393509]
57. Guha IN, Parkes J, Roderick P, Chattopadhyay D, Cross R, Harris S, Kaye P, Burt AD, Ryder SD, Aithal GP, Day CP, Rosenberg WM. Noninvasive markers of fibrosis in nonalcoholic fatty liver disease: Validating the European Liver Fibrosis Panel and exploring simple markers. Hepatology 2008;47:455–60. [PubMed: 18038452]
58. Harrison SM, Oliver D, Arnold HLM, Gogia SM, Neuschwander-Tetri BAM. Development and Validation of a Simple NAFLD Clinical Scoring System for Identifying Patients Without Advanced Disease. Gut. 2008
59. Rosenberg WM, Voelker M, Thiel R, Becka M, Burt A, Schuppan D, Hubscher S, Roskams T, Pinzani M, Arthur MJ. Serum markers detect the presence of liver fibrosis: a cohort study. Gastroenterology 2004;127:1704–13. [PubMed: 15578508]
60. Ratziu V, Massard J, Charlotte F, Messous D, Imbert-Bismut F, Bonyhay L, Tahiri M, Munteanu M, Thabut D, Cadranel JF, Le Bail B, de Ledinghen V, Poynard T. Diagnostic value of biochemical markers (FibroTest-FibroSURE) for the prediction of liver fibrosis in patients with non-alcoholic fatty liver disease. BMC Gastroenterol 2006;6:6. [PubMed: 16503961]
61. Yoneda M, Mawatari H, Fujita K, Endo H, Iida H, Nozaki Y, Yonemitsu K, Higurashi T, Takahashi H, Kobayashi N, Kirikoshi H, Abe Y, Inamori M, Kubota K, Saito S, Tamano M, Hiraishi H, Maeyama S, Yamaguchi N, Togo S, Nakajima A. Noninvasive assessment of liver fibrosis by measurement of stiffness in patients with nonalcoholic fatty liver disease (NAFLD). Dig Liver Dis 2008;40:371–8. [PubMed: 18083083]
62. Wong GL, Wong VW, Choi PC, Chan AW, Chum RH, Chan HK, Lau KK, Chim AM, Yiu KK, Chan FK, Sung JJ, Chan HL. Assessment of Fibrosis by Transient Elastography Compared With Liver Biopsy and Morphometry in Chronic Liver Diseases. Clin Gastroenterol Hepatol. 2008
63. Baranova A, Younossi ZM. The future is around the corner: Noninvasive diagnosis of progressive nonalcoholic steatohepatitis. Hepatology 2008;47:373–5. [PubMed: 18220279]
64. Krasnoff JB, Painter PL, Wallace JP, Bass NM, Merriman RB. Health-related fitness and physical activity in patients with nonalcoholic fatty liver disease. Hepatology 2008;47:1158–66. [PubMed: 18266250]

