Non-alcoholic Fatty Liver Disease: Pharmacotherapy

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INTRODUCTION

Hepatic steatosis (commonly called fatty liver) is mostly an asymptomatic liver disease, which is diagnosed mostly as a part of an unrelated condition. It was considered to be a benign consequence of chronic alcohol intake. In absence of alcohol intake of >20 g/day, it is termed as non-alcoholic fatty liver disease (NAFLD). Non-alcoholic fatty liver disease consists of accumulation of fat within hepatocytes with/without inflammatory changes. The fatty change and the inflammation spectrum are similar to the alcoholic fatty liver disease. While primary or idiopathic NAFLD forms the major part of this disease spectrum, we should always address secondary causes leading to fatty changes in liver. Management consists of general measures of risk reduction like: instituting weight loss program, diet control, exercise, weight loss drugs, use of insulin sensitizers like metformin and thiozolidinediones, use of cytoprotective agents like vitamin E, betaine and hypolipidemics like statins.

In this Review we shall address the mechanism of action of these management strategies, efficacy as seen in clinical trials, and critically evaluate the current evidence for their use in view of recent guidelines and recommendations.[1]

LIFESTYLE MODIFICATION

Weight Reduction

A 1 year weight loss intervention in 15 subjects with non-alcoholic steatohepatitis (NASH) that achieved only an average 3 Kg weight loss resulted in an improvement in histology in 9 subjects.[2,3] Those with improved histology were found to have had greater weight loss, improved liver transaminases, and decreased liver fat. Weight reduction is one of the most effective strategies to reverse fatty changes accumulated in hepatocytes. It can be achieved by diet control, exercise, use of weight loss drugs or bariatric surgery.

Diet Control

This is currently the most efficacious strategy in countering steatosis, biochemical and histological changes. Initial studies were[4–11] inadequately powered to detect effect on various parameters; however, a systemic review of these studies and various case series showed that various types of diet alteration led to significant reduction in liver aminotransferases and hepatic steatosis as seen on ultrasound.[12] A preliminary study, done in 6 subjects with NAFLD has shown that the oral administration of 6.5 mL olive oil enriched with omega-3 polyunsaturated fatty acids (ω-3 PUFA) for 12 months improve the liver echo texture and decrease circulating liver enzyme and triglycerides. Recent studies have showed improvement both in steatosis and biochemical parameters[13–16] by diet control. Lifestyle modification by diet, exercise or combination of interventions for weight loss has consistently led up to 40% (range 30–75) change in liver fat as detected in magnetic resonance spectroscopy (MRS). The degree of fat loss was proportional to intensity of weight reduction in these studies provided the weight loss ranged between 5% and 10%.[3,7,10] In general 500 Kcal of deficit per week leads to 1 pound reduction[12] of weight each week and energy restriction of 25–30 Kcal/Kg/day leads to a weight loss of up to 10 after 6 months.[13,14] However, reports involving more intensive weight reduction up to 1.6 Kg/week in morbidly obese patients has led to increased risk of portal fibrosis, so caution has to be exercised at tempo of weight reduction.

Thus, even though weight reduction as less as 3–5% can lead to improvement both in NAFLD histology and biochemical parameters; a significant reduction of 10% or more will have a beneficial effect on necro-inflammation as well.

Exercise

Exercise increases insulin sensitivity; however in various studies it has been shown to be less effective than diet control both in weight reduction and improvement in hepatic histology.[6,7] Exercise has not shown consistent effect on other necro-inflammatory changes in hepatocytes.[17–20]

PHARMACOTHERAPY: THERAPEUTIC AGENTS

Pharmacotherapy for Weight Loss

Orlistat

Orlistat has been the most studied weight loss medication as a potential treatment for NASH. This medication inhibits gastric and pancreatic lipase and has been shown to prevent 30% of dietary triglycerides from being absorbed. Pilot studies with orlistat given for 6 months along with dietary counseling showed promising improvement in serum aminotransferases as well as hepatic steatosis and inflammation.[21] Two subsequent randomized placebo-controlled trials treated patients between 6 and 9 months with significant improvement in hepatic steatosis seen in both orlistat groups.[21,22] However, orlistat is effective treatment for NASH only in the setting of significant weight loss, and as an only modestly successful weight loss agent, it falls short as a treatment panacea for NASH.

