CHAPTER

# 67

# Diabetic Hepatopathy

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## INTRODUCTION

There is a high prevalence of diabetes in India estimated at 67 million. Asians have a high susceptibility for type II diabetes mellitus (DM), develop diabetes at younger age and have a higher risk of diabetes complications. Common complications reported are nephropathy, retinopathy, neuropathy, coronary artery disease, peripheral vascular disease and increased risk of infections. The prevalence, morbidity and mortality from liver disease has been largely overlooked.

Liver disease is an important cause of death in type 2 diabetes. Diabetes, by most estimates, is now the most common cause of liver disease. Cryptogenic cirrhosis, of which diabetes is, by far, the most common cause, has become the third leading indication for liver transplantation. A large study of patients with & without Type II DM followed up for 10 years showed that the incidence of non-alcoholic CLD and HCC was 2 fold greater in diabetic patients compared when compared with non-diabetic patients. . In the population-based Verona study, cirrhosis was the fourth leading cause of death and accounted for 4.4% of diabetes-related deaths. The standardized mortality ratio (SMR), for cirrhosis was 2.52 compared with 1.34 for cardiovascular disease (CVD).[1] Thus the importance of liver disease in diabetics has been grossly under estimated.

Virtually the entire spectrum of liver disease is seen in patients with diabetes. Diabetes causes increased risk of acute liver failure, chronic non-alcoholic fatty liver disease (NAFLD), cirrhosis, hepatocellular carcinoma (HCC) and mortality due to liver diseases. Insulin resistance is the key pathogenic mechanism leading to fat deposition in liver. Multiple other factors such as oxidative stress, mitochondrial dysfunction and circulating cytokines in diabetics contribute to disease progression. Diabetes is an independent risk factor for fibrosis which is key determinant of progressive liver disease. 20-25% of diabetic patients with steatosis progress to steatohepatitis (NASH), out of which about 20% further progress to cirrhosis over 10-15 years. Associated features of metabolic syndrome such as obesity, dyslipidaemia also add to risk and progression of early liver disease to liver fibrosis and cirrhosis.

**Table 1: Diabetic Hepatopathy**

| | |
|---|---|
| Liver diseases caused by diabetes | Liver diseases aggravated by diabetes |
| Glycogenic hepatopathy | NAFLD / NASH |
| Diabetic hepatosclerosis | NASH related Liver cirrhosis |
| | Hepto cellular carcinoma |

Liver diseases related to diabetes (either caused or aggravated by) may be called diabetic hepatopathy. It comprises of a number of conditions as shown in Table1.

## NAFLD IN DIABETES- THE PROBLEM AND EPIDEMIOLOGY

Diabetes leads to a significantly increased prevalence and severity of NAFLD. NAFLD encompasses a broad spectrum of disease severity, ranging from isolated steatosis (NAFL) to a more severe form with variable degrees of inflammation, ballooning, liver cell necrosis and fibrosis defined as non-alcoholic steatohepatitis (NASH). Among the various histological features of NASH, fibrosis strongly correlates with end stage liver disease and higher mortality.[2,3] Patients with diabetes have more fatty liver as compared to age, gender and BMI matched controls.[4] Even in non-diabetic individuals it has been shown that increasing levels of HbA1c and insulin resistance is associated with increased risk of NAFLD.[5] Impaired glucose tolerance and abnormal fasting glucose is present in 25% patients with simple steatosis versus 55% of those with NASH.[6] In a large study of serial liver biopsies it was seen that patients with NASH, rather than NAFL, were more likely to be diabetic (56% vs 21%) and patients with advanced fibrosis or cirrhosis were more likely to be diabetic than those without advanced fibrosis (89% vs 47%).[7] These evidences collectively show that diabetes confers the highest risk for NAFLD and specially NASH.

The prevalence of NAFLD in Indian population ranges from 11-32% and about 4-5% have NASH. In comparison, the prevalence of NAFLD in diabetics is 60-65% and 20-25% of these patients have NASH.[8] When diabetes is associated with obesity the prevalence of NAFLD is >90% and that of NASH is 30-40%. In a recent study of obese Type II diabetic patients with normal liver enzymes who underwent liver biopsy, it was shown that more than 50% had NASH.[9]

In a large study the standardized mortality ratio of cirrhosis was higher in diabetics (2.52).[10] The presence of diabetes is an independent risk factor for fibrosis in patient with NAFLD.[11] There is also a higher risk and poorer prognosis of HCC in cirrhosis (esp. in association with hepatitis C).[12] There is also evidence that diabetes impairs sustained viral response to antiviral therapy in chronic

