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Review Article

Non Alcoholic Fatty Liver Disease: Does It Really Matters?

Mohammed Alim,[1] Rakesh Sahay,[2] Mohammed Ibrahim[3]
[1] Jawaharlal Nehru Technological University, Kukatpally, Hyderabad
[2]Osmania General Hospital, Hyderabad
[3]Department of Pharmaceutical Biotechnology, Nizam Institute of Pharmacy, Deshmukhi, Pochampally (M), Near Ramoji Film City, Nalgonda 508284, Andhra Pradesh, India.

ABSTRACT
In past few decades the incidence and prevalence of Non-Alcoholic Fatty Liver Disease (NAFLD) has been increasing in western and Asian countries. Several lines of evidence have indicated a pathogenic role of insulin resistance, and a strong association with type 2 diabetes (T2MD) and metabolic syndrome. Currently Vitamin E has been recommended as firdst line treatment for Non-alcoholic Fatty liver disease in patients who are not alcoholics. India has the largest number of people with diabetes. Moreover, Asian Indians are more prone to insulin resistance and have increased waist circumference and body fat (particularly visceral fat), features that are described as the Asian Indian phenotype. However limited data is available on prevalence and incidence of NAFLD in India. In the present review we tried to explore the current pathophysiology and treatment options and how important is the disease condition.
Keywords: Non Alcoholic Fatty Liver Disease, Oxidative stress, Insulin resistance

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Address for Correspondence:
Mohammed Ibrahim
Department of Pharmaceutical Biotechnology, Nizam Institute of Pharmacy, Deshmukhi, Pochampally (M), Near Ramoji Film City, Nalgonda 508284, Andhra Pradesh, India.
E mail: ibrahim_cce@rediffmail.com
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INTRODUCTION
Ludwig named Nonalcoholic steatohepatitis (NASH) in the year 1980 which is now consider as one of the manifestations of the broader nonalcoholic fatty liver disease (NAFLD) spectrum. [1] Non-alcoholic steatohepatitis is the most extreme form of NAFLD, which is considered significant reason of cirrhosis of the liver of unknown cause.[2] Non-alcoholic fatty liver disease (NAFLD) is fatty inflammation of the liver when this is not due to excessive alcohol use.

Recent basic and epidemiologic data reveal that the spectrum of NAFLD is closely associated with obesity, diabetes, and hyperlipidemia, a constellation of clinical problems that arise from insulin resistance[3] No proven treatment for patients with NAFLD is currently available. Weight reduction with diet changes are typically suggested as the first step in the treatment of patients with this condition[4]

Epidemiology:

The prevalence ofNAFLD and NASH in general population is increasing, in obese populations, NAFLD may be present in 75% of subjects. Indeed, in the morbidly obese, steatosis (NAFLD)has been found in almost all subjects, with NASH being present in 25–70% of these individuals. However, these studies were mainly done in western populations. South Asians (people belonging to India, Pakistan, Bangladesh, Nepal, Sri Lanka and Malaysia) in general and Asian Indians in particular, have very high rates of diabetes, insulin resistance and premature CAD which are observed as risk

factors for NAFLD.In India the prevalence is expected to be around 19% in adult population (amrapurkar 2007), moreover, a recentclinic-based study suggests differences in the clinicopathological profile of Indian patients with NAFLD[5].

Pathophysiology: There is great interest in the study of NAFLD, and there are new insights into its pathogenic process. Currently, in addition to insulin resistance, endocrine, immunologic, and central nervous system factors are attracting interest as explanatory variables associated with this chronic liver disease. The exact cause of NAFLD is still unknown. However, obesity and insulin resistance probably play a strong role in the disease process. The precise reasons and mechanisms by which the disease progresses from one stage to the next are the subject of much research and debate. Few theories on pathophysiology have been discussed here.

Immune Response

The regulatory process associated with the immune-mediated damage is not completely understood. The role of the immune response in chronic liver diseases, including NAFLD, has been studied in several animal-based experiments and human trials, which have demonstrated the importance of several cytokines in the inflammatory component of NAFLD. The involvement of leptin in NAFLD has been clearly described; the main profile of NAFLD patients is hyperleptinemia with resistance to the physiologic effects of leptin, [6,7,8] but this resistance profile hasnot been clearly described.

