**INTRODUCTION:**

Diabetes Mellitus (DM) is a complex metabolic condition defined by the level of hyperglycemia giving rise to risk of micro vascular or macro vascular complications. DM is associated with reduced life expectancy and significant morbidity due to micro or macro vascular complications and impaired quality of life. Current estimates suggests that there are 170 million people suffering from diabetes worldwide and this number is going up to 266 million by year 2030. The prevalence of diabetes in India is around 10% i.e. 31 million people are suffering from diabetes and this number will increase to 80 million by year 2030. Indians develop diabetes at younger age, lower degree of obesity and have increased risk of chronic diabetic complications. Asians have strong genetic susceptibility for type II diabetes. Hence diabetes is a major public health concern in India. Various complications related to micro vascular or macro vascular diseases like retinopathy, nephropathy, neuropathy, ischemic heart disease/peripheral vascular disease and increased risk of infection have been reported. There is increased mortality due to these complications. Liver disease is often overlooked as a complication of diabetes. In fact VERONADIA-diabetes population based study has shown that among patients with diabetes standardized mortality rate from cirrhosis was higher than that of cardiovascular disease. Though association of diabetes with cirrhosis has been recognized for more than 100 years, liver disease in diabetes remains under estimated.

The liver is a key organ involved in glucose metabolism and energy homeostasis. Major amount of carbohydrates absorbed from the gastrointestinal track undergo hepatic processing and subsequent storage as glycogen or metabolism into amino acids or fatty acids. Hyperglycemia occurs owing to combination of processes, increased rate of hepatic glucose output secondary to insulin resistance and diminished peripheral uptake.

The relation between the diabetes and liver disease can be in three different ways – 1) liver disease causing diabetes 2) diabetes contributing or causing liver disease and 3) risk factors for liver disease and diabetes are similar.

**Diabetes due to liver disease**: Cirrhosis is associated with impaired glucose tolerance (GT) in more than 80% of the patients. Overt diabetes is seen around 20% of cirrhotics. Insulin resistance is a feature in patients with liver cirrhosis in the absence of diabetes. Pathogenesis of diabetes and cirrhosis includes peripheral and hepatic insulin resistance and decreased beta cell function. Increased mortality and increased risk of HCC has been shown in patients of cirrhosis who develop diabetes.

**Hepatitis C and Diabetes Mellitus**: Type II DM is common in Hepatitis C (HCV) infection as compared to the controls. Risk of developing DM increases two to three folds in patients infected with HCV. Post liver or renal transplant increase incidence of DM is correlated with the HCV infection. The proposed mechanism of HCV related DM suggests role of virus mediated hepatic and peripheral insulin resistance, up regulation of TNF alpha production and beta cell dysfunction. HCV seems to induce hepatocytes insulin resistance via direct action and indirect action i.e. paracrine mechanisms. This data are mostly from the experimental models of hepatoma cell lines and the transgenic mice. Confirmatory data from chronic hepatitis C patients is awaited. In a recently published study it was shown that HCV is associated with peripheral and hepatic insulin resistance in non obese, non diabetic patients with chronic HCV infection. The host factor age, race, gender, family history of DM and obesity may also play important role. Development of DM also depends upon hepatic parenchymal damage and fibrosis. In India the prevalence of HCV ranges from 0.3% to 4% in general population while prevalence of DM is around 10%. In a prospective study we demonstrated increased prevalence of DM in patients of HCV as compared to the patients with hepatitis B and controlled population. In non cirrhotic patients increased prevalence is also seen in chronic HCV infections and hence HCV infection may be a predisposing factor for development of DM in Indian population in addition to the presence of other risk factors for DM.

**Impact of DM on liver disease**: The strong epidemiological evidence suggest risk of chronic liver disease, cirrhosis, HCC and increased mortality due to liver disease is seen in patients of diabetes compared to the controlled population. There is an evidence for increased incidence of acute liver failure in patients with diabetes who are on anti hyper glycemic therapy.

Most common form of liver disease in patients with diabetes is non alcoholic fatty liver disease (NAFLD). 20-50% patients with NAFLD have diabetes. Diabetic patients with NAFLD
Table 1: Diabetes and Liver Disease

1. Liver disease causes diabetes
2. Diabetes contributes to or causes liver disease
3. Risk factor for liver disease and diabetes are same e.g. alcoholic liver disease with alcoholic chronic pancreatitis

Table 2: Impact of Diabetes on Liver Disease

<table>
<thead>
<tr>
<th>Condition</th>
<th>Incidence</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Liver failure</td>
<td>Increased</td>
<td>3a</td>
</tr>
<tr>
<td>Chronic Liver disease</td>
<td>Increased</td>
<td>2a</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>Increased</td>
<td>2a</td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td>Increased</td>
<td>1a</td>
</tr>
<tr>
<td>Increased mortality due to liver disease</td>
<td>Increased</td>
<td>2a</td>
</tr>
</tbody>
</table>