65. Bellentani S, Dalle Grave R, Suppini A, Marchesini G. Behavior therapy for nonalcoholic fatty liver disease: The need for a multidisciplinary approach. Hepatology 2008;47:746–54. [PubMed: 18098321]
66. Huang MA, Greenson JK, Chao C, Anderson L, Peterman D, Jacobson J, Emick D, Lok AS, Conjeevaram HS. One-year intense nutritional counseling results in histological improvement in patients with non-alcoholic steatohepatitis: a pilot study. Am J Gastroenterol 2005;100:1072–81. [PubMed: 15842581]
67. Zivkovic AM, German JB, Sanyal AJ. Comparative review of diets for the metabolic syndrome: implications for nonalcoholic fatty liver disease. Am J Clin Nutr 2007;86:285–300. [PubMed: 17684197]
68. Ouyang X, Cirillo P, Sautin Y, McCall S, Bruchette JL, Diehl AM, Johnson RJ, Abdelmalek MF. Fructose consumption as a risk factor for non-alcoholic fatty liver disease. J Hepatol 2008;48:993–9. [PubMed: 18395287]
69. Harrison SA, Brunt E, Fecht WJ, Neuschwander-Tetri BA. Orlistat (Xenical) in the treatment of overweight patients with nonalcoholic steatohepatitis (NASH): A multi-centered, randomized, prospective trial. Gastroenterology 2007;132:A809.
70. Vemuri VK, Janero DR, Makriyannis A. Pharmacotherapeutic targeting of the endocannabinoid signaling system: drugs for obesity and the metabolic syndrome. Physiol Behav 2008;93:671–86. [PubMed: 18155257]
71. Van Gaal LF, Rissanen AM, Scheen AJ, Ziegler O, Rossner S. Effects of the cannabinoid-1 receptor blocker rimonabant on weight reduction and cardiovascular risk factors in overweight patients: 1-year experience from the RIO-Europe study. Lancet 2005;365:1389–97. [PubMed: 15836887]
72. Pi-Sunyer FX, Aronne LJ, Heshmati HM, Devin J, Rosenstock J. Effect of rimonabant, a cannabinoid-1 receptor blocker, on weight and cardiometabolic risk factors in overweight or obese patients: RIO-North America: a randomized controlled trial. JAMA 2006;295:761–75. [PubMed: 16478899]
73. Teixeira-Clerc F, Julien B, Grenard P, Tran Van Nhieu J, Deveaux V, Li L, Serriere-Lanneau V, Ledent C, Mallat A, Lotersztajn S. CB1 cannabinoid receptor antagonism: a new strategy for the treatment of liver fibrosis. Nat Med 2006;12:671–6. [PubMed: 16715087]
74. Gary-Bobo M, Elachouri G, Gallas JF, Janiak P, Marini P, Ravinet-Trillou C, Chabbert M, Cruccioli N, Pfersdorff C, Roque C, Arnone M, Croci T, Soubrie P, Oury-Donat F, Maffrand JP, Scatton B, Lacheretz F, Le Fur G, Herbert JM, Bensaid M. Rimonabant reduces obesity-associated hepatic steatosis and features of metabolic syndrome in obese Zucker fa/fa rats. Hepatology 2007;46:122–9. [PubMed: 17526015]
75. Lowell JA, Shenoy S, Ghalib R, Caldwell C, White FV, Peters M, Howard TK. Liver transplantation after jejunoileal bypass for morbid obesity. J Am Coll Surg 1997;185:123–7. [PubMed: 9249079]
76. Wills CE. Long-term Follow-up of Jejunoileal Bypass Patients with Preoperative Cirrhosis of the Liver. Obes Surg 1994;4:37–39. [PubMed: 10742761]
77. Hocking MP, Davis GL, Franzini DA, Woodward ER. Long-term consequences after jejunoileal bypass for morbid obesity. Dig Dis Sci 1998;43:2493–9. [PubMed: 9824141]
78. Levy P, Fried M, Santini F, Finer N. The comparative effects of bariatric surgery on weight and type 2 diabetes. Obes Surg 2007;17:1248–56. [PubMed: 18074502]
79. Sears D, Fillmore G, Bui M, Rodriguez J. Evaluation of Gastric Bypass Patients 1 Year After Surgery: Changes in Quality of Life and Obesity-Related Conditions. Obes Surg. 2008
80. Sjostrom L, Lindroos AK, Peltonen M, Torgerson J, Bouchard C, Carlsson B, Dahlgren S, Larsson B, Narbro K, Sjostrom CD, Sullivan M, Wedel H. Lifestyle, diabetes, and cardiovascular risk factors 10 years after bariatric surgery. N Engl J Med 2004;351:2683–93. [PubMed: 15616203]
81. Tessier DJ, Eagon JC. Surgical management of morbid obesity. Curr Probl Surg 2008;45:68–137. [PubMed: 18267155]
82. Braghetto I, Korn O, Valladares H, Gutierrez L, Csendes A, Debandi A, Castillo J, Rodriguez A, Burgos AM, Brunet L. Laparoscopic sleeve gastrectomy: surgical technique, indications and clinical results. Obes Surg 2007;17:1442–50. [PubMed: 18219770]
83. Furuya CK Jr. de Oliveira CP, de Mello ES, Faintuch J, Raskovski A, Matsuda M, Vezozzo DC, Halpern A, Garrido AB Jr. Alves VA, Carrilho FJ. Effects of bariatric surgery on nonalcoholic fatty

liver disease: preliminary findings after 2 years. J Gastroenterol Hepatol 2007;22:510–4. [PubMed: 17376042]

