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Hepatic steatosis and Type 2 diabetes: current and future treatment considerations

John Richard¹ and Ildiko Lingvay^{†,1}

¹UT Southwestern Medical Center, Department of Internal Medicine – Division of Endocrinology, 5323 Harry Hines Blvd, Dallas, TX 75390-8857, USA

Abstract

Hepatic steatosis, considered the first step in the pathophysiologic continuum of non-alcoholic fatty liver disease, is estimated to afflict 30% of the US population and over 75% of patients with Type 2 diabetes. Given the expected rise in the prevalence of obesity and Type 2 diabetes in the following decades, hepatic steatosis will, if not already, become an epidemic. The consequences of hepatic steatosis are numerous, and range from progression to chronic liver disease, with its associated morbidity and mortality, to worsening insulin resistance and Type 2 diabetes, as well as being an independent contributor to cardiovascular disease. All such consequences are more likely to occur in patients with Type 2 diabetes who are already at high risk of cardiovascular events. In this article we review the evidence behind the available therapeutic options for hepatic steatosis, and identify challenges and unmet needs in the field.

Keywords

FXR agonists; hepatic steatosis; incretin mimetics; metabolic syndrome; metformin; non-alcoholic fatty liver disease; obesity; thiazolidinediones; Type 2 diabetes

Hepatic steatosis is the first step in a spectrum of liver diseases termed non-alcoholic fatty liver disease (NAFLD). The spectrum of disease ranges from simple steatosis to non-alcoholic steatohepatitis (NASH), fibrosis and cirrhosis [1]. In the general US population the prevalence of NAFLD is estimated at 30% [2], but much higher estimates are reported if certain high-risk conditions are present: Hispanic ethnicity [2], obesity, Type 2 diabetes and the metabolic syndrome. In patients with Type 2 diabetes, the prevalence of NAFLD is as high as 75% [1]. Considering the rising prevalence of obesity and Type 2 diabetes in the USA and worldwide [3], NAFLD has reached, or is likely to reach, epidemic proportions.

Non-alcoholic fatty liver disease is already emerging as the most common cause of chronic liver disease worldwide [3], a trend that will only worsen in the coming decades. More so, NAFLD is thought to be an independent determinant of cardiovascular disease (CVD) [4], in addition to clustering in individuals who already have multiple cardiovascular risk factors, a relationship that leads to an increased risk of undesired outcomes in this patient population. NAFLD is therefore a complex problem with implications far beyond the liver.

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[†]Author for correspondence: Tel.: +1 214 648 2779 Fax: +1 214 648 8548 ildiko.lingvay@utsouthwestern.edu.

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Pathophysiology

In the two-hit model of NAFLD pathogenesis first described by Day and James, hepatic fat accumulation is the 'first hit' and is required for liver injury to develop [5]. The fatty liver then becomes vulnerable to a 'second hit', leading to hepatocyte injury, inflammation and fibrosis. Hepatic steatosis, defined as ectopic accumulation of triglycerides (TGs) in hepatocytes, develops when free fatty acid (FFA) uptake and synthesis in the liver exceeds its oxidation and excretion into the bloodstream. This imbalance can occur under the following circumstances: excess FFAs produced by adipose tissue or taken in through diet; increased hepatic lipogenesis; and impaired hepatic FFA elimination [6].

Obesity and the metabolic syndrome are commonly associated with NAFLD, in fact so closely that hepatic steatosis has been proposed to become one of the diagnostic criteria of the metabolic syndrome. Yet the mechanistic sequence of the association between NAFLD and insulin resistance (and diabetes) is not fully understood. Studies have shown that NAFLD predicts the incidence of diabetes independently of traditional risk factors, including obesity, peripheral insulin resistance and the metabolic syndrome [7], suggesting that NAFLD would have a direct causal effect on the development of diabetes, perhaps by promoting hepatic insulin resistance. Uncontrolled diabetes also promotes or worsens hepatic steatosis, thus fueling a vicious cycle that closely ties the two conditions together.