Rimonabant

The endocannabinoid (EC) system is involved in the regulation of food intake and body weight and as such, represents a novel target for medical therapy of NASH. The EC receptors are generally located in liver, skeletal muscle, adipocytes, and pancreas. Rimonabant is a selective CB1 receptor antagonist that has been shown to decrease hepatic lipogenesis and increase satiety, adiponectin levels, and glucose uptake, thereby improving insulin levels and lipid profiles and leads to improvement in liver enzymes and weight loss and decreases hepatic fat but does not lead to any histological improvement.[21,23] This agent was initially developed as a weight loss medication and has been well studied in two large randomized placebo-controlled multicenter trials.[24,25] In a meta-analysis NNH (number needed to harm) for discontinuation due to adverse side effect was 14, which were significantly low as compared to NNH of 39 for orlistat. Due to these reasons it is not recommended as therapy for NASH as of now.

Insulin Sensitizers

Metformin

Though mode of action of metformin is unclear, it has been postulated that it acts by decreasing hepatic gluconeogenesis increasing peripheral and hepatic insulin sensitivity, slowing intestinal glucose absorption, and reducing serum lipid levels and hepatic fatty acid oxidation and it has been shown to decrease steatosis in murine models as well. Initial trials of metformin[26–28] showed decreased steatosis and inflammation but no change in fibrosis, while in an open label study using 2 g/day of metformin for 48 weeks NASH was improved

only in one-third of the patients,[29,30] further trials of metformin[31–36] revealed a non-significant benefit.[29,30] However, a recent meta-analysis concluded that 6–12 months of metformin plus lifestyle intervention did not improve aminotransferases or liver histology, compared with lifestyle intervention alone, independently of metformin dose or the presence of diabetes. Currently there is a weak support for evidence-based recommendations of metformin use for management of NAFLD.[37]

Thiozolidinediones

Thiozolidinediones bind to peroxisome proliferator-activated receptor (PPAR)-y, a nuclear receptor expressed in the liver, muscle, and adipose tissue that regulates adipocyte differentiation, fat metabolism, and inflammation. Activation of the receptor leads to multiple potential beneficial effects for NASH including inhibiting hepatic fatty-acid synthesis,[38] remodeling adipose tissue to sequester fatty acids,[39] promoting an insulin sensitive profile by increasing adiponectin levels,[40] and decreasing pro-inflammatory cytokines. Initial randomized controlled trials (RCTs) on thiozolidinediones improved aminotransferases and hepatic steatosis but had variable effects on necro-inflammation and fibrosis.[41–44] While study by Aithal showed significant improvements in metabolic and histologic parameters, most notably liver injury and fibrosis over a 12-month period of pioglitazone therapy in nondiabetic subjects with NASH.[45]

In PIVENS study though there was an improvement in NASH (47% vs 21%, p = 0.05) on taking pioglitazone at 30 mg/day for 12 month, primary end point of necro-inflammation and fibrosis was not affected.[46] But a recent meta-analysis have shown a significant benefit with glitazones in patients without diabetes, in all histological and biochemical outcomes, most importantly including fibrosis (WMD = 0.29, 95% CI 0.078–0.51, *P* = 0.008).[47] Taking into account generally beneficial effect of thiozolidinediones on NASH, it is recommended for use in biopsy proven NASH.[1]

However, recently there have been concerns about side effects pioglitazones in congestive heart failure (CHF), coronary artery disease (CAD), osteoporosis, and bladder cancer and even death.[48] This limits the potential number of candidates in whom pioglitazones can be given for treatment. Further since pioglitazones cause weight gain, it further decreases avenues for its use in metabolic syndrome.

