

INTRODUCTION

Non-alcoholic fatty liver disease includes a spectrum of condition ranging from simple steatosis to steatohepatitis (NASH-characterised by hepatocyte ballooning, lobular inflammation with or without fibrosis) to cirrhosis. NAFLD and diabetes share common risk factors like obesity and insulin resistance, but there exists a complex relationship between diabetes and NAFLD. One condition may accelerate the progression of other. Both the conditions have been found to increase the risk of macro-vascular and micro vascular complications.

EPIDEMIOLOGY AND NATURAL HISTORY

The overall prevalence of NAFLD in Asian countries varies from 9-40% and in western countries from 15-40%. In India, the prevalence of NAFLD is around 9-32% in the general population, but it is 12.5-87.5% in patients with type 2 diabetes mellitus as reported in various studies (Table 1). Data on NAFLD in type 1 diabetes mellitus are scanty. Taghar et al have reported prevalence of NAFLD of 44.4% in a series of 250 type 1 diabetes mellitus patients. Studies showing prevalence of NASH by liver biopsy in diabetes with NAFLD are scanty and it is estimated to be 63-87% which is much higher when compared to non-diabetics. Diabetes has also been associated with increased prevalence of substantial fibrosis in NASH. Diabetes has been demonstrated to be an independent risk factor for progression of advanced fibrosis in longitudinal studies. Patients with cirrhosis secondary to NASH are at increased risk of developing hepatocellular carcinoma (HCC). Moreover, HCC can occur in NASH with cirrhosis.

Table 1: Prevalence of NAFLD in diabetic patients in India

Author Name	Study Year	Number of Subjects	Prevalance
Gupte et al	2004	100	34% (M: 38.6%, F: 29.5%)
Mohan V et al	2009	541	32% (M: 35.1%, F: 29.1%)
Uchil D et al	2009	1003	22.6% (M: 29%, F: 13.9%)
Prasant M et al	2009	204	35.7% (M: 38.1%, F: 26.4%)
SPRINT Study group(Sanjay Kalra et al)	2013	522	56.5% (M: 54.3%,F: 60%)

PATHOGENIC MECHANISMS OF DEVELOPMENT OF NAFLD IN DIABETES

Factors causing NAFLD and its progression in diabetes is not well understood, but are likely to be an interplay of genetic factor, disordered lipid metabolism, disturbance of glucose metabolism related to insulin resistance, increased oxidative stress, dysregulation of gut microbiota and inflammation. The “two hit ” hypothesis was proposed early, but the new proposed model for pathogenesis of NASH is “multiple parallel hits ” hypothesis. The main concept is that different events occur in parallel, not consecutively.

- A. Genetic Factor

Polymorphism of adiponutrin/patanin like phospholipase domain 3(PNPLA3) has been be an important susceptible gene. Mutation of other genes like microsomal triglyceride transfer protein (MTP), apolipoprotein-c3 (Apo c3), genes encoding TNL- α , IL-6 and angiotensin-II receptor.
- B. Insulin Resistance

It leads to increased lipase activity leading increased release of free fatty acids (FFA) from adipose tissue to hepatic and systemic circulation. Insulin resistance also leads to up regulation of sterol regulatory element binding protein (SERB-1) which reduces the disposal of free fatty acid by inhibiting their uptake and oxidation by mitochondria.
- C. Lipid Toxicity

Toxic lipid metabolites play an important role in causing inflammation. The thought to contribute to NAFLD progression are cholesterol, diacylglycerol (DAG) and glycosphingolipid.
- D. Oxidative Stress and Hepatic Inflammation

The oxidative stress generated from reactive oxygen sepsis augments the inflammatory process by NFK- β , c-JunN terminal kinase activation and toll like receptor signalling.
- E. GUT Microbiota Dysbiosis and Endotoxemia

Modification of composition of gut microbiota (increased Firmicutes and decreased Bacteroides) could increase the permeability of gut and translocation of bacterial endotoxins such as lipopolysaccharides which can induce inflammation.

Hepatic steatosis increases liver insulin resistance in liver through accumulation of fatty acid metabolites like DAG. The effect of hepatic steatosis in rodent model seems to be linked to decrease signalling of IRS-1 and IRS-2 causing increase hepatic glucose production and impaired glycogen synthesis. There is also evidence that insulin secretion may be defective in people with NAFLD through sustained elevation of FFA leading to pancreatic β -cell lipotoxicity.