**Table 2: Non invasive scoring systems for severity of fibrosis**

| Scoring System | Parameters / Calculation | Cut off for severe fibrosis / cirrhosis |
|---|---|---|
| APRI | 1. AST Level<br>2. Platelet count<br>APRI=[{AST(IU/L) / AST _ULN (IU/L)} X100] / Platelet Count ($10^9$/L) | >1 |
| FIB4 | 1. Age<br>2. AST & ALT Levels<br>3. Platelet count<br>FIB4= age (year) x AST (IU/L) / Platelet Count ($10^9$/L x [ALT (IU/L) $^{1/2}$] | >3.25<br>< 1.45 has negative predictive value |
| ELF (enhanced liver fibrosis) | 1. Tissue inhibitor of metalloproteinases 1 (TIMP-1)<br>2. Amino-terminal propeptide of type III procollagen (PIIINP)<br>3. Hyaluronic acid (HA) | >10.51 |

hepatitis C. Diabetes increases complications of cirrhosis such as rate of liver failure, higher mortality in refractory ascites & increased episodes of hepatic encephalopathy.

Liver disease in diabetics is a major public health problem. It can be estimated that out of the 67 million diabetics in India, the prevalence would be NAFL in 40 million, NASH in >7 million and cirrhosis in >1.5 million. There is also an annual risk of about 2-3% of the cirrhotic patients developing hepatocellular carcinoma.

NAFL is a relatively benign condition in general population with a risk of cirrhosis in <2% of population. On the other hand, NASH has a 10 fold higher risk of liver related death and doubling risk of cardio vascular disease. Identification and aggressive treatment of NASH in diabetics is important to prevent disease progression.

In a study, the prevalence of NAFLD in diabetics in India was 56.5% and the mean AST & ALT level was 54 U/L and 56 U/L respectively. It implies that patients with even a mild elevation of AST/ ALT are a risk factor for NAFLD/ NASH.

## NASH DIAGNOSIS IN DIABETICS

The diagnosis of NASH in diabetics is no different than in general population and is based on non-invasive markers, liver fibroscan or liver biopsy. Some of the associated risk factors for NASH are: (1) Age > 45, (2) Obesity (BMI > 25 Kg/meter), (3) Low albumin, (4) Low platelet count & (5) High AST / ALT ratio.

A number of non-invasive scoring systems have been devised for assessment of liver fibrosis. (Table 2). Simple blood tests such as AST, ALT and platelet counts are inexpensive and easily available. These levels can be used to calculate AST, platelet ratio index (APRI) and FIB4 scores which correlate with severity of fibrosis and can be used in resource limited settings such as our population. The sensitivity and specificity of these tests are higher only in the extremes of fibrosis, i.e., either no fibrosis or severe fibrosis. The Enhanced Liver Fibrosis (ELF) score is an ECM (Extra cellular matrix) marker set consisting of TIMP1, PIIINP & Hyaluronic acid. ELF score of 10.51 or above correlates with severe fibrosis. Newer techniques such as transient elestrography (Fibroscan) is more accurate and shows better correlation with Metavir scoring than APRI & $FIB_4$ and is preferable where equipment and cost is not an issue.

Liver biopsy followed by the use of Metavir scoring system remain the gold standard to assess degree of fibrosis. However, liver biopsies in our setting are infrequent due to high cost, invasiveness, associated morbidity and the need for expert interpretation.

## TREATMENT OF NAFLD IN DIABETES

### Diet and life style modification

Treatment of NAFLD / NASH is life style modification with diet and exercise, control of associated metabolic factors, optimization of diabetic control and use of specific drugs for NASH. Till date, however, there are no approved drugs for treatment of NASH.

The most fundamental intervention is life style modification with diet and exercise which can lead to significant improvement in transaminases and histology. The recommended exercise is 40-45 minutes of brisk walking daily for at least 5 days of a week. A low caloric diet is advised in obese patients aiming for a gradual weight loss of 0.5-1kg/week. The goal should be for a 10% weight loss initially. Weight loss of >1.6kg/week can worsen histology. Weight reduction >7% sustained over 48wks is associated with histological improvement. Weight loss of 5-10% significantly reduces intrahepatic triglycerides by about 40%.[13] However, less than 50% of Indian patients achieve the necessary weight loss due to poor compliance to diet and exercise.