However as of date, pioglitazones are definitely the most preferred insulin sensitizers and recommended over metformin in NASH.

Alfa-glucosidase Inhibitor (Acarbose)

Postprandial hyperglycemia, one of the characteristic features of insulin resistance, also induces oxidative stress generation, being involved in dysfunction of pancreatic beta cells and vascular wall cells in the metabolic

syndrome. Acarbose improves postprandial hyperglycemia by delaying the release of glucose from complex carbohydrates in the absence of an increase in insulin secretion, the beneficial aspects of acarbose could be ascribed to improvement of insulin sensitivity in type 2 diabetes and newly diagnosed hypertension. Given the pathological link between NASH and insulin resistance, acarbose may become a promising therapeutic strategy for the treatment of patients with NASH.

However, large clinical trials will provide us with more definite information whether acarbose treatment can improve insulin sensitivity and reduce the risk of progression of liver diseases in patients with NASH.

Second Generation Sulfonylureas

Second generation sulfonylureas, such as repaglinide and nateglinide, have also been considered as possible NAFLD treatment options. Ten diabetic patients with biopsy-proven NASH were randomized by Morita and colleagues to receive nateglinide 270 mg daily with diet and exercise or diet and exercise alone for 20 weeks.[49] In the nateglinide group, improvements were noted in postprandial glucose, hemoglobin A_{1C}, glucose tolerance test results, liver function tests, and imaging and histological findings of NAFLD. Suffice it to say, these and other possible treatment options require further study and validation.

Cytoprotective Agents

Vitamin E

Antioxidants intuitively are intriguing has a potential therapy. Pathophysiologically, oxidative stress appears to be a part of mitochondrial and endoplasmic reticulum stress. Vitamin E acts by decreasing lipid peroxidation and its antioxidant properties prevent hepatocellular injury.[50–54] The evidence for vitamin E use is generally based on non-blinded and underpowered studies. Meta-analysis done before PIVENS and TONIC studies[55] suggested that vitamin E primarily causes decreases in aminotransferases, improvement in steatohepatitis while having no benefit in hepatic fibrosis.[3] PIVENS[50] study showed that pure form of alfa-tocoherol administered at 800 IU/day for 96 weeks led to improvement in liver histology of non-diabetic NASH in 42% of participants as opposed to 19% receiving placebo. The NNT (numbers needed to treat) for a significant benefit in this study was low 4.4 and hence clinically important.

However, recently there has been a controversy on effect of high dose vitamin E on all—because of mortality with some studies finding an association[56–58] while others could not see an association.[59–61] A recent RCT suggested that even low dose of vitamin E at 400 IU/day could result in a very small but absolute increase in prostatic cancer risk of 1.6/1000/1000 person years.[62]

In light of current evidence vitamin E is recommended at a dose of 800 IU/day in biopsy proven non-diabetic NASH while it is not recommended in NAFLD in diabetics, on-biopsied NASH patients or cryptogenic cirrhosis.

Ursodeoxycholic Acid

Ursodeoxycholic acid (UDCA) is the non-hepatotoxic epimer of chenodeoxycholic acid. Ursodeoxycholic acid replaces endogenous bile acids, which are hepatotoxins, has membrane stabilizing and cytoprotective effects on mitochondria as well as immunological effects. It is believed that by decreasing bile acids, UDCA protects against hepatocyte injury and decreases oxidative stress in patients with NAFLD. Ursodeoxycholic acid has been used in the treatment of some hepatobiliary diseases for nearly 2 decades.[63–66] A pilot study of UDCA or clofibrate in the treatment of non-alcohol-induced steatohepatitis found significant improvement in alkaline phosphatase, ALT, GGT, and hepatic steatosis treatment with UDCA for 12 months without any clinical benefit of clofibrate.[63]

High dose UDCA (23–28 mg/Kg) or placebo failed to improve the overall histology in 185 patients with NASH in comparison with placebo.[64] Ratziu et al used slightly higher doses of UDCA (28–35 mg/Kg) in a RCT of 126 patients for 1 year. This treatment led to a decrease in ALT and improved fibrotest results. There was no repeat liver biopsy at the end of this study.[66] In another pilot study by Singh et al,[67] high dose UDCA (600 mg BID) for a mean duration of 6 months were found to improve both biochemical parameters and liver histology in diagnosed cases of NASH.