84. Mummadi R, Kasturi KS, Chennareddygari S, Sood G. Effect of Bariatric Surgery on Nonalcoholic Fatty Liver Disease (NAFLD): Systemic Review and Meta-analysis. Clnical Gastroenterology and Hepatology.
85. Dallal RM, Mattar SG, Lord JL, Wastson AR, Cottam DR, Eid GM, Hamad G, Rabinovitz M, Schauer PR. Results of laparoscopic gastric bypass in patients with cirrhosis. Obes Surg 2004;14:47–53. [PubMed: 14980033]
86. Kral JG, Thung SN, Biron S, Hould FS, Lebel S, Marceau S, Simard S, Marceau P. Effects of surgical treatment of the metabolic syndrome on liver fibrosis and cirrhosis. Surgery 2004;135:48–58. [PubMed: 14694300]
87. Kirpichnikov D, McFarlane SI, Sowers JR. Metformin: an update. Ann Intern Med 2002;137:25–33. [PubMed: 12093242]
88. Hattori Y, Suzuki K, Hattori S, Kasai K. Metformin inhibits cytokine-induced nuclear factor kappaB activation via AMP-activated protein kinase activation in vascular endothelial cells. Hypertension 2006;47:1183–8. [PubMed: 16636195]
89. Lin HZ, Yang SQ, Chuckaree C, Kuhajda F, Ronnet G, Diehl AM. Metformin reverses fatty liver disease in obese, leptin-deficient mice. Nat Med 2000;6:998–1003. [PubMed: 10973319]
90. Angelico F, Burattin M, Alessandri C, Del Ben M, Lirussi F. Drugs improving insulin resistance for non-alcoholic fatty liver disease and/or non-alcoholic steatohepatitis. Cochrane Database Syst Rev. 2007CD005166
91. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002;346:393–403. [PubMed: 11832527]
92. Girard J. Mechanisms of action of thiazolidinediones. Diabetes Metab 2001;27:271–8. [PubMed: 11452221]
93. Yki-Jarvinen H. Thiazolidinediones. N Engl J Med 2004;351:1106–18. [PubMed: 15356308]
94. Watkins PB. Insight into hepatotoxicity: The troglitazone experience. Hepatology 2005;41:229–30. [PubMed: 15657920]
95. Scheen AJ. Hepatotoxicity with thiazolidinediones: is it a class effect? Drug Saf 2001;24:873–88. [PubMed: 11735645]
96. Riera-Guardia N, Rothenbacher D. The effect of thiazolidinediones on adiponectin serum level: a meta-analysis. Diabetes Obes Metab 2008;10:367–75. [PubMed: 17645557]
97. Caldwell SH, Hespenheide EE, Redick JA, Iezzoni JC, Battle EH, Sheppard BL. A pilot study of a thiazolidinedione, troglitazone, in nonalcoholic steatohepatitis. Am J Gastroenterol 2001;96:519–25. [PubMed: 11232700]
98. Neuschwander-Tetri BA, Brunt EM, Wehmeier KR, Oliver D, Bacon BR. Improved nonalcoholic steatohepatitis after 48 weeks of treatment with the PPAR-gamma ligand rosiglitazone. Hepatology 2003;38:1008–17. [PubMed: 14512888]
99. Promrat K, Lutchman G, Uwaifo GI, Freedman RJ, Soza A, Heller T, Doo E, Ghany M, Premkumar A, Park Y, Liang TJ, Yanovski JA, Kleiner DE, Hoofnagle JH. A pilot study of pioglitazone treatment for nonalcoholic steatohepatitis. Hepatology 2004;39:188–96. [PubMed: 14752837]
100. Shadid S, Jensen MD. Effect of pioglitazone on biochemical indices of non-alcoholic fatty liver disease in upper body obesity. Clin Gastroenterol Hepatol 2003;1:384–7. [PubMed: 15017657]
101. Sanyal AJ, Mofrad PS, Contos MJ, Sargeant C, Luketic VA, Sterling RK, Stravitz RT, Shiffman ML, Clore J, Mills AS. A pilot study of vitamin E versus vitamin E and pioglitazone for the treatment of nonalcoholic steatohepatitis. Clin Gastroenterol Hepatol 2004;2:1107–15. [PubMed: 15625656]
102. Belfort R, Harrison SA, Brown R, Darland C, Finch J, Hardies J, Balas B, Gastaldelli A, Tio F, Pulcini J, Berria R, Ma JZ, Dwivedi S, Havranek R, Fincke C, DeFronzo R, Bannayan GA, Schenker S, Cusi K. A placebo-controlled trial of pioglitazone in subjects with nonalcoholic steatohepatitis. N Engl J Med 2006;355:2297–307. [PubMed: 17135584]
103. Ratziu V, Giral P, Jacqueminet S, Charlotte F, Hartemann-Heurtier A, Serfaty L, Podevin P, Lacorte JM, Bernhardt C, Bruckert E, Grimaldi A, Poynard T. Rosiglitazone for nonalcoholic steatohepatitis: one-year results of the randomized placebo-controlled Fatty Liver Improvement