In addition to the association with the metabolic syndrome and diabetes, NAFLD is thought to independently promote CVD. Studies have shown that individuals with hepatic steatosis have significantly greater carotid intima-media thickness (a marker of CVD) than those without steatosis [8], as well as impaired endothelial function and lower adiponectin levels [9] – which promote CVD. The independent association between NAFLD and CVD is best supported by a large study that followed 2100 patients with Type 2 diabetes over 6 years and showed a hazard ratio (HR) of 1.96 for CVD in these patients, even after adjustment for gender, age, smoking, diabetes duration, HbA1c, LDL-cholesterol and medication use [10].

In conclusion, hepatic steatosis, diabetes and the metabolic syndrome are all intrinsic parts of the same disease process driven primarily by overnutrition, all promoting a metabolic milieu that further exacerbates each component, and ultimately leads to an increased risk of CVD morbidity and mortality.

Diagnosis

The diagnosis of hepatic steatosis and NAFLD is one of the biggest unmet needs in the field. The diagnosis of NAFLD is often suspected in patients with asymptomatic elevation of amino-transferase levels, radiologic findings suggestive of fatty liver, or unexplained persistent hepatomegaly in the absence of alcohol abuse and other causes, such as viruses, autoimmune responses, metabolic or hereditary factors, and drugs or toxins [1]. However, the clinical diagnosis and liver-function tests have a poor predictive value with respect to histologic involvement [11], and approximately 75% of patients with confirmed hepatic steatosis have normal liver function tests [12]. Liver biopsy is the gold standard for determining severity and confirming the diagnosis of NAFLD; however, it is an invasive procedure with possible serious complications, and is subject to sampling variability. It would be neither practical nor safe to perform liver biopsies in all patients suspected of having NAFLD; therefore, we are left to find suitable alternatives that provide quality information with limited adverse events. There are a variety of imaging tools at our disposal including ultrasonography (US), computed tomography (CT), MRI and magnetic resonance spectroscopy (MRS) to qualify and/or quantify steatosis. The effectiveness of US, CT, MRI and MRS at detecting hepatic steatosis was compared in a meta-analysis of 46 articles that involved 4715 patients, and found that the overall performance of MRI and MRS was better

than that for CT and US [13]. MRS has several additional advantages over other diagnostic techniques; it is the only truly noninvasive quantitative method, has low detection thresholds (therefore being able to diagnose early disease), is less susceptible to sampling variability (compared with biopsy), has low operator variability and does not expose the patient to radiation (unlike CT).

Unfortunately, the biggest shortcoming of all imaging techniques at this time is the inability to qualify any histological changes. The ideal diagnostic test would be noninvasive, quantitative and reflect not only the degree of steatosis, but also the histological changes associated with NASH and cirrhosis. Such a test should also be relatively simple and cheap, so it can be implemented on a large population scale, given the high prevalence of this condition and its predicted rise in the coming decades.

Several new diagnostic techniques are currently being developed in an effort to improve the diagnostic and staging accuracy of NAFLD. Fibroscan is a noninvasive method for evaluating liver stiffness through the use of pulse-echo ultrasound. It has the advantage of being noninvasive, it evaluates a large area of the liver thus eliminating sampling variability, and is more sensitive for detecting injury than currently used serological markers [14]. This method assumes that liver stiffness correlates well with the degree of fibrosis, yet it has one important weakness; fatty infiltration interferes with the wave velocity itself, thus results are less reliable in this population [14], rendering it as a more useful technique in liver conditions that are less associated with steatosis. Magnetic resonance elastography is another new technique that appears to have good diagnostic accuracy in staging fibrosis and is unrelated to BMI [15]. However, further studies are needed to clearly define its role in patients with hepatic steatosis and fibrosis.