Omega-3-fatty acids

Omega-3-fatty acids have been used traditionally for hypertriglyceridemia. There have been many animal studies[68] but not much has been achieved in human trials.[62]

Hence omega-3-fatty acids are currently not approved for treatment of NAFLD or NASH but may be considered to address hypertriglyceridemia in setting of NASH or NAFLD.

Hypolipidemic Agents

Statins

Statins competitively inhibit 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA), which is a rate limiting step of cholesterol synthesis by occupying a portion of the active site of enzyme.

This leads to a reduction in intrahepatic cholesterol which in turn leads to increase in low-density lipoprotein (LDL) receptors on hepatocytes, which in turn bind to serum LDL and decrease their concentration in blood.

Patients with NAFLD should be risk stratified and their risk factors should be addressed.[70] While there exists a theoretical risk of rise of aminotransferases with statin use, many studies have conclusively established that statins are safe for use in chronic liver disease and NAFLD.[71–75] Several studies suggest that statins improve histology and liver enzymes in patients with NASH.[75–83] A secondary analysis of GREACE study also showed that statins improved liver enzymes and cardiovascular outcomes in subset with NAFLD. On basis of this evidence statins are currently recommended to treat dyslipidemia in NAFLD.

Miscellaneous Therapeutic Approaches

Other therapeutic non-mainstream pharmacological approaches have also been investigated where evidence is less robust based on small clinical trials and animal studies, and these are currently not recommended by standard guidelines. These consist of:

Altering Macronutrient Content

This approach focuses on various approaches in modifying type of diet.

1. Altering PUFA to saturated fatty acid (SFA) ratio in NASH patients. Zivkovic[77] suggested that diets consisting of low glycemic index promote insulin sensitivity.
2. Modification of various types of fat. Excess amount of SFA leads to steatosis while monounsaturated fatty acids rich foods like olive oil, are thought to be beneficial because they decrease triglycerides, LDL, serum cholesterol, and maintain high-density lipoprotein (HDL).
3. Polyunsaturated fatty acid ratio alteration. Ratio-6 to ω-3 PUFA is important in predicting insulin resistance. Increased ω-6/ω-3 PUFA ratio is an important predictor of insulin resistance[85], while consumption of foods like fish oil and walnuts which are rich in ω-3 PUFA (alfa-linolenic acid) show improvement in serum triacylglycerol level, liver enzyme level, and hepatic steatosis.[68]
4. Fructose content—High fructose content has been suggested to lead to hepatic lipogenesis, hypertriglyceridemia, and hepatic insulin resistance.[86]
5. Trans fatty acid—The use of trans fatty acids is generally discouraged.

Thus, despite the macronutrient composition manipulation appears to lack robust evidence; general concept of foods with low glycemic index, no fructose, increased ω-3 PUFA, monounsaturated fatty acid (MUFA), and decreased SFA seem to be generally recommended for healthy lifestyle.

Incretin Analogs

Peptide derivative of glucagon like protein-1-receptor agonists like exenatide have been explored as therapeutic agents for NASH. They promote insulin

secretion, decrease gastric, emptying prevent excess glucagon secretion, and cause weight loss. Nausea is a dose dependent effect of exenatide, which is addressed with dose titration.[21] There have also been case reports of decreased steatosis and improved liver enzymes in diabetic treated with glucagon-like peptide-1 (GLP-1) analogs.

However, as of now in absence of adequate number of RCTs it is not recommended for specific treatment of NASH.

