Diabetes and the Liver

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Diabetes mellitus is a disorder of impaired carbohydrate metabolism with varied systemic effects. The effects of diabetes on the blood vessels i.e. microangiopathy affecting the eyes and kidnes, macroangiopathy affecting the brain, heart and feet and nerves (neuropathy) are well known. However diabetes can have an association with other organs as well but this is not so well recognized. In this review, we shall discuss the relationship between diabetes and the liver. Before this however it is essential to discuss briefly some aspects of glucose metabolism itself.

Glucose derived by the breakdown of carbohydrates present in the food, is absorbed into the portal circulation and is transported to the liver. The liver utilizes the glucose to build up glycogen reserves (glycogenesis). The liver in its turn helps to maintain blood glucose levels within normal range. This is done by releasing glucose into the blood, whenever its level falls either by gluconeogenesis or by glycogenolysis.

The various tissues of the body absorb this glucose present in the circulating blood and utilize it to obtain the energy they require for their normal functioning. Insulin usually aids in the transport of the glucose into the cells of tissues like the muscle and adipocytes. Other tissues like the nerves and the brain do not require insulin for the transport of glucose into their cells. Once in the cell, the glucose molecule is quickly converted to glucose-6-phosphate, which then enters the next pathways, namely glycolysis. Marotta and associates[1] propose different patterns of glucose metabolism derangement in diabetics with chronic liver disease which include abnormal GTTs (glucose tolerance test). They go on to suggest that a galactose test (GaTT) can be more reliable in this case to help clearly demarcate the usual forms of diabetics from those suffering from glucose intolerance secondary to liver disease.

Many a time, liver disease leads to diabetes and diabetes inturn makes a patient more prone to liver disease. At times they occur at almost the same time and it is very difficult to say which led to which. To aid in a better understanding of the two diseases, their interrelationship during disease is dealt with as shown in Table 1.

Table 1 : Liver and diabetes : possible connections

I.	**Liver abnormalities secondary to diabetes mellitus**
•	Glycogen deposition
•	Fatty liver and non-alcoholic steatohepatitis
•	Fibrosis and cirrhosis
•	Biliary disease, cholelithiasis and cholangitis
•	Complications of treatment of diabetes
•	Viral hepatitis
•	Cancer of the liver
II.	**Diabetes mellitus and abnormalities of glucose homeostasis that occur secondary to liver disease**
•	Viral hepatitis
•	Cirrhosis
•	Hepatocellular carcinoma
•	Fulminant hepatic failure
•	Post orthotopic liver transplantation
III.	**Liver disease occuring coincidentally with diabetes mellitus and abnormalities of glucose homeostasis**
•	Haemochromatosis
•	Glycogen storage disease
•	Autoimmune biliary disease
•	As a component of autoimmune polyglandular syndrome

I. Liver disease secondary to diabetes mellitus

Glycogen deposition

The presence of insulin in the blood stimulates glycogen synthesis in the liver. Therefore it would be safe to assume that insulin deficient states must be accompanied by reduced glycogen synthase activity and inturn reduced amounts of glycogen deposits in the live.[2-4] However paradoxically some studies have described the presence of excess glycogen deposits in the liver.[5,6]

Ferrannini and his associates have demonstrated that both these effects are seen in diabetic rats.[7] In their study on acutely diabetic rats, the activity of liver glycogen synthase and hepatic glycogen reserves were

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found to fall in recently diabetic rats. However, in long-term diabetic rats there was increased glycogen deposits along with increased synthase activity. This correlates with the pattern seen in humans (diabetic patients). Most diabetics have raised liver glycogen, frequently due to hyperglycemia and increased levels of counter-regulatory hormones like cortisol.

The clinical symptoms include hepatomegaly, abnormal liver tests (raised liver enzymes like aminotransferases) and pain in the right upper quadrant. Better metabolic control by switching over to insulin injections has been recommended for the regression of the hepatomegaly and other clinical features.[5]

Fatty liver and steatohepaitis

Fatty liver is commonly seen in type 2 diabetics regardless of their glycemic status, and in type 1 diabetics with poor glycemic control. This sometimes progresses to fatty hepatitis and fibrosis and cirrhosis. Inspite of this the commonest changes seen are changes in the fat content of the liver.[5,6,8] Clinically, patients with the fatty liver show signs of hepatomegaly and raised or normal serum aminotransferases. Bilurubin levels generally remain unaffected. Though abdominal ultrasound can easily pickup the fatty liver, they fail to detect the microscopic changes that occur in the early stages of the disease. Factors like, obesity, alcoholic liver disease, chronic malnutrition and exocrine pancreatic insufficiency are the differential diagnosis as they too display fatty changes in the liver.

Whether a liver biopsy is indicated in diabetic patients with fatty hepatomegaly is still a point of debate. Some specialists believe that a routine liver biopsy in all diabetics with hepatomegaly is required to make an accurate diagnosis. Others are of the opinion that, there is no correlation between the degree of biochemical alterations and the severity of the histological findings, hence reducing the reliability of a biopsy. Other causes for fatty changes in the liver include hepatotoxins like carbon tetrachloride, abeta-lipoproteinemia, Wilson's disease, drugs such as estrogen, glucocorticoids and tamoxifen.