with Rosiglitazone Therapy (FLIRT) Trial. Gastroenterology 2008;135:100–10. [PubMed: 18503774]

104. Guruprasad PA, James AT, Philip VK, Adam L, Stephen DR, Ian S, Andrew SA, Jan GF, Linda M, Jonathan W. Randomized, placebo controlled trial of pioglitazone in non-diabetic subjects with nonalcoholic steatohepatitis (NASH). Gastroenterology. 2008
105. Lutchman G, Modi A, Kleiner DE, Promrat K, Heller T, Ghany M, Borg B, Loomba R, Liang TJ, Premkumar A, Hoofnagle JH. The effects of discontinuing pioglitazone in pateints with nonalcoholic steatohepatitis. Hepatology 2007;46:424–9. [PubMed: 17559148]
106. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N Engl J Med 2007;356:2457–71. [PubMed: 17517853]
107. Ding X, Saxena NK, Lin S, Gupta NA, Anania FA. Exendin-4, a glucagon-like protein-1 (GLP-1) receptor agonist, reverses hepatic steatosis in ob/ob mice. Hepatology 2006;43:173–81. [PubMed: 16374859]
108. Poon T, Nelson P, Shen L, Mihm M, Taylor K, Fineman M, Kim D. Exenatide improves glycemic control and reduces body weight in subjects with type 2 diabetes: a dose-ranging study. Diabetes Technol Ther 2005;7:467–77. [PubMed: 15929678]
109. Bugianesi E. Nonalcoholic fatty liver disease (NAFLD) and cardiac lipotoxicity: Another piece of the puzzle. Hepatology 2008;47:2–4. [PubMed: 18161723]
110. Ekstedt M, Franzen LE, Mathiesen UL, Thorelius L, Holmqvist M, Bodemar G, Kechagias S. Long-term follow-up of patients with NAFLD and elevated liver enzymes. Hepatology 2006;48:865–73. [PubMed: 17006923]
111. Loria P, Lonardo A, Bellentani S, Day CP, Marchesini G, Carulli N. Non-alcoholic fatty liver disease (NAFLD) and cardiovascular disease: an open question. Nutr Metab Cardiovasc Dis 2007;17:684–98. [PubMed: 17560098]
112. Targher G. Non-alcoholic fatty liver disease, the metabolic syndrome and the risk of cardiovascular disease: the plot thickens. Diabet Med 2007;24:1–6. [PubMed: 17227317]
113. Adams LA, Lymp JF, St Sauver J, Sanderson SO, Lindor KD, Feldstein A, Angulo P. The natural history of nonalcoholic fatty liver disease: a population-based cohort study. Gastroenterology 2005;129:113–21. [PubMed: 16012941]
114. Ong JP, Pitts A, Younossi ZM. Non-alcoholic fatty liver disease (NAFLD) is associated with higher overall mortality and liver related mortality. Journal of Hepatology 2008;48:S5–S5.
115. Marchesini G, Bugianesi E, Forlani G, Cerelli F, Lenzi M, Manini R, Natale S, Vanni E, Villanova N, Melchionda N, Rizzetto M. Nonalcoholic fatty liver, steatohepatitis, and the metabolic syndrome. Hepatology 2003;37:917–23. [PubMed: 12668987]
116. McCullogh AJ. The clinicla features, diagnosis and natural history of nonalcoholic fatty liver diseases. Clin Liver Dis 2004;8:521–33. viii. [PubMed: 15331061]
117. Mofrad P, Contos MJ, Haque M, Sargeant C, Fisher RA, Luketic VA, Sterling RK, Shiffman ML, Stravitz RT, Sanyal AJ. Clinical and histologic spectrum of nonalcoholic fatty liver disease associated with normal ALT values. Hepatology 2003;37:1286–92. [PubMed: 12774006]
118. Villanova N, Moscatiello S, Ramilli S, Bugianesi E, Magalotti D, Vanni E, Zoli M, Marchesini G. Endothelial dysfunction and cardiovascular risk profile in nonalcoholic fatty liver disease. Hepatology 2005;42:473–80. [PubMed: 15981216]
119. Chalasani N, Deeg MA, Crabb DW. Systemic levels of lipid peroxidation and its metabolic and dietary correlates in patients with nonalcoholic steatohepatitis. Am J Gastroenterol 2004;99:1497–502. [PubMed: 15307867]
120. Pacifico L, Cantisani V, Ricci P, Osborn JF, Schiavo E, Anania C, Ferrara E, Dvisic G, Chiesa C. Nonalcoholic fatty liver disease and carotid atherosclerosis in children. Pediatr Res 2008;63:423–7. [PubMed: 18356751]
121. Fracanzani AL, Burdick L, Raselli S, Pedotti P, Grigore L, Santorelli G, Valenti L, Maraschi A, Catapano A, Fargion S. Carotid artery intima-media thickness in nonalcoholic fatty liver disease. Am J Med 2008;121:72–8. [PubMed: 18187076]
122. Targher G, Bertolini L, Padovani R, Rodella S, Zoppini G, Zenari L, Cigolini M, Falezza G, Arcaro G. Relations between carotid artery wall thickness and liver histology in subjects with nonalcoholic fatty liver disease. Diabetes Care 2006;29:1325–30. [PubMed: 16732016]