Betaine

Betaine, a component of the metabolic cycle of methionine, raises S-adenosylmethionine levels, which may reduce hepatic steatosis.[87] An eight-week trial of betaine supplementation in patients with NASH compared with placebo showed reductions in ALT, AST, and GGT levels, and steatosis in the treatment group. A pilot trial in NASH patients treated with dose of 20 mg/day of betaine for 12 months led to improvement in aminotransferases level and histology.[88] However, RCTs are necessary before betaine can be prescribed as a specific therapy for NASH.

Pentoxifylline

It is a cytoprotective agent which inhibits tumor necrosis factor-alfa (TNF-α). It has been widely used in alcoholic hepatitis. Many case reports and pilot trials suggested that anti-inflammatory properties of pentoxifylline might decrease TNF-α and interleukin-6 (IL-6) levels in body and hence they are generally beneficial in steatohepatitis treatment.[89,90] A statistical pooling of effects on TNF-α and IL-6 in control and pentoxifylline group did not yield a significant difference in the meta-analysis. Since nausea is a very common and significant side effect of this medication, many patients discontinue it. Drop-out rates of up to 50% has been reported, which limits the clinical efficacy of this drug.[89,90] Hence, pentoxifylline is not currently recommended for specific therapy of NASH.

Ezetimibe

Ezetimibe due to its lipid lowering properties on triglycerides and LDL has been suggested for treatment in NASH for some pilot studies. However, there have been no clinical trials to support its use and hence it is not recommended for specific therapy of NASH.

Angiotensin Receptor Blockers

Angiotensin receptor blockers (ARBs) have been shown to have hepatoprotective properties in addition to their role in treatment of hypertension and CHF. Some human pilot studies have suggested that ARBs might improve liver aminotransferases and provide histological benefit.[91,92]

However, large RCTs are needed before incorporating them for specific treatment of NASH.

Probiotics

Probiotics have been proposed as a treatment option for patients with NAFLD and NASH because of their balancing role on the flora of the gut that may act as a potential source of hepatotoxic oxidative injury.[93]

Probucol

Probucol acts by increasing the rate of LDL metabolism and hence has lipid-lowering agent and anti-oxidant properties making it potentially useful for the patients with NASH.[94,95]

Carnitine

Carnitine is required for the transport of fatty acids from the cytoplasm into the mitochondria, where oxidation occurs. It is also thought to decrease oxidative stress.[96] In a recent RCT, the addition of 1 g L-carnitine to a diet and exercise program vs diet and exercise alone for 24 weeks resulted in decreased steatosis, hepatocellular injury, parenchymal inflammation and fibrosis in 74 NASH patients.[97] L-carnitine may be a useful tool either as mono- or combination therapy for the management of NASH but further research is needed to solidify these results.

Combination Therapy

A randomized 2 years placebo-controlled trial of UDCA (12–15 mg/Kg/day) with vitamin E (400 IU twice a day) (UDCA/Vit. E), improved laboratory values and hepatic steatosis of patients with NASH.[52] Single therapy with vitamin E or combined therapy with UDCA caused recovery of NAFLD in 60% of patients; although adding UDCA had no significant effect on treatment outcome. Small sample size could cause a pitfall in this study that limits ability to establishing equivalence of two modalities.[98] In a 10-year single center experience, the combination therapy of UDCA with vitamin E significantly improved liver function tests and also were very well-tolerated.[99]