A variant form of fatty liver, called non alcoholic steatohepatitis (NASH) also needs mention. This is clinically distinct from fatty liver disease and is characterised by elevated liver enzymes with liver biopsies appearing identical to those seen in alcoholic hepatitis. These patients however, do not consume alcohol in quantities known to cause hepatic injury. Typically, NASH patients are obese, diabetic, middle aged women with asymptomatic hepatomegaly[9,10] or hyperlipidemia. Histologically, the symptoms of NASH range from, the most commonly encountered fatty changes to fibrosis, necrosis, and cirrhosis. Mallory bodies are also frequently seen. The diagnosis of NASH rests on liver biopsy findings once the role of alcohol in contributing to the liver changes seen is ruled out. The therapy recommended for NASH is gradual weight reduction and treatment with ursodeoxycholic acid.

Does diabetes result in cirrhosis?

Unlikely. Cirrhosis has been found to occur more frequently in diabetics than in the general popoulation. However it is unlikely that diabetes per se predisposes to cirrhosis. It is more likely that confounding factors like obesity, fatty liver, hepatitis, and NASH may have a role to play in the increased frequency of cirrhosis seen in diabetics.

Biliary and gall bladder disease

Cholelithiasis and cholecystitis have been observed in increased frequencies in diabetic patients. Here again, the true picture may be distorted by the co-existence of obesity and hyperlipidemia (which are known to promote gall stone formation). The diabetic patient may be given the same treatment as that given to non-diabetic patients with the similar problem. A direct association between diabetes and gall bladder disease has yet to be proved.

Viral hepatitis in diabetic patients

Diabetic patients seem to be more prone to viral hepatitis infections. This might be due to the frequent medical interventions that diabetic patients have to go through, which may serve to increase the risk of their acquiring hepatitis (mainly hepatitis C and hepatitis B). Use of disposable syringes and needles will help control the spread of hepatitis. There are isolated reports cited where the transmission of the hepatitis virus was traced to spring loaded injecting devices.

Diabetes mellitus as a cause of cancer of the liver

There have been reports of an increased risk of developing primary liver cancers and cancers of the biliary tract.[11,12] Even after ruling out concomitant contributory factors such as alcoholism, cirrhosis and hepatitis they have been observed to occur quite frequently. The mechanisms involved in the progression to malignancy however remain unclear. This risk of developing cancer does not seem to be affected by the type of diabetes seen.[13] Lawson *et al*[14] have sug-

gested that the association is strongest in diabetic patients on drug treatment. Further studies are required to determine if any specific agent may play a role in this propensity towards developing cancer at a later stage.

Treatment for diabetes and the probability of liver dysfunction

Many of the oral hypoglycaemic agents used in the management of diabetes undergo hepatic metabolism and hence hepatic dysfunction may alter their pharmacokinetics. On the other hand, some of the drugs are potentially hepatotoxic even in therapeutic doses. Sulfonylureas are commonly associted with hepatic toxicity, with chlopropamide being the most toxic of this class. Other commonly used sulfonylureas like glibenclamide and tolbutamide can also cause chronic hepatic and necroinflammatory changes.

The biguanide drug, metformin is excreted unchanged in the urine, and hence its pharmacokinetics is not affected by hepatic dysfunction. It is important however to remember that although metformin does not undergo hepatic metabolism, hepatic dysfunction can potentiate the development of lactic acidosis, one of the serious side effects of metformin therapy. Hence metformin is contraindicated in any hepatic dysfunction.

The new drug troglitazone has cuased a lot of concern in the recent past for its potential to cause severe hepatic damage.[15,16] Troglitazone is a thiazolidine derivative used in the management of type 2 diabetes. Clinical trials have shown that liver abnormalities (increased serum alanine aminotransferase levels / ALT levels) develop in patients commonly between one month and seven months of starting the treatment. It has also been shown that the ALT levels return to baseline values after discontinuation of the therapy. Some researchers believe that though some patients have given evidence of hepatic damage early on during the treatment, these symptoms resolve with continued treatment, suggesting that the liver seems to adjust to the changes induced by the drug. The liver injuries are predominantly hepatocellular in nature with some evidence of cholestatic change.

There is no demonstrable association between the elevated ALT levels and sex, age, the daily drug dose or concomittant medication. Many believe that the toxicity is idiosyncratic in nature. Shibuya and associates attribute the liver damage to hypersensitivity to troglitazone.[15] It is hence prudent that appropriate caution should be exercised while managing a diabetic patient with hepatic dysfunction. While prescribing potential hepatotoxic drugs like troglitazone, it is recommended that the serum ALT levels be monitored at the start of the treatment, monthly for the first six months of the treatment and then every two months for the rest of the first year. After the first year, periodic monitoring is recommended for the duration of the treatment.

In March 2000, troglitazone was banned in the USA as it was linked to 65 deaths due to liver failure. However the next generation drugs namely rosiglitazone and pioglitazone have been approved in the USA and they are believed to be 100 times more potent that troglitazone with virtually no liver toxicity.