New biochemical markers are also being evaluated as diagnostic tools, the most promising thus far being serum cytokeratin (CK) M30 and M65 antigens. A Japanese study showed higher levels of these biomarkers in NAFLD patients versus controls. In addition, increases in these antigens strongly correlated with increases in alanine transaminase (ALT) levels in NAFLD patients [16]. Another study showed CK M30 and M65 to have a sensitivity of 60.0 and 68.9% and a specificity of 97.4 and 81.6%, respectively, in diagnosing NASH [17].

Various scores have been developed in order to predict fibrosis using clinical tools, thus eliminating the need for invasive testing. In a study comparing noninvasive fibrosis-scoring systems, the FIB-4 score, calculated as:

$$age ([yr] \times AST [U/L]) / \left((PLT [10^9/l]) \times (ALT [U/L])^{\frac{1}{2}} \right)$$

[18] had the best diagnostic accuracy for excluding advanced fibrosis in NAFLD patients when compared with aspartate aminotransferase (AST)/ALT ratio, BARD score and NAFLD fibrosis score. The FIB-4 score showed a negative-predictive value of 95% [19].

Treatment

Most interventions evaluated for the treatment of NAFLD are those commonly used for the treatment of Type 2 diabetes – thiazolidinediones, metformin, incretin mimetics, insulin, weight loss, exercise and diet – and exert a rather indirect effect through improvement in insulin resistance and glycemia. These interventions have also been the most efficacious for NAFLD to date – not surprising considering the high degree of interplay between these conditions. Other treatments tested – such as antioxidants, probiotics, farnesoid X receptor (FXR) agonists, statins and ARBs – harness various other pathways thought to be involved

in the development of hepatic steatosis, yet not all have proven effective. Later we review the current state of the clinical data pertaining to the treatment of NAFLD.

The major problem in this field is the scarcity of definitive clinical trials. There are very few high-quality, randomized, blinded, adequately powered, controlled studies of sufficient duration and with adequate outcomes. In addition, many studies have excluded patients with diabetes, a surprising fact considering that this population is disproportionately affected by this condition.

Lifestyle interventions & weight loss

Obesity is strongly associated with the development and progression of NAFLD, therefore weight loss has been hypothesized to be a target therapy for NAFLD. Moderate weight loss via caloric restriction in obese adults has been shown to improve insulin resistance, intrahepatic lipid content, liver enzymes and hepatic histology [20]. Some of the same improvements have been demonstrated with weight loss in obese adolescents, which is important given the rise in the prevalence of obesity and NAFLD among children. Moderate calorie restriction (1200–1500 kcal/day) in obese adolescents leads to significant body weight loss, as well as decreased intrahepatic triglyceride content, and improved hepatic and skeletal muscle insulin sensitivity [21].

Even in the absence of weight loss, significant reduction in abdominal and visceral fat was found in subjects performing regular exercise for 4 weeks [22], suggesting a beneficial effect of exercise independent of weight loss. Several studies have now shown that exercise therapy improves hepatic steatosis in the absence of changes in BMI [23,24].

Improvement in hepatic steatosis with intensive lifestyle modifications was also achieved in patients with diabetes. The Look AHEAD trial evaluated the change in hepatic steatosis in patients with diabetes after 4 years of intensive lifestyle intervention strategies leading to weight loss. Compared with the control group, the intervention successfully reduced both hepatic steatosis and the risk of advancement of NAFLD [25]. Lifestyle changes and weight loss, if achieved and sustained, are the most effective means of preventing and reversing NAFLD in patients with and without diabetes.

Bariatric surgery

Bariatric surgery is an effective means to achieve significant long-term weight loss and provides researchers with a model to study the reversibility of the effects of morbid obesity on metabolism. Improvement in hepatic steatosis and even fibrosis was documented following all types of bariatric surgery, with the gastric bypass procedure being the most effective [26]. A study by Weiner of morbidly obese patients with NASH undergoing bariatric surgery (including Roux-en-Y gastric bypass, gastric banding and biliopancreatic diversion with duodenal switch) showed improvements in hypertension, Type 2 diabetes, steatosis, necro-inflammatory activity and hepatic fibrosis after surgery compared with baseline [27]. In a recent study of NAFLD patients receiving bariatric surgery, Bell and colleagues have shown significant improvements in the metabolic syndrome, grade and stage of liver disease, as well as liver histology [28].