PERSONALIZED MANAGEMENT IN NON-ALCOHOLIC FATTY LIVER DISEASE

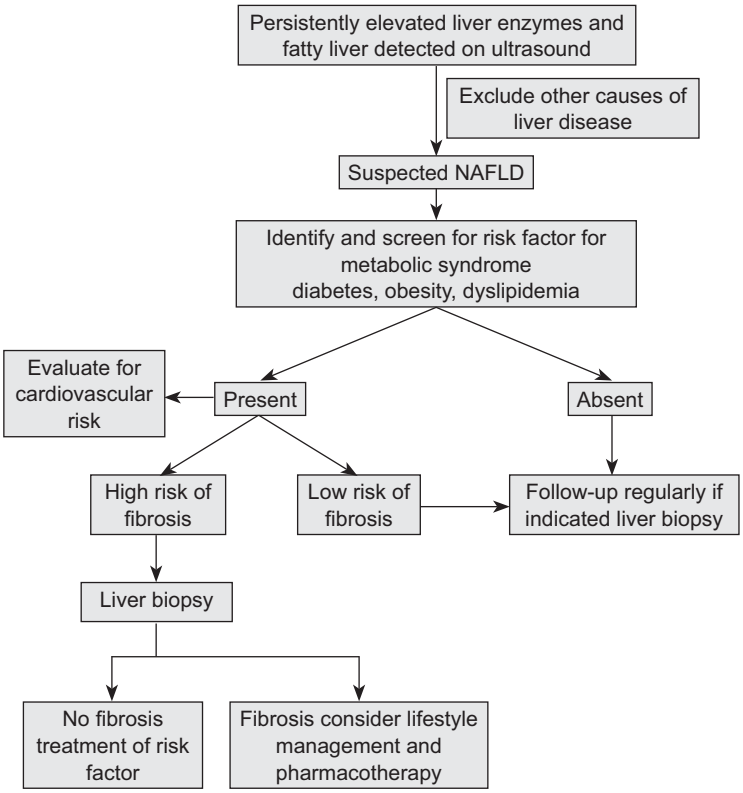
Non-alcoholic fatty liver disease classically refers to a spectrum of pathology from steatosis to steatosis with inflammation (NASH), which is not caused by alcohol abuse.

Clubbing several diverse molecular and epigenetic defects under same diagnosis can result in adverse and inefficient patient management. With the advances in molecular medicine and diagnostics, diseases like NAFLD and diabetes mellitus type-2 that are currently considered and managed as single entities would split into several distinct entities which might differ

in management, like what is happening currently in oncology: where we target a drug to a particular receptor. Thus, exploration of the molecular and genetic basis of NAFLD will allow us to classify them separately, manage them appropriately, and reduce the side effects[100] A simplified algorithm for approach to NAFLD and pharmacotherapy is summarized in Algorithm 1 and 2, respectively.