**Table 3: Therapeutic agents for T2DM and their effect NAFLD/NASH in clinical trials**

| Treatment | Mechanism of action | AST/ALT | Liver fat by imaging | Liver histology |
|---|---|---|---|---|
| Oral | | | | |
| Metformin | Insulin-sensitizer | ↓ | ↓, ⇔ | Unchanged |
| **Pioglitazone** | **Insulin-sensitizer PPARγ agonist** | ↓ | ↓ | **Improved** |
| Sitagliptin | DPP-4 inhibitor | ↓ | n/a | n/a |
| Vildagliptin | DPP-4 inhibitor | ↓ | ↓ | n/a |
| Canagliflozin | Inhibits renal glucose reabsortion | ↓ | n/a | n/a |
| Dapagliflozin | Inhibits renal glucose reabsortion | ↓ | n/a | n/a |
| Injectable | | | | |
| Exenatide | GLP-1 receptor agonist | ↓ | ↓ | n/a |
| **Liraglutide** | **GLP-1 receptor agonist** | ↓ | ↓ | **Improved** |
| Insulin | | n/a | ↓ | n/a |

## Treatment of Associated Metabolic Factors

The association of obesity, dyslipidemia and hypertension is common in diabetes. Treatment of the associated metabolic factors is important to reduce the prevalence and severity of NAFLD. Obesity is treated with life style measures and orlistat has been effectively used for weight reduction. Bariatric surgery is an effective treatment for obesity and has been shown to markedly improve diabetes. It also improves histological features in NAFLD and smaller studies have shown regression in liver fibrosis, although there has been mild increase in fibrosis seen during long-term follow up. The drug of choice for dyslipidemia are statins which reduce lipid levels, cardiovascular risk and additionally improve AST / ALT levels, although its effect on liver histology remains controversial. The drug of choice for hypertension are angiotensin receptor blockers such as losartan & telmisartan which have also got liver protective effect and some small studies have shown a reduction in HCC risk.

## Treatment of Diabetes in patients with liver disease

Optimizing control of blood sugar is important to prevent liver disease progression. While there are theoretical concerns about altered drug metabolism and hepatotoxicity, only patients with evidence of liver failure such as ascites, coagulopathy, or encephalopathy have altered drug metabolism Since most oral hypoglycaemic agents are metabolized in liver, there is a higher risk of hypoglycaemia and requires close blood sugar monitoring. The choice of oral hypoglycaemic drug should ideally be based on its ability to control blood sugar along with the ability to improve LFT, reduce hepatic fat and improve liver histology. Trials of OHA are scanty in patients with CLD. An overview of drugs and their ability to improve hepatic parameters is shown in Table 3.

Insulin sensitizers such as biguanides and thiazolidine-diones appear to be the most attractive option.

## Metformin

This is the first line agent in management of Type II DM. In a large study despite improvement in HbA1c and weight there was no significance histological improvement in liver.[14] The use of metformin in diabetics with severe liver disease remains controversial. It also reduces the risk of HCC in patients with cirrhosis.[15] In a recent retrospective analysis, patients with diabetes and cirrhosis using metformin had a longer median survival rates than those who discontinued metformin.[1] It is now considered a useful drug in patients with compensated cirrhosis but is relatively contraindicated in patients with decompensated cirrhosis and individuals with ongoing alcohol abuse because of risk of lactic acidosis.

## Thiazolidinediones (TZDS)

In the PIVENS study of non-diabetics with NASH, pioglitazone showed improvement in LFT and liver histology, although the effect on fibrosis was not significant.[17] Pioglitazone showed a significant improvement in hepatic steatosis and necroinflammation in a 6 months study of diabetic patients [(18)]. A recent study by Cusi et al[19] showed a significant histological benefit in steatosis, NASH and fibrosis showing that pioglitazone may modify the natural history of liver disease in diabetes. Adverse effects of pioglitazone have always been a concern but congestive cardiac failure is rare and is related to diastolic dysfunction. Mild bone loss occurs mainly in females. An earlier concern about bladder cancer risk was recently dispelled by a prospective study showing lack of association between pioglitazone and bladder cancer.[20]

## Sulphonylureas in Diabetic Patients with Liver Disease

Sulfonylureas are generally safe in patients with liver disease but may not overcome the insulin resistance and defects in insulin secretion seen in patients with coexistent alcoholic liver disease and pancreatic damage this group of drug is largely metabolized in liver. There has also been a concern about increased risk of HCC and overall mortality in diabetics.[21] Sulfonylureas with a short half-life such as glipizide, glyburide or glimipride can be used in these patients. Gliclazide, is extensively metabolized in the liver and is relatively contraindicated in severe hepatic insufficiency.

### α-Glucosidase inhibitors

The $\alpha$-glucosidase inhibitors may be particularly useful in patients with liver disease because they act directly on the gastrointestinal tract to decrease carbohydrate digestion and glucose absorption thereby decreasing postprandial hyperglycemia

A randomized double-blind trial evaluated the use of acarbose for the control of postprandial hyperglycemia in patients with compensated liver cirrhosis and type 2 diabetes. .Glycemic control improved significantly in both the fasting and postprandial state. In a recent placebo-controlled cross-over trial in patients with hepatic encephalopathy, acarbose significantly decreased fasting and postprandial glucose as well as A1C .There was also a reduction in blood ammonia levels, which paralleled an increase in bowel movement frequency. . While the labeling of acarbose has a warning for patients with liver disease, it appears to be safe and effective in patients with hepatic encephalopathy and type 2 diabetes.