123. Akabame S, Hamaguchi M, Tomiyasu K, Tanaka M, Kobayashi-Takenaka Y, Nankano K, Oda Y, Yoshikawa T. Evaluation of vulnerable coronary plaques and non-alcoholic fatty liver disease (NAFLD) by 64-detector multislice computed tomography (MSCT). Circ J 2008;72:618–25. [PubMed: 18362435]

124. Perseghin G, Lattuada G, De Cobelli F, Esposito A, Belloni E, Ntali G, Ragogna F, Canu T, Scifo P, Del Maschio A, Luzi L. Increased mediastinal fat and impaired left ventricular energy metabolism in young men with newly found fatty liver. Hepatology 2008;47:51–8. [PubMed: 17955548]

125. Targher G, Bertolini L, Padovani R, Poli F, Scala L, Tessari R, Zenari L, Falezza G. Increased prevalence of cardiovascular disease in Type 2 diabetic patients with non-alcoholic fatty liver disease. diabet Med 2006;23:403–9. [PubMed: 16620269]

126. Chalasani N, Aljadhey H, Kesterson J, Murray MD, Hall SD. Patients with elevated liver enzymes are not at higher risk for statin hepatotoxicity. Gastroenterology 2004;126:1287–92. [PubMed: 15131789]

127. Chalasani N. Statins and hepatotoxicity: focus on patients with fatty liver. Hepatology 2005;41:690–5. [PubMed: 15789367]

128. Vuppalanchi R, Teal E, Chalasani N. Patients with elevated baseline liver enzymes do not have higher frequency of hepatotoxicity from lovastatin than those with normal baseline liver enzymes. Am J Med Sci 2005;329:62–5. [PubMed: 15711421]