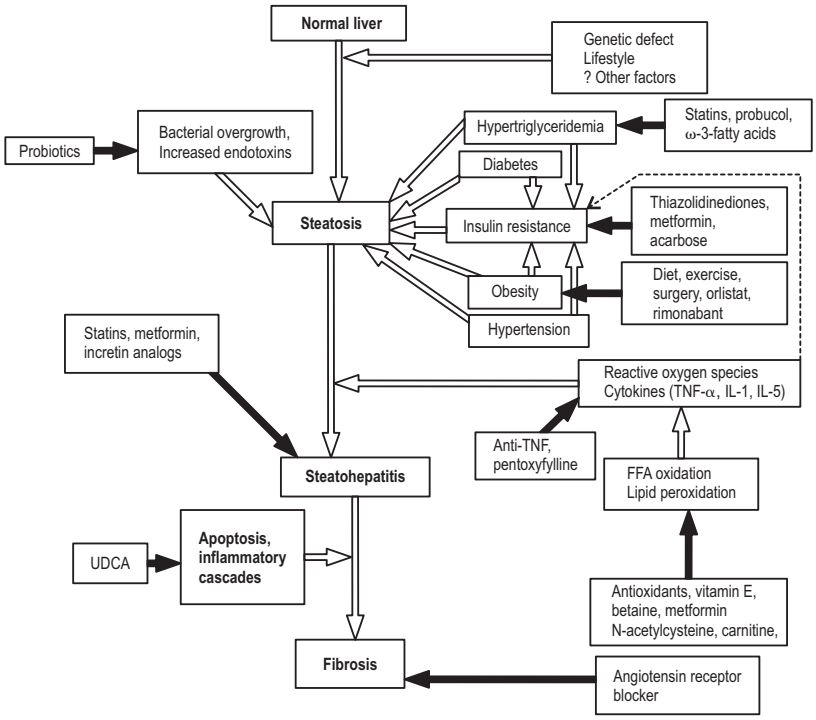
CONCLUSION

Non-alcoholic fatty liver disease is an important cause of chronic liver disease worldwide. Weight loss, lifestyle modification, and exercise should form the key stone of any treatment regime addressing NAFLD. Insulin sensitizers like thiozolidinediones, antioxidants like vitamin E, and statins also have a role in treatment of biopsy proven NASH. Other therapeutic approaches offer promise but have to be validated in large RCTs before being used as a specific therapy of NASH.



Algorithm 1. Algorithmic approach to non-alcoholic fatty liver disease.

NAFLD: non-alcoholic fatty liver disease.



Algorithm 2. Pharmacotherapy of non-alcoholic fatty liver disease.
TNF: tumor necrosis factor; IL: interleukin; FFA: free fatty acid; UDCA: ursodeoxycholic acid.

CLINICAL CASE

A 45-year-old male resident of Delhi comes to the medicine OPD with elevated liver enzymes over past 1 year. He has a significant history of weight gain in past 5 years. He is a social drinker, active smoker, and occasionally complains of right hypochondrial pain and dyspepsia, which has been more frequent in past 7 days. He has past medical history of dyslipidemia, hypertension, and impaired fasting glucose. He has been taking telmisartan 40 mg for his blood pressure control for past 3 years. On physical examination, he is obese with body mass index (BMI) of 31.4, his blood pressure is 138/86 mmHg, and pulse rate is 82/minute. He has mild *Acanthosis nigricans*. He has no hepatosplenomegaly or stigmata of chronic liver disease. Remainder of physical and other systemic examination is within normal limits.

Investigations reveal hemoglobin (Hb) 13.2 g%, TLC 6,800, DLC P60 L32 M4 E4, platelet count 2,10,000/μL, fasting glucose 122 mg%, his lipid profile consists of LDL 146 mg%, HDL 42 mg%, triglycerides 320 mg%, total cholesterol is 252 mg%, his liver profile shows total bilirubin of 0.7 mg/dL, direct bilirubin 0.3 mg/dL, INR 1.1, aspartate aminotransferase (AST) 64, alanine aminotransferase (ALT) 98, alkaline phosphatase (ALP) 106 mg/dL, S. albumin is 4.2 mg/dL, and globulin 2.3 mg/dL. He has been worked up for viral hepatitis, autoimmune disease, hemochromatosis and Wilson's disease,

and all serologies are negative. His ultrasound report says: hepatomegaly with diffuse heterogenosity suggestive of fatty liver.

Q 1. What factors would lead to a suspicion of NAFLD in this patient?

A history of obesity, dyslipidemia, impaired fasting glucose, unexplained rise of liver aminotransferases, and central obesity with acanthosis nigricans raise suspicion of NAFLD.

Other cause of liver diseases like alcohol consumption: <20 g/day in male and 10 g/day in female, viral hepatitis (HbsAg, anti-hepatitis C virus [anti-HCV]), Wilson's disease (serum ceruloplasmin), hemochromatosis (ferritin, transferrin), auto-immune liver disease (antinuclear antibodies [ANA], anti-mitochondrial antibody [AMA]), history of ayurvedic, alternative treatment with herbal/drugs with high metal content should be ruled out before pointing to a diagnosis of NAFLD in these patients. Baseline anthropometric assessment must be done in patient of metabolic syndrome. Serum ferritin might be raised in these patients as a marker of inflammation.

Q 2. What is the difference between NAFLD and NASH?

Non-alcoholic steatohepatitis is a subset of NAFLD that has in addition to steatohepatitis, a histological evidence of hepatocyte injury like inflammation of lobules, ballooning degeneration, and perivenular or perisinusoidal fibrosis. Non-alcoholic fatty liver disease prevalence has been documented to be 18–25% in worldwide studies, while prevalence of NASH is suspected to be 3–6%. Non-alcoholic fatty liver disease prevalence is much higher in patients of diabetes and metabolic syndrome to the tune of 65–75%.