### DPP – IV Inhibitors in NAFLD

These are widely prescribed as adjunctive oral therapy in Type II diabetic mellitus. They improve hepatic steatosis, liver inflammation in animal's models of diet induced obesity.[22] DPP-IV inhibition is associated with improved sugar control and reduced AST / ALT levels.[23] Reduction of hepatic triglyceride has also been demonstrated. Overall DPP-IV inhibitors have modest effect in current studies and larger studies are required to establish their role in diabetes with NASH.

### GLP-1 Agonists

A significant decrease in AST / ALT levels and hepatic steatosis was observed with liraglutide in a dose of 1.8mg in a meta-analysis of 6 RCTs.[24] Another study showed a 42% relative reduction of intra hepatic triglyceride with the use of these agents. In the most comprehensive study to date, the LEAN trial showed benefit when 52 patients with biopsy-proven NASH were treated for 48 weeks with liraglutide at a dose of 1.8 mg per day.[25] Only one-third of the population had T2DM, but overall patients were obese and had evidence of insulin resistance. After treatment, 39 % of liraglutide treated patients had resolution of NASH compared to only 9 % in the placebo arm. While fibrosis did not improve with liraglutide, more patients in the placebo arm experienced worsening of fibrosis ($p = 0.04$). Patients treated with liraglutide had a significant reduction of body weight, fasting plasma glucose and A1c levels.

Overall treatment of NAFLD in diabetics with GLP-1 agonists appears attractive but larger long term studies are required.

### SGLT2 Inhibitors

Studies have shown decrease in hepatic triglyceride and other inflammatory biomarkers when treated with these agents.[26] The administration of canagliflozin (100 or 300 mg per day) for 52 weeks is associated with a reduction in plasma AST / ALT levels, especially at the higher dose, but their impact on liver histology is unknown.[27] Considering that these pharmacologic agents improve hyperglycemia, induce weight loss, and may improve insulin sensitivity, they are actively being explored for the treatment of NAFLD/NASH in patients with T2DM.

## DIABETES & CIRRHOSIS

The drug treatment of diabetes in cirrhosis has already been discussed.

Patients with compensated cirrhosis need special attention at nutrition and life style management. Optimal control of diabetes improves outcome. Patient with decompensated cirrhosis need management of complications. Outcome can be improved with nutrition, life style management, diabetes control, reduction of portal pressure in patients with large varices, and prevention of infection especially in those with ascites (A.F. protein < 1.5, S Creat > 1.2). Rational drug use and avoidance of hepatotoxic agents is important. Patients with cirrhosis should be vaccinated for hepatitis A & B.

## GLYCOGENIC HEPATOPATHY

This is a relatively rare and under recognized entity. It occurs in poorly controlled type I diabetics usually in the age groups 8-25 years. Patients present with abdominal pain, hepatomegaly and significantly high transaminase levels (50-1600IU/L). Definitive diagnosis can be made on biopsy which shows markedly increased glycogen storage in hepatocyte cytoplasm and nuclei. There is usually no fat, inflammation or fibrosis in the liver. Treatment is to obtain strict blood sugar control which improves the condition within one month.

## DIABETIC HEPATOSCLEROSIS

This is a micro vascular disease leading to deposition of collagen and basement membrane in peri-sinusoidal space and leads to high alkaline phosphatase level. The collagenisation correlates with diabetic macroangiopathy. The prevalence and clinical significance of this condition and treatment remains unclear. It is however, accepted that this condition represents a hepatic microvascular complication in diabetics.

## CONCLUSION

Diabetic hepatopathy commonly leads to high prevalence of liver disease, high morbidity, and mortality. Specific liver diseases caused by diabetes are glycogenic hepatopathy and diabetic hepatosclerosis. Diabetes increases the prevalence of NAFLD and increases its severity with development of cirrhosis leading to high morbidity and mortality. It is also more commonly associated with hepatocellular carcinoma, especially in patients with Hepatitis C. Early diagnosis and aggressive management may prevent disease progression. Lifestyle modification with diet and exercise, treatment of associated metabolic factors, and optimal diabetes control, especially using oral hypoglycemic agents which also have beneficial effects on liver function and histology, is advantageous. Bariatric surgery may be considered in obese diabetics since it leads to weight loss and simultaneous improvement in

diabetes. Patients with end stage liver disease should be considered for liver transplantation.

Screening for liver disease in diabetics is recommended in routine practice.



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