Of note is the importance of paced weight loss following any weight-loss intervention. Andersen and colleagues have shown an increase in portal fibrosis in patients who lost weight at a rate higher than 1.6 kg/week following a gastric bypass procedure [29]. Similar case results are available in patients following severe diet restriction, thus moderation is recommended even where proven beneficial interventions are concerned.

Metformin

Metformin is the first-line agent for the treatment of diabetes and is the most popular hypoglycemic agent. It exerts its hypoglycemic effect mainly by decreasing hepatic insulin resistance and reducing hepatic glucose output, therefore, it is plausible that metformin also has a beneficial effect on hepatic steatosis as well. While its effect on hepatic steatosis has been evaluated in several studies [30–32], not all showed a benefit, and there is not a single adequately designed study to definitively answer the question of metformin effectiveness on hepatic steatosis. Bugianesi and colleagues studied the effects of metformin on NAFLD and found that aminotransferase levels were significantly decreased. In a subset of metformin-treated patients liver biopsies showed significant decreases in liver fat, necroinflammation and fibrosis [33]. However, there are several shortcomings of this study, including the use of a nonsensitive outcome (liver-function tests) and lack of an adequate control group. Given the totality of available information about metformin, it is likely that it benefits patients with hepatic steatosis, at least to some degree.

Glitazones

Glitazones induce activation of PPAR γ , which causes improvement in insulin sensitivity and promotes fatty acid uptake into adipocytes rather than the liver, thus reducing hepatic steatosis [34]. These agents have unequivocally shown significant improvement in hepatic steatosis (upwards of 50% reduction of fat content), including in patients with diabetes [35]. Specifically, pioglitazone has been used in diabetic patients with NASH, showing improved glycemic control, normalization of elevated aminotransferases, decreased hepatic fat content and improved hepatic steatosis compared with placebo [36]. Researchers have also explored pioglitazone's effects in nondiabetic patients with NASH, showing improvements in glycemic control, ALT, and improved liver injury and fibrosis compared with placebo [37]. Sanyal and colleagues have confirmed these same results using pioglitazone in nondiabetic patients with NASH, showing improved aminotransferases and hepatic histology [38]. There is even a suggestion that a short-term therapy with glitazones may produce sustained histological response even after the medication is discontinued [39]. Yet, despite their effectiveness, their popularity has decreased greatly due to cardiovascular safety concerns. It is unclear what the future of these agents will be, yet it is unlikely that their use will become widespread again; even less likely in patients with NAFLD in the absence of diabetes.

Insulin

Insulin promotes lipogenesis; therefore, the expectation would be that exogenous insulin therapy for diabetes would further promote hepatic steatosis. Several preliminary studies suggest otherwise, yet not enough data are currently available to conclude whether insulin treatment is beneficial or detrimental to hepatic steatosis. When insulin and metformin was initiated in patients with newly diagnosed Type 2 diabetes, hepatic steatosis was reduced within 3 months by 45%, with 75% of the study subjects achieving a normal level [40].

Statins & other cholesterol-lowering agents

Statins inhibit the enzyme HMG-CoA reductase, which plays a central role in the production of cholesterol in the liver. It was thought that treatment with statins would lower hepatic fat content, yet in clinical studies this was not proven. Nelson and colleagues randomized patients with biopsy-proven NASH to receive simvastatin versus placebo for 12 months, and measured serum aminotransferases and repeated liver biopsies to assess for improvement. The study showed no improvement in aminotransferases, hepatic steatosis, necrosis or stage of fibrosis within or between groups [41]. Despite having no beneficial effect on hepatic steatosis, statins do not worsen liver function in the setting of hepatic steatosis, and can be used safely in this population. Diabetic patients with lipid dyscrasias and fatty liver would

still benefit from the cardiovascular risk reduction that statin therapy provides, despite its limited effectiveness on hepatic steatosis.