LINK OF DIABETIC COMPLICATIONS WITH NAFLD

NAFLD has been shown to be associated with increased prevalence of both micro-vascular and macro-vascular complications in diabetics. Cardiovascular disease is the leading cause of death in patients with advanced NAFLD. Presence of NASH appears to have greater risk than simple steatosis. NASH has also been shown to be associated with increased mortality from all causes and liver related causes.

Few studies have shown increase presence of microalbuminuria and chronic kidney disease in patients with NAFLD, though it needs to be confirmed from larger prospective studies. There are studies showing higher prevalence of diabetic retinopathy in patients with diabetes and NAFLD. Presence of NAFLD has also been linked to increase risk left ventricular diastolic dysfunction in diabetes, but needs conformation by further studies.

TREATMENT

Main goal of treatment is to improve liver fibrosis. Unfortunately no treatment to date has been proven to prevent fibrosis in NASH in any large scale randomised controlled trial (RCT).

1. Life Style Intervention

Sustained weight loss has been associated with marked improvement in liver enzymes and hepatic steatosis, but not fibrosis.

2. Bariatric Surgery

Though it is one of the definite modality of treatment for weight loss, there is no RCT as a treatment for NASH.

3. Effect of Antidiabetic Medication

A. Insulin

There is little direct evidence that insulin will improve histological picture of NASH. HbA1C reduction by insulin is more strongly associated with improvement in liver fibrosis. Large scale RCT is necessary to confirm any direct beneficial effect.

B. Metformin

Several recent meta-analyses have concluded that metformin is not effective for treatment of NASH. TONIC trial has demonstrated improvement only in hepatocyte ballooning, but there is no

significant difference in other histological pictures or improvement in ALT.

C. Pioglitazone

Several studies including PIVENS have demonstrated significantly decrease in liver enzymes, hepatic steatosis, and inflammation, but no significant regression in fibrosis.

D. Liraglutide

LEAN trial, the first RCT of liraglutide in NASH (both diabetics and non-diabetics) has demonstrated definite resolution of NASH, especially improvement in steatosis and ballooning but, there was no significant change in NAFLD activity score (NAS). So it can be a promising therapeutic option in type2 diabetes mellitus with NASH.

E. DPP-4 Inhibitor

Only some short term clinical trials have been published and no study has demonstrated any improvement in histological picture of NASH.

F. SGLT-2 Inhibitor

Though the administration of canaglifozin has been found to reduce liver aminotransferases and body weight its effect on NASH needs further study.

4. Other Drugs

A. STATIN- There is no convincing data on improvement in histological picture in NASH, but may reduce macro-vascular events in patients with dyslipidemia.

B. Omega-3FATTY Acids- It has been demonstrated to reduce liver steatosis, liver inflammation and decrease in transaminases .

C. Vitamin E - In PIVENS study higher rate of improvement in NAS score was demonstrated with vitamin E 800IU/day. There was also significant improvement in hepatic steatosis, inflammation and ballooning, but no improvement in fibrosis. But safety in long term use is a matter of concern.

D. Pentoxifylline- In recent meta-analysis it has been demonstrated to improve transaminases, NAS and hepatic lobular inflammation, but no significant improvement in steatosis and ballooning. Few studies involving small number of patients have also reported improvement in fibrosis.

E. Angiotensin Receptor Blockers- In a small study of 54 patients with NASH, Telmisartan group had greater improvement in hepatic steatosis, necro-inflammation and fibrosis.

F. Ursodeoxycholic acid - The clinical benefit has not been convincingly proved.

G. Ezetimibe- In two small clinical trials it has been demonstrated to reduce transaminases and hs-CRP

and improve NAS on liver biopsy, but needs RCT to prove efficacy.

- H. Obeticholic Acid (Farnesoid X-Receptor Agonist) - In FLINT trial higher rate of resolution of NASH, NAS and improvement in fibrosis score has been demonstrated and appears to be a promising agent.

CONCLUSION

There are limited number of studies on epidemiology and natural history of NAFLD in diabetes. The relationship between diabetes and NAFLD is complex and is not clear. Lifestyle interventions aimed at weight loss remains the corner stone of management. Among the anti-diabetic drugs pioglitazone and liraglutide appears to be potentially useful. Other drug like obeticholic acid and pentoxifylline appears promising, but larger RCT is required to prove their efficacy before a firm recommendation.

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