129. Lewis JH, Mortensen ME, Zweig S, Fusco MJ, Medoff JR, Belder R. Efficacy and safety of high-dose pravastatin in hypercholesterolemic patients with well-compensated chronic liver disease: Results of a prospective, randomized, double-blind, placebo-controlled, multicenter trial. Hepatology 2007;46:1453–63. [PubMed: 17668878]

130. Kaneda H, Hashimoto E, Yatsuji S, Tokushige K, Shiratori K. Hyaluronic acid levels can predict severe fibrosis and platelet counts can predict cirrhosis in patients with nonalcoholic fatty liver disease. J Gastroenterol Hepatol 2006;21:1459–65. [PubMed: 16911693]

131. Yoneda M, Fujita K, Inamori M, Tamano M, Hiriishi H, Nakajima A. Transient elastography in patients with non-alcoholic fatty liver disease (NAFLD). Gut 2007;56:1330–1. [PubMed: 17470477]

132. Talwalkar JA, Yin M, Fidler JL, Sanderson SO, Kamath PS, Ehman RL. Magnetic resonance imaging of hepatic fibrosis: emerging clinical applications. Hepatology 2008;47:332–42. [PubMed: 18161879]

133. Szczepaniak LS, Nurenberg P, Leonard D, Browning JD, Reingold JS, Grundy S, Hobbs HH, Dobbins RL. Magnetic resonance spectroscopy to measure hepatic triglyceride content: prevalence of hepatic steatosis in the general population. Am J Physiol Endocrinol Metab 2005;288:E462–8. [PubMed: 15339742]

134. Tsuda N, Okada M, Murakami T. Potential of gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid (Gd-EOB-DTPA) for differential diagnosis of nonalcoholic seatohepatitis and fatty liver in rats using magnetic resonance imaging. Invest Radiol 2007;42:242–7. [PubMed: 17351431]

135. Portincasa P, Grattagliano I, Lauterburg BH, Palmieri VO, Palasciano G, Stellaard F. Liver breath tests non-invasively predict higher stages of non-alcoholic steatohepatitis. Clin Sci (Lond) 2006;111:135–43. [PubMed: 16603025]

136. Solga SF, Alkhuraishe A, Cope K, Tabesh A, Clark JM, Torbenson M, Schwartz P, Magnuson T, Diehl AM, Risby TH. Breath biomarkers and non-alcoholic fatty liver disease: preliminary observatios. Biomarkers 2006;11:174–83. [PubMed: 16766393]

137. Horoz M, Bolukbas C, Bolukbas FF, Sabuncu T, Aslan M, Sarifakiogullari S, Gunaydin N, Erel O. Measurement of the total antioxidant response using a novel automated method in subjects with nonalcoholic steatohepatitis. BMC Gastroenterol 2005;5:35. [PubMed: 16283935]

138. Hui JM, Hodge A, Farrell GC, Kench JG, Kriketos A, George J. Beyond insulin resistance in NASH: TNF-alpha or adiponectin? Hepatology 2004;40:46–54. [PubMed: 15239085]

139. Musso G, Gambino R, Biroli G, Carello M, Faga E, Pacini G, De Michieli F, Cassader M, Durazzo M, Rizzetto M, Pagano G. Hypoadiponectinemia predicts the severity of hepatic fibrosis and pancreatic Beta-cell dysfunction in nondiabetic nonobese patients with nonalcoholic steatohepatitis. Am J Gastroenterol 2005;100:2438–46. [PubMed: 16279898]

140. Wieckowska A, Papouchado BG, Li Z, Lopez R, Zein NN, Feldstein AE. Increased hepatic and circulating interleukin-6 levels in human nonalcoholic steatohepatitis. Am J Gastroenterol 2008;103:1372–9. [PubMed: 18510618]

141. Haukeland JW, Damas JK, Konopski Z, Loberg EM, Haaland T, Goverud I, Torjesen PA, Birkeland K, Bjoro K, Aukrust P. Systemic inflammation in nonalcoholic fatty liver disease is characterized by elevated levels of CCL2. J Hepatol 2006;44:1167–74. [PubMed: 16618517]