Owing to the role of Niemann-Pick C1-like 1 has recently been explored because of its potential function in facilitating the hepatic accumulation of cholesterol. Thus ezetimibe (a Niemann-Pick C1-like 1 protein antagonist) could be a good option for improving NAFLD [42]. A 24-month single-arm study evaluating ezetimibe (10 mg/day) in patients with NAFLD showed significant improvement in NAFLD-related markers such as visceral fat, fasting insulin, HOMA-R (a marker of insulin resistance), TG, LDLs, ALT and C-reactive protein. Most importantly, significant histological improvement in steatosis was also seen following ezetimibe treatment versus baseline [43]. Ezetimibe may prove a more effective option for NAFLD patients with dyslipidemia than statins.

Ursodeoxycholic acid & antioxidants

Ursodeoxycholic acid (UDCA) is a bile acid known to be a cyto-protective agent, which prevents apoptosis induced by a variety of stress stimuli, thereby potentially inhibiting the catalyst of transition from hepatic steatosis to NASH. A study by Lindor and colleagues evaluated NASH patients for 2 years using UDCA at a dose of 13–15 mg/kg/day and found that, while safe and well tolerated, it was no better than placebo at improving liver histology [44]. A similar study in NASH patients using high-dose UDCA (13–15 mg/kg/day) versus placebo also showed no improvement in overall histology [45]. By contrast, a 12-month study by Ratziu *et al.* of even higher doses of UDCA (28–35 mg/kg/day) did show improvements in ALT and serum fibrosis markers compared with placebo, but no hard end points such as histological improvements were shown in this study or in other studies of UDCA to date [46].

Vitamin E is an antioxidant that also serves to prevent the 'second hit' associated with progression of NAFLD by counteracting oxidative stressors. Studies by Dufour *et al.* and Vajro *et al.* evaluated the effectiveness of UDCA and vitamin E in obese patients with elevated transaminases and hepatic steatosis or biopsy proven NASH, but neither showed any significant benefit [47,48]. By contrast, an article by Sanyal and colleagues evaluating the effects of treatment with vitamin E (800 IU daily) in nondiabetic patients for 96 weeks on NASH showed significant improvements in aminotransferase levels and hepatic steatosis but not fibrosis compared with placebo [38]. This suggests that further studies are likely to be needed to confirm the effectiveness of vitamin E and its role in NAFLD treatment.

Angiotensin receptor blockade

Suppressing the renin–angiotensin system with ARBs has been shown to promote beneficial metabolic effects. Telmisartan and irbesartan activate PPAR γ and therefore decrease insulin resistance [49]. ARBs have also been shown to improve liver pathology through the reduction of activated hepatic stellate cells [50]. Clinical studies have shown that ARBs can improve liver function tests as well as varying degrees of liver pathology associated with NAFLD; however, the improvements were minimal, often not statistically significant [51,52]. Based on the current data, ARBs should not be considered as first-line therapy in patients with NAFLD only, but could be used in patients with hypertension who also have NAFLD.

Probiotics

Probiotics are live organisms that normally live within the colon, assisting with digestion. They are thought to impact the development of NAFLD by competitively inhibiting and possibly eradicating pathogenic strains that promote disease. They may also alter the inflammatory effects of pathogenic strains in the intestines through changes in cytokine

signaling, improved epithelial barrier function and direct decreases in proinflammatory cytokines (e.g., TNF- α). In fact, researchers reported that a combination probiotic compound, VSL#3, performs all of these functions in a mouse model [53]. Loguercio and colleagues also studied the effects of this compound on human subjects with biopsy-proven NAFLD and they measured markers of oxidative stress, showing a significant decrease in the stress markers tested, suggesting that manipulation of intestinal flora could be a possible adjunctive therapy in patients with NAFLD [54]; however, no further studies looking at changes in histology with this treatment have been undertaken thus far. Although not enough data are currently available to support such a treatment, it is quite an intriguing area with potential for clinical efficacy. Several studies evaluating this mechanism and treatment are currently underway, thus more information will be available within the next few years.