II. Diabetes secondary to liver disease

Cirrhosis and chronic liver disease

There is evidence that diabetes mellitus is more frequently found in patients with chronic liver disease (CLD).[17,18] Cirrhosis seems to be a major isk factor in patients with CLD. This post cirrhotic diabetes is associated with higher plasma insulin levels, suggesting insulin resistance.

Sato *et al*[19] have demonstrated that CLD patients who develop abnormal glucose tolerance, have defects in the respiratory activity of the liver cells. It is important to realize that cirrhotic patients may show normal or low HbA1c levels inspite of having altered glucose metabolism. HbA1c is therefore not a reliable test in cirrhotic patients.[20]

Viral hepatitis

The association between viral hepatitis and diabetes mellitus is of great significance. The hepatitis C virus (HCV) and its genotype 2a has been largely associated with diabetes.[21] What is the possible causative role of HCV in diabetes? Some scientists suggst that pancreatic β cells might be an extrahepatic target of HCV.[22] Fraser and assocaites[23] have shown that although there is an association between HCV and diabetes, there is no association between diabetes and hepatitis B infection. There is also at least one report in the literature which has shown a negative association between HCV and diabetes. The speculation about the role of HCV needs to be settled by further studies.

Hepatitis C infection has been cited as a major cause of hepatic disease in India and has been shown to be widely prevalent among patients with liver dysfunction.[24-26] There is presently no vaccine available for hepatitis C and hence prevention right now rests solely on taking appropriate precautions to avoid

spread of the infection (screening of blood, proper sterilisation of equipment etc.).

Treatment of viral hepatitis with interferons has also resulted in the development of diabetes. There are also reports of exacerbation of diabetes during such treatment with reversible increase in insulin requirement during interferon therapy.[27,28] Caution must therefore be exercised while treating such patients with interferon. Viral hepatitis can also result in chronic liver disease and cause destruction of the liver which by themselves could contribute towards a diabetogenic state.

Hepatocellular carcinoma

Hepatocellular carcinomas may in some cases cause hyperglycemia. This has been associated with the production of IGF-II (insulin like growth factors) by the primary hepatocellular carcinoma lines (PHC).[29] Since hepatocellular carcinomas might be a consequence of chronic viral infection, it might also inturn contribute to the progression to diabetes.

Diabetes following liver transplantation

Post orthotopic liver transplant patients are seen to be associated with a predisposition to developing diabetes.[30] "Post transplant diabetes mellitus (PTDM)" has been shown to have an association with prior hepatitis C infection. A direct or immune mediated pancreatic effect of the virus has been suggested.

It must be noted that transplant patients are also prescribed heavy doses of steroids, which might predispose them to developing diabetes. The use of the immunosuppressants like FK506 and cycloporine has been linked to the development of diabetes, though glucose tolerance may return to normal levels once the drugs are stopped. Other metabolic abnormalities that are frequently associated after transplant include, obesity, hyperlipidemia and post transplant bone disease.[31] The incidence of diabetes requiring insulin is around 10% in the first six months while that of diabetes requiring oral drugs is around 20%. Successful transplantation has been performed in diabetics with liver disease through these patients are at risk of developing progressive neuropathy.

Fulminant hepatic failure

The development of hyperglycemia folowing fulminant hepatic failure has been observed. This is probably caused due to destruction of hepatocytes and loss of glycemic reserve.

III. Liver disease concomittant with diabetes and abnormalities of glucose

Haemochromatosis

Haemochromatosis is commonly associated with both liver and pancreatic abnormalities probably caused due to iron deposition in the two organs. 75-80% of the patients with haemochromatosis show abnormal glucose tolerance and 50% of the thalassemic patients show abnormal glucose tolerance.[32] Studies suggest that insulin resistance secondary to hepatic or extra hepatic iron deposition precedes the β cell dysfunction and onset of diabetes. Haemochromatosis may also lead on to cirrhosis and hepatocellular carcinomas. Phlebotomy and treatment with iron chelating agents has not been shown to prevent the development of abnormal glucose tolerance in chronically transfused patients.

Chronic liver disease associated with haemochromatosis may have a role to play in the deterioration of glucose tolerance. More intensive chelation therapy may be accorded to prevent liver damage. Chronically transfused patients are also at a higher risk of contracting hepatitis viruses through blood borne infections.

Glycogen storage disease

This is an inherited metabolic disorder due to abnormal glucose-6-phosphatase or other enzymes involved in glycogen breakdown. It results in excess accumulation of glycogen in the liver, but this is not available for glycogenolysis. Thus frequent carbohydrate intake is required to compensate for this deficient glucose homeostasis.

Autoimmune biliary disease

This consists of the following components : a) Primary biliary cirrhosis - it has been reported in patients with autoimmune polyglandular syndrome (APS). It could be regarded as a component of APS together with components like IDDM, hypogonadism and Hashimoto's thyroiditis, b) Primary sclerosing chlangitis (PSC) and autoimmune biliary cirrhosis have also been associated with a higher frequency of glucose intolerance.[33]

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