Leptin administration to rodents has been shown to increase liver fatty acid oxidation and to decrease hepatic steatosis by activating the PPAR-α system, and to diminish the expression of several lipogenic genes[9] Another pathway associated with the immune response in NASH that has not been investigated in detail involves Chitotriosidase (Chit), an enzyme that belongs to the family of glycosyl hydrolases. In humans, levels of Chit expression are significantly higher in NASH patients than NAFLD patients or control patients, and there is a positive correlation between CHIT expression and the degree of NASH. Plasma levels of Chit activity are higher in NASH patients than in NAFLD patients. The expression of TNFα correlates with Chit induction in NASH and steatosis patients, whereas in control subjects, there is no correlation between CHIT and TNFα mRNA levels [10]

Insulin Resistance

Various factors participate in the regulation of insulin sensitivity, including a complex network of endocrine signals in which adiponectin plays a key role. The discovery of leptin has made an important contribution to our understanding of the relationship between the nervous system and obesity, and therefore of the relationship between the nervous system and NAFLD[11,12]

In a study by Uno et al[13]direct role of the vagal afferent and efferent neural branchesin the regulation of liver insulin sensitivity has been demonstrated. They performed selective hepatic vagotomy on mice in whichPPARγ2 was over expressed using an adenovirus vector and administered a pharmacologic β-adrenergic blocker. They demonstrated that 1) β-adrenergic nerve function enhances lipolysis in adipose tissues of mice that overexpressPPARγ2, 2) the hepatic vagus nerve mediates the remote effects of hepatic PPARγ2 expression, 3) activation of the afferent vagal nerve at the liver mediates the remote effects of hepatic PPARγ2 expression on peripheral lipolysis, and 4) the effects of PPARγ2 on glucose metabolism are dependent on the afferent vagal and efferent sympathetic nerves. This hypothesis was extended not only to the insulin sensitivity pathway but also to liver fibrosis, as confirmed by other studies in which both surgical and chemical methods of cholinergic enervation decreased expression of bone morphogeneticprotein-6 and transforming growth factor-β1 in carbon tetrachloride-induced liver fibrosis of rats[14] This mode of action has also been described for other elements of metabolic syndrome[15,16]

Oxidative Stress

Oxidative stress and mitochondrial dysfunction role has been described widely, however not all processes involved have been clarified, mainly the role of oxidative stress in diseases associated with obesity. In particular, pathways for sterol regulatory element binding protein 1c-related fatty acid synthesis and PPARα are upregulated in the livers of mice fed an HFD. In contrast, the pathway for fatty acid synthesis is downregulated n adipose tissue. In contrast to the pathways involving fatty acid metabolism, oxidative stress pathways are coordinately upregulated in both the liver and adipose tissue, but the mRNA expression level of TNFα in the liver and adipose tissue of mice fed an HFD for 6 weeks is similar to that of control mice. Furthermore, the plasma level of TNFα was below the detection limit of the enzyme-linked immunosorbent assay in both groups. These data suggest that the production of

ROS may be an initial key event that triggers HFD-induced insulin resistance. [17]

Apoptosis

Apoptosis is a mode of cell death used by multicellular oganisms to dispose of unwanted cells under a diversity of conditions, including NAFLD. In subjects with NASH, the number of TUNEL-positive cells is greater than that of controls[18] This clinical evidence indicates that this pathway is relevant to the pathophysiology of NASH. Apoptosis is associated with oxidative stress. Liver injury is often linked with the induction of protective factors such as antiapoptotic members of the Bcl-2 protein-family. Bcl-2 is notably upregulated in NASH (an increase of 112-fold) and is almost absent in control specimens. Despite upregulation of Bcl-2, apoptosis is increased in steatohepatitis, which confirms that the protective response is insufficient under these conditions. In contrast to Bcl-2, no significant changes were found in Bcl-xL expression, suggesting that this protein is not implicated in a possible protective liver pathway against steatohepatitis. New advances have been made since the initial description of the role of Fas in NASH, within which upregulation of Fas contributes to hepatocyte cell death. [19]

Treatment

Treatment of NAFLD requires a consideration of which patients require treatment. Because not all cases progress to advanced liver disease, and because the goal of treatment is to improve liver-related outcomes from a liver standpoint efforts should be focused on patients with steatohepatitis and not simple steatosis. Several approaches have been used to differentiate simple steatosis and steatohepatitis. The clinical presentation of patients with simple steatosis is similar to the presentation in NASH, therefore clinical presentation cannot reliably distinguish between the two. Demographic and clinical parameters like age, gender, race, body mass index, dyslipidemia, or diabetes cannot reliably differentiate between simple steatosis and steatohepatitis. [20]

To date, no large reliable clinical trials have demonstrated efficacy in altering the natural history of NAFLD. Based on current understanding of the pathogenesis of NAFLD, investigational therapy has been targeted at reducing intrahepatic oxidant stresses and improving insulin resistance.