Farnesoid X receptor agonists

The FXR is a bile sensor that plays important roles in the regulation of bile acid and cholesterol homeostasis, glucose metabolism and insulin sensitivity. INT-747 is a semisynthetic FXR agonist that has been shown to increase insulin secretion and enhance adipocyte lipid storage and secretion of adiponectin and leptin. This compound is being tested in diabetic patients with NAFLD to evaluate any significant improvements in glucose-disposal rates, fibrosis markers and weight loss in the treatment arm compared with controls; results are pending. WAY-362450, another synthetic agonist of FXR, has shown a significant reduction in inflammatory cell infiltration and hepatic fibrosis in an animal model of NASH [55]. These compounds are in early-phase development and more results will be available soon.

Glucagon-like peptide 1 agonists

Glucagon-like peptide 1 (GLP-1) agonists lower glucose levels after a meal by promoting insulin production and secretion by the pancreatic β -cell by slowing gastric emptying and by inhibiting glucagon secretion. Treatment of diabetic patients with exenatide, a GLP-1 mimetic, is associated with improved glucose control and significant weight loss [56], which would confer an indirect beneficial effect on hepatic steatosis. It has also been demonstrated that GLP-1 receptors are present on hepatocytes and their activation produces a direct effect on hepatic steatosis [57]. In a case report, Tushuizen *et al.* reported improvement of liver enzymes and reduction in hepatic fat content as determined by spectroscopy after exenatide treatment [58]. In addition, in a meta-analysis of the LEAD program by Armstrong *et al.*, several thousand patients with NAFLD treated with liraglutide showed a reduction in ALT as well as NAFLD fibrosis score [59]. These are quite promising agents for the treatment of NAFLD, especially in the setting of diabetes, but further confirmatory clinical studies are needed.

Summary

Non-alcoholic fatty liver disease is a condition of large magnitude with potentially very serious outcomes. The rising prevalence of obesity, diabetes and the metabolic syndrome are fueling the rise in NAFLD cases, and possibly its severity. This epidemic is demanding new diagnostic and treatment approaches; however, the best approach remains controversial given the lack of strong data to support the various options at our disposal. Diet, exercise, weight loss, bariatric surgery and thiazolidinediones all have a proven clinically significant beneficial effect, decrease liver function tests and improve abnormal liver histology associated with NAFLD. These should be considered as first-line therapy in patients with NAFLD. Early hopeful results are available for metformin, insulin, GLP-1 agonists, probiotics and FXR agonists, but all of these still require confirmatory studies, and their clinical utility in NAFLD will hopefully be elucidated within the next few years. ARBs exert

a slight beneficial effect and should not be considered first-line agents in treating NAFLD but should be considered in select patients with hypertension and hepatic steatosis. Vitamin E, UDCA and statins have not shown to be beneficial and should not be used for this indication. Of note, statins can be used safely and should be used in patients with diabetes and NAFLD even if liver function tests are abnormal, provided other causes of liver disease have been excluded.

Expert commentary

Treatment studies in NAFLD abound, yet there are surprisingly few high-quality and definitive trials in the field, especially in patients with Type 2 diabetes, leading to a lack of consensus regarding the best treatment options. Lifestyle interventions, weight loss and PPAR γ agonists are the only interventions consistently proven to be effective. No other therapeutic intervention has significant and consistent data to support its large-scale use. With lifestyle interventions so difficult to implement and sustain, and the safety concerns recently raised of PPAR γ agonists, there is a clear need for high-quality studies evaluating the effectiveness of other therapeutic interventions and also comparative studies among different treatment options. The following are just a few of the shortcomings of many of the available studies that future studies would need to overcome:

- Uncontrolled, nonrandomized studies;
- Short duration of the intervention;
- Inconsistent outcome measures;
- Exclusion of patients with diabetes;
- Contradictory results.