142. Marchesini G, Brizi M, Bianchi G, Tomassetti S, Zoli M, Melchionda N. Metformin in non-alcoholic steatohepatitis. Lancet 2001;358:893–4. [PubMed: 11567710]

143. Nair S, Diehl AM, Wiseman M, Farr GH Jr. Perrillo RP. Metformin in the treatment of non-alcoholic steatohepatitis: a pilot open label trial. Aliment Pharmacol Ther 2004;20:23–8. [PubMed: 15225167]

144. Uygun A, Kadayifci A, Isik AT, Ozgurtas T, Deveci S, Tuzun A, Yesilova Z, Gulsen M, Dagalp K. Metformin in the treatment of patients with non-alcoholic steatohepatitis. Aliment Pharmacol Ther 2004;19:537–44. [PubMed: 14987322]

145. Bugianesi E, Gentilcore E, Manini R, Natale S, Vanni E, Villanova N, David E, Rizzetto M, Marchesini G. A randomized controlled trial of metformin versus vitamin E or prescriptive diet in nonalcoholic fatty liver disease. Am J Gastroenterol 2005;100:1082–90. [PubMed: 15842582]

146. Schwimmer JB, Middleton MS, Deutsch R, Lavine JE. A phase 2 clinical trial of metformin as a treatment for non-diabetic paediatric non-alcoholic steatohepatitis. Aliment Pharmacol Ther 2005;21:871–9. [PubMed: 15801922]

147. Loomba R, Lutchman G, Kleiner D, Borg B, Feld J, Modi A, Ghany M, Heller T, Doo E, Park Y, Ricks M, Denkinger B, Premkumar A, Sumner A, Liang J, Hoofnagle JH. Pilot study of metformin in patients with nonalcoholic steatohepatitis. Hepatology October;2006 :44. [PubMed: 16799985]

148. Nobili V, Manco M, Ciampalini P, Alisi A, Devito R, Bugianesi E, Marcellini M, Marchesini G. Metformin use in children with nonalcoholic fatty liver disease: An open-label, 24-month, observational pilot study. Clin Ther 2008;30:1168–76. [PubMed: 18640473]

Table 1

Co-morbidities commonly associated with NAFLD

Established conditions	Emerging conditions
Obesity	Obstructive sleep apnea
Type2 Diabetes/Glucose intolerance	Hypothyroidism
Dyslipidemia	Obstructive sleep apnea
Metabolic syndrome	Hypopituitarism

Table 2

Non-invasive biomarkers previously studied or currently under evaluation

	Serum biomarkers	Imaging studies	Breath tests
Fibrosis	BARD score[58] Fibrotest NAFLD fibrosis score[56] ELF/OELF[57, 59] Hyaluronic acid[130]	Transient elastography[61, 131] MR elastography[132] MR spectroscopy[133, 134]	[^{13}C] methacetin[135] [^{13}C] ketoisocaproate[135] Ethanol[136] Acetone[136]
Oxidative stress	TBARS[119] Oxidized-LDL[119] Total antioxidant response[137] Total lipid peroxide levels[137]		
Hepatocyte apoptosis	CK-18 fragments[51, 53]		
Inflammation	TNF-α/adiponectin ratio[138, 139] hsCRP[29] IL-6[140] CC-chemokine ligand-2[141]		

Table 3

Strategies to enhance patient compliance in lifestyle modification

- Communicate with empathy
- Be sensitive to general stigma against obesity
- Discuss pros and cons of proposed changes to lifestyle
- Explore reasons for perpetual poor dietary and exercise choices
- Encourage self-efficacy
- Offer specific choices of food and exercise
- Design individualized program of eating and physical activity
- Explain treatment and its benefits