Weight Loss

Patients with NAFLD or metabolic syndrome are encouraged to adopt a program of diet and exercise with the goal of weight loss as a first step in their treatment.

The antiobesity drugs, orlistat and sibutramine have been studied for their effects on steatohepatitis.[21,22]

Insulin Sensitizing Agents

Among the insulin sensitizing agents used for the treatment of NASH, thiazolidinediones (TZDs) have been studied the most and have shown the most favorable results. TZDs increase fatty acid oxidation and decrease fatty acid production within the liver. Insulin sensitivity is improved both peripherally and within the liver. Several studies on the effects of TZDs on NAFLD and NASH report favorable results [23, 24] including improved transaminases and steatosis. [24,25] The effect of TZDs on fibrosis is variable, improving in some, unchanged in others, but not worsening. Several studies have examined the utility of metformin in the management of NAFLD and NASH. Significant improvement in transaminases, insulin, and C-peptide levels and necroinflammatory activity were noted in the metformin group, however the difference was not statistically significant.[26]

Antihyperlipidemic Agents

Only a few studies have examined the efficacy of statins for NAFLD treatment. A pilot study by Rallidis and colleagues examined pravastatin use in four NASH patients for six months; they found improvement in inflammation in three patients and improvement in steatosis inone patient.[27]There is some suggestion that fibrates, such as clofibrate, gemfibrozil, and fenofibrate may have some benefit in NAFLD treatment. Significant improvements in alkaline phosphatase levels were only noted with Clofibrate[28] A four-week study showed that gemfibrozil improved ALT levels, but histological data was not obtained[29] Because pioglitazone, a PPAR-γ agonist with weak PPAR-α activity, has shown some benefit in NAFLD treatment, it is possible that fenofibrate may have some benefits well, due to its PPAR-α activity; this however has not been evaluated in any trials[30]

Antioxidants

Oxidative stress is considered a major contributor asthe "second hit" in the pathogenesis of NAFLD and NASH, justifying the study of several antioxidants in NAFLD treatment. A large randomized, multicenter, double-blinded, placebo-controlled trial of pioglitazone and Vitamine E is currently in progress by investigators from NASH Network[31] These researchers have enrolled 247 patients who will

receive pioglitazone 30mg qd, vitamin E 800 IU qd or placebo for 96 weeks. The primary outcome, improvement according to defined histological criteria, will be based on paired liver biopsies. The results are expected to shed more light on the efficacy of treatment with vitamin E.

Other antioxidants such as betaine and N-acetyl-cysteine (NAC) have also been studied for their purported antifibrotic effects [32-35]. Some researchers have surmised that endotoxins producedby gut flora may also contribute to oxidative stressin the liver, and that alterations in that flora may have beneficial effect upon the liver. Most of the support comes from results in animal models. [36,37]Only two small open label studies have been conducted with probioticsin patients with NAFLD.[38,39]

Ursodeoxycholicacid (UDCA) is a naturally occurring bile acid believed to have cytoprotective and immunomodulator properties and may decrease apoptosis[40]Satapathy and colleagues obtained histological evidence of improvement in 2007, in a trial treating 9 patients with biopsy-proven NASH with pentoxifylline 400 mg tid for 12 months[41] Significant transaminase improvement was again noted. Upon follow-up liver biopsy, improvement in steatosis and lobular inflammation was noted in 55% of patients, decreased stages according to Brunt's criteria was noted in 67% of patients, and fibrosis improved in four out of the six patients with fibrosis at baseline.

New Treatments

Incretin analogues, such as exenatide and sitagliptin, increase glucose-dependant insulin secretion, decrease inappropriate glucagon secretion, and increase satiety by delaying gastric emptying.[42]Second generation sulfonylureas, such as repaglinideand nateglinide, have also been considered as possible NAFLD treatment options[43]

CONCLUSION

Currently Vitamin E has been recommended as first line of treatment for NAFLD. However NAFLD is strongly believed to be because of Insulin resistance and metabolic syndrome. More studies are needed to clarify the specific pathophysiology and treatment. Research in these areas may help in finding proper treatment strategy for NAFLD.

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