The most promising emerging treatment for NAFLD is the incretin mimetics class, especially the GLP-1 agonists. These agents are proven to lower glycemia and promote weight loss, and probably improve blood pressure. Preliminary studies showed a positive effect on hepatic steatosis and further controlled studies are underway. If the initial observations are confirmed, these will likely become the preferred agents to address multiple co-morbidities in this patient population.

In addition, commonly used antidiabetic agents, such as metformin and insulin, should be further studied to specifically evaluate their role in the treatment of patients with Type 2 diabetes and hepatic steatosis. Several studies have shown that metformin reduces hepatic steatosis, yet other studies showed no beneficial effect and therefore the role of metformin is still debated. Insulin, an adipogenic hormone, would be expected to worsen hepatic steatosis, yet limited studies to date suggest otherwise.

Five-year view

The next 5 years will prove exciting as this field of study continues to evolve, and with the increasing prevalence of obesity our approach to NAFLD must continue to improve. The three biggest research needs in the field are:

- Furthering our knowledge of the NAFLD pathophysiology and especially its interplay with CVD and diabetes;
- The development of sensitive and noninvasive diagnostic tests, which can accurately assess the extent of the disease and predict its progression;

- Expanding our treatment armamentarium with effective agents, which not only slow down the disease course, but also reverse the metabolic milieu that promotes CVD.

All these areas will see progress within the next few years, as a multitude of studies is currently underway.

As the molecular pathways of NAFLD are unveiled, we are likely to see new targeted agents, such as the FXR agonist class. Just as important as finding new agents will be the evaluation of drugs we already use in patients with diabetes – such as insulin, metformin or incretin mimetics. Because NAFLD and diabetes coexist in a high percentage of patients, knowledge about the effect of commonly used antidiabetic medications on NAFLD may lead to changes in the treatment algorithms. While PPAR γ agonists have been proven as effective agents for both conditions, safety concerns have now caused a significant decrease in their use. It is likely that, if proven effective, incretin mimetics will become the first-line treatment choice for patients diagnosed with both conditions.

Furthermore, the field is lacking comparative studies among effective agents, a need that will have to be filled in the next decade. Newer and more costly agents should have a significant efficacy advantage over metformin to justify their use. Ultimately, we need to keep in mind that the major morbidity of our patients with NAFLD arises from CVD; therefore, effective interventions should prove not only to decrease the progression of liver disease, but ultimately to improve cardiovascular morbidity and mortality.

Key issues

- Hepatic steatosis is the first stage in the disease continuum of non-alcoholic fatty liver disease. Up to 30% of patients with hepatic steatosis progress to non-alcoholic steatohepatitis, and 30% of patients with non-alcoholic fatty liver disease progress to cirrhosis.
- Hepatic steatosis is present in up to 75% of patients with Type 2 diabetes.
- The prevalence of hepatic steatosis is expected to rise significantly along with that of obesity and Type 2 diabetes.
- Hepatic steatosis is becoming the most common cause of chronic liver disease, and also contributes to worsening Type 2 diabetes and cardiovascular disease.
- The majority of patients with hepatic steatosis are asymptomatic and have normal liver-function tests.
- Liver biopsy is the gold standard of diagnosis but it is invasive; alternatively, imaging techniques can be employed but these do not yet have the ability to estimate the degree of histological changes.
- Proven successful therapeutic interventions for hepatic steatosis comprise of lifestyle modifications (e.g., low-calorie diet and/or exercise), bariatric surgery and PPAR γ agonists.
- Therapeutic interventions that likely improve hepatic steatosis but currently lack confirmatory clinical data comprise of metformin, glucagon-like peptide 1 agonists, farnesoid X receptor agonists and ARBs.

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