We for the first time showed NASH related liver disease was present in 6% patients with chronic liver disease in India. DM, obesity, steroid treatment and hyper lipidemia were risk factors in these patients. NASH was predominantly seen in male population. In our subsequent publication we compared the chronic liver disease pattern in diabetics vs non diabetic. NASH related cirrhosis and cryptogenic cirrhosis were common form of chronic liver disease in diabetics while alcohol and hepatitis viruses were common cause of liver disease in non diabetic chronic liver disease. In our study there was no relation between duration of diabetes in patients with NASH and NASH with cirrhosis. This can be explained on the basis of insulin resistance being responsible for the pathogenesis of NASH. Hence NASH may develop long before development of overt diabetes. Currently NASH is considered to be hepatic manifestation of metabolic syndrome. Patients with NASH have an increased risk of developing cardiovascular and liver morbidity. It was not clear whether they have increased risk of diabetes and metabolic syndrome. In various retrospective and prospective studies it is realized that patients with NASH in general community have three fold increased risk of developing diabetes and 50% increased risk of developing the metabolic syndrome. The risk of diabetes and metabolic syndrome may be related concomitant central obesity and insulin resistance. 30 - 40% patients with NASH without diabetes when subjected for CT test have either impaired GT or frank diabetic GT. This fact emphasize that NASH is a hepatic manifestation of metabolic syndrome and diabetes is one of the complications. Patients of NASH who develop diabetes have progressive liver disease.

Addressing the issue of prevalence of NAFLD in diabetic population we carried out a prospective study on 148 consecutive diabetic patients without clinical evidence of liver disease. These patients went abdominal sonography and liver function test. 49 patients had evidence of fatty liver on ultrasound. 32 out of these 49 patients under went liver biopsy. Out of 32 patients undergoing liver biopsy 10% had severe NASH (Grade III & IV fibrosis). While assessing the predictors for fibrosis in diabetic patients with NASH we could not find any non-invasive markers helpful in predicting the severity of liver disease, age, BMI, transaminases, triglycerides did not have significant predictive value. In patients with diabetes and NASH we studied the risk factors like obesity, central obesity, dyslipidemia, family history of chronic liver disease. There was no correlation between various risk factors. In our studies we confirmed the link between diabetes and NAFLD but the chronological relation is not clear. NASH precedes the development of diabetes. Risk factors like obesity, central obesity dyslipidemia and family history do not predict development of NASH in diabetics.

High incidence of type II diabetes has been demonstrated in patients with cryptogenic cirrhosis in our study also 57% of cryptogenic cirrhosis patients had diabetes. It is estimated that 10-16% case of NASH progress to cirrhosis. NASH when it progress to cirrhosis looses most of its characteristics and on histology there is no evidence steatosis. High incidence of diabetes and absence of any other identifiable cause attributable to cirrhosis goes to prove that these patients are NAFLD related cirrhosis.

Diabetes and HCC: DM is identified risk factor for HCC. DM is shown to increase the risk of HCC by two to four folds even after adjusting for other predisposing factors. In our prospective case control study we demonstrated diabetes associated with more advanced HCC and poor outcome. Diabetes appears to increase the recurrence of HCC after potentially curative therapy regardless of etiology of liver disease.

Diabetic hepatosclerosis: Diabetic hepatosclerosis is recently described as micro vascular disease manifested by increased alkaline phosphatase and deposition of collagen and basement membrane in the perisinusoidal space. Collagenization
of space of disse positively co-relates with the diabetic macroangiopathy. The prevalence and clinical significance of DSH is still unclear. DSH may represent a hepatic form of micro vascular disease in DM. 46

Glycogenic hepatopathy: It is characterized by the poor glycemic control hepatomegaly and glycogen hepatocytes. This condition is similar to Mauriac’s disease seen in children in type I diabetes. 47

Post transplant Diabetes Mellitus: Incidence post liver transplant DM is reported to be from 4% to 31% Post transplant DM may be associated with HCV, alcoholic cirrhosis immunosuppressive medication like, cyclosporine, tacrolimus, cortico steroids. Post transplant morbidity and mortality is increased in patients who developed diabetes. 48-50

Conclusion: There is a very strong correlation between diabetes and liver disease. There are various mechanisms of this association. NAFLD is common from liver disease in diabetics. Both share common pathogenesis i.e. insulin resistance. NAFLD is precursor of diabetes. Diabetes is marker of progressive NAFLD leading to cirrhosis, HCC and increased mortality.

REFERENCES:
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**Fig. 2: Hepatitis C & Diabetes Mellitus**


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