Q 3. What is the difference in prognosis of NAFLD and NASH?

Non-alcoholic fatty liver disease has generally low risk of progression to cirrhosis while NAFLD patients with NASH histology follow one-third rule i.e., one-third will be stable, one-third will regress, and one-third will progress to cirrhosis.

Q 4. How would you differentiate between NAFLD and NASH?

Liver biopsy is the gold standard for providing a clear cut evidence of steatohepatitis.

Other non-invasive approaches are magnetic resonance imaging (MRI), computed tomography (CT) scan, transient elastography (FibroScan®). All of these modalities are developing, however, none of them has proven to be a clear cut alternative to liver biopsy. Serum biomarkers like hyaluronic acid, C-reactive protein (CRP), cytokeratin 18, adipocytokines have also been used. Scoring system has been used consisting of combination of clinical indices and biomarkers. But they have not had universal validation as of now.

Q 5. Would you go for liver biopsy in this patient?

Liver biopsy is the gold standard for diagnosis of NASH and its preference might vary according to medical practitioners. In general, indicators which sway clinicians in favor of liver biopsy are presence of diabetes, obesity, age over 50 years, AST/ALT > 0.8, high triglycerides, worsening of liver enzymes on therapy.

In these patients apart from raised triglycerides, other factors don't support liver biopsy at this point. So a trial of lifestyle changes and medical therapy should be given before doing liver biopsy. However, if and when liver biopsy is done: the hepatic histology must be graded (necro-inflammatory activity) and staged (fibrosis). There are systems in place for documenting hepatic histology. Brunt classification is a commonly used system.

Q 6. How does treatment of isolated fatty liver (NAFLD without NASH) differ from biopsy proven NASH or patients at high risk of developing NASH?

Lifestyle modification should be applied to both group consisting of weight reduction (energy intake of 25–30 Kcal/Kg/day or targeting a caloric reduction of 500 Kcal initially, increasing the activity level), other methods might consist of taking foods with low glycemic index, altering macronutrient composition (high intake of PUFA, less SFA, increasing intake of ω-3 PUFA).

However, in addition to these measures a trial of medical therapy should be considered of patients with biopsy proven NASH or at a high risk of NASH (morbidly obese, diabetics, raised AST).

Q 7. What are the drugs with definitive benefit in NAFLD based on current evidence?

Based on recent AASLD guidelines, thiozolidinediones should be preferred as insulin sensitizers; vitamin E in dose of 800 IU/day is beneficial in biopsy-proven NASH. Statins might be given in case of dyslipidemia in NAFLD patients, while ω-3-fatty acids should be given in patients of hypertriglyceridemia.

Q 8. How many patients of NASH deteriorate and go on to require liver transplant?

While 15–30% of NASH patients go on to develop progressive liver disease only 2–5% of them actually require liver transplant.

Q 9. What is the role of statin in this patient?

This patient has three risk factors according to adult treatment panel (ATP)-3 guidelines. His Framingham risk score is between 10–20%. Hence, LDL cut off to start drug therapy is >130 mg/dL. Hence, he should be started on statins and continued till his LDL goal of <130 mg/dL is met. Nicotinic acid and ω-3-fatty acids might be considered to address hypertriglyceridemia in this patient in case statins are not effective.

Based on evidence and information provided, the patient described in the case above did not go for liver biopsy, was advised lifestyle modification, abstinence from smoking, and caloric reduction. He was started on atorvastatin of 20 mg/day for dyslipidemia; pioglitazone 15 mg/day, and the side effects of these medicines were explained to him.

Liver function tests were repeated after 63 months, there was improvement in aminotransferases AST 44 IU/L, ALT 52 IU/L, LDL 120 mg%. Lifestyle modification was continued.

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