Table 4

Selected studies of metformin in patients with NAFLD

Author (ref)	N	Design	Comparator	Population	Duration	Liver enzymes	Histology
Marchesini et al[142]	14	Open label Single arm	None	Adults Mostly non-diabetic	4 mo	Improved	Not evaluated
Nair et al[143]	15	Open label Single arm	None	Non-diabetics	12 mo	Improved	Improved inflammation
Uygun et al[144]	36	Open label	Calorie restricted diet	Non-diabetics	6 mo	Improved	Improved inflammation
Bugianesi et al[145]	55	Randomized clinical trial	Calorie restricted diet	Non-diabetics	12 mo	Improved	Improved steatosis, inflammation and fibrosis
Schwimmer et al[146]	10	Open label Single arm	None	Non-diabetics	6 mo	Improved	Not evaluated
Loomba et al[147]	14	Open label Single arm	None	Non-diabetics	48 wks	Improved	Improved steatosis and inflammation
Nobili et al[148]	57	Open label	Antioxidant	Non-diabetics	24 months	No difference	No difference

Table 5

Randomized controlled trials of TZDs consisting at least 50 randomized patients

First author (Ref)	n	Study design	Duration	Histological Improvement- Pre & Post				Mean weight gain	Comments
				Histologic variable	TZD	Placebo	TZD vs. Placebo		
Belfort[102]	55	Hypocaloric diet + Pioglitazone *versus* Hypocaloric diet + Placebo *Diabetics + Non-diabetics	6 mo	Steatosis	Yes	No	Yes	2.5 kg	TZD group had significant increase in serum adiponectin levels and this inversely correlated with improved hepatic steatosis
				Inflmm	Yes	Yes	Yes		
				Ballooning	Yes	No	Yes		
				Fibrosis	Yes	No	Borderline		
				NAS	Yes	No	Yes		
Ratziu[103]	63	Rosiglitazone *versus* Placebo * Diabetics + Non-diabetics	12 mo	Steatosis	Yes	No	Yes	1.5 kg	- Primary end point was >30% reduction in hepatic steatosis and predictors of response included rosiglitazone treatment, lack of diabetes at entry and greater steatosis at baseline - No active lifestyle modification in either groups - Ranked assessment of pre-and post-treatment biopsies showed improved steatosis, ballooning and fibrosis in the rosiglitazone group - Relatively lower NAS at entry may at least in part explain why there was no change in NAS was seen in this study
				Inflamm	No	No	No		
				Ballooning	No	No	No		
				Fibrosis	No	No	No		
				NAS	No	No	No		
Gurupras ad [104]	74	Diet + exercise + Pioglitazone *versus* Diet + exercise + Pioglitazone * Only non-diabetics	12 mo	Steatosis	Yes	Yes	No	2.6 kg	NAS score reported. Placebo group had mean weight loss of 3.5 kg but TZD group had mean weight gain of 2.6 kg
				Inflamm	Yes	No	No		
				Ballooning	Yes	Worse	Yes		
				Fibrosis	Yes	No	No		
				NAS	N/A	N/A	N/A		

Table 6

Various agents in evaluation to treat NASH in Humans (www. Clinicaltrials.gov)

Agent	Nature of the Study
Metformin vs. Vit E vs. Placebo (TONIC)	Phase III, multicenter, RCT
Pioglitazone vs. Metformin vs. placebo (PIVENS)	Phase III, multicenter, RCT
Omega-3 fatty acids	Phase II, pilot study
Polyunsaturated fatty acids	Phase II, pilot study
Orlistat	Phase III, multicenter study
Silophus	Phase II, pilot study
Silymarin	Phase II, multicenter RCT
Rimonabant	Phase IIb, multicenter RCT
Recombinant leptin	Phase II, pilot study
Pentoxiphylline	Phase II, pilot study
Pentoxiphylline vs. Pioglitazone	Phase II, pilot study
Exendatide	Phase II, pilot study
Rosi vs.Rosi + metformin vs. rosi + losartan	Phase III, single center
SAMe	Phase II, pilot study
Iron depletion	Phase II, pilot study
CP 945598	Phase IIb, multicenter RCT
TRO 19622[†]	Phase II, pilot study
ASP9831[Ψ]	Phase II, pilot study
L-Alanine	Phase II, pilot study

[†]Cholesterol like small molecule and is a potent neuroprotective agent in-vitro. May have mitochondrial protective effects

[Ψ]Novel PDE4 inhibitor which may be improve hepatic inflammation and fibrosis