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The Problem of Fatty Liver Disease (FLD) in Diabetics

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The diabetics are 50% more likely to develop liver disease. Particularly fatty liver disease. Fatty liver disease is incredibly common in overweight people (type II diabetics); nearly everyone with excess weight on their abdomen has some degree of fatty liver. Diabetics, specially Type II are prone to carrying excess weight on their abdomen, but even slim diabetics often have a fatty liver. The liver relevant all biochemical parameters were measured in diabetics and compared with the estimated parameters of non diabetics, a significant differences were noticed among both groups in relation with the enzymatic profile and hepato-proteins etc. It was concluded by this work that diabetics are extremely prone to develop fatty liver disease.

Keyword: Steatohepatitis, Syndrome X, Hepatic enzymes, Prothrombin time, Albumin

Introduction

It is well known that diabetes increases the risk of kidney disease, nerve damage, blood vessel damage, infections, blindness and heart disease, but even today it is not realized that diabetes have terrible adverse effects on the liver. Insulin resistance (syndrome X) is the driving force behind the development of fatty liver. Type 1 diabetes usually develops in childhood, although by the time they are in their mid 30s, most type 1 diabetics have developed insulin resistance as well in India. People with insulin resistance have high levels of insulin in their bloodstream. Insulin signals to ones liver to manufacture fat, especially triglycerides and cholesterol. This promotes the accumulation of fat inside the liver, inside other organs, inside arteries and as general body fat stores. As insulin levels become higher and

higher, insulin loses its ability to control blood sugar levels. Therefore the blood sugar level creeps upwards, eventually getting high enough to qualify as diabetes. The vast majority of diabetics have a fatty liver. One do not need to be overweight to have a fatty liver; the condition is very common in slim people even.

The Hepato-damaging Effect of Diabetes: The liver plays a central and crucial role in the regulation of carbohydrate metabolism. Its normal functioning is essential for the maintenance of blood glucose levels and of a continued supply to organs that require a glucose energy source. This central role for the liver in glucose homeostasis offers a clue to the pathogenesis of glucose intolerance in liver

diseases but little insight into the mechanisms of liver disease in diabetes mellitus.

- The liver uses glucose as a fuel and also has the ability to store it as glycogen and synthesize it from non carbohydrate precursors (gluconeogenesis).
- Glucose absorbed from the intestinal tract is transported via the portal vein to the liver. Although the absolute fate of this glucose is still controversial, some authors suggest that most of the absorbed glucose is retained by the liver so that the rise in peripheral glucose concentration reflects only a minor component of postprandial absorbed glucose. Therefore, it is possible that the liver plays a more significant role than does peripheral tissue in the regulation of systemic blood glucose levels following a meal.
- Many cells in the body, including fat, liver, and muscle cells, have specific cell membrane insulin receptors, and insulin facilitates the uptake and utilization of glucose by these cells. Glucose rapidly equilibrates between the liver cytosol and the extracellular fluid. Transport into certain cells, such as resting muscle, is tightly regulated by insulin, whereas uptake into the nervous system is not insulin-dependent.
- Glucose can be used as a fuel or stored in a macromolecular form as polymers: starch in plants and glycogen in animals. Glycogen storage is promoted by insulin, but the capacity within tissues is physically limited because it is a bulky molecule.
- Insulin is formed from a precursor molecule, pre-insulin, which is then cleaved to pro-insulin. Further maturation results in the conversion of proinsulin into insulin and a smaller peptide called C-peptide.
- A small amount of pro-insulin enters the circulation. It has a half-life 3–4 times longer than that of insulin because it is not metabolized by the liver. However, pro-insulin has <10% of the biological activity of insulin.
- Insulin is metabolized by insulinase in the liver, kidney, and placenta. About 50% of insulin secreted by the pancreas is removed

by first-pass extraction in the liver. Insulin promotes glycogen synthesis (glycogenesis) in the liver and inhibits its breakdown (glycogenolysis). It promotes protein, cholesterol, and triglyceride synthesis and stimulates formation of very-low-density lipoprotein cholesterol. It also inhibits hepatic gluconeogenesis, stimulates glycolysis, and inhibits ketogenesis. The liver is the primary target organ for glucagon action, where it promotes glycogenolysis, gluconeogenesis, and ketogenesis.

- Glucose that is taken up by a cell may be oxidized to form energy (glycolysis). It is oxidized to pyruvate in the cytosol, and electrons generated from this process are transferred to the mitochondria. Pyruvate generated by this Emden-Meyerhof pathway is oxidized to acetyl CoA in the mitochondria, which in turn undergoes further oxidation by the Krebs tricarboxylic acid cycle. Nearly 36 moles of high energy phosphate are generated from each molecule of glucose by aerobic glycolysis.
- If oxygen not be available, pyruvate is converted to lactate by the action of lactate dehydrogenase. Lactate is a potential fuel, or it may be converted back to glucose. The formation of glucose from lactate and various non carbohydrate precursors is known as gluconeogenesis and occurs mainly in the liver and kidneys.
- The liver, kidney, intestine, and platelets contain the enzyme glucose-6-phosphatase, which produces glucose from glucose-6-phosphate and is the final step in the production of glucose via gluconeogenesis. This enzyme is absent in other tissues. Glucose that is metabolized peripherally may therefore be converted back to glucose or to hepatic glycogen via gluconeogenesis with lactate as the primary substrate. This is known as the Cori cycle.
- In type 2 diabetes, excessive hepatic glucose output contributes to the fasting hyperglycemia. Increased gluconeogenesis is the predominant mechanism responsible for this increased glucose output, while

glycogenolysis has not been shown to be increased in patients with type 2 diabetes. Hyperglucagonemia has been shown to augment increased rates of hepatic glucose output, probably through enhanced gluconeogenesis.

Liver Disease Occurring as a Consequence of Diabetes Mellitus

Glycogen-Deposition -Excess glycogen accumulation in the liver is seen in 80% of diabetic patients. Glycogen synthesis in the liver is impaired in diabetes due to defective activation of glycogen synthase. However, studies attesting to this were usually performed on animals with recently induced diabetes. In patients with chronic diabetes, glycogen accumulation is seen, and it is postulated that long-standing insulin deficiency may actually facilitate synthase activity. This and enhanced gluconeogenesis may account for the net accumulation of glycogen in diabetes.

- The mechanism of cytoplasmic glycogen deposition is uncertain but is perhaps related to the large variations in glucose concentration and frequent insulin dosing. No correlation between hepatic glycogen content and fasting blood glucose levels has been demonstrated. There is also no demonstrable association between the type of diabetes or the fat content of the hepatocytes and the presence of glycogen.
- The mechanism for nuclear glycogen deposition is also unclear, with the stored glycogen resembling muscle glycogen more than hepatocyte cytoplasmic glycogen. It is postulated that glycogen is actually synthesized in the nucleus and has been found in 60–75% of diabetic patients. Nuclear glycogen deposition is also seen in sepsis, tuberculosis, some patients with hepatitis (particularly autoimmune chronic hepatitis), Wilson's disease, and cirrhosis.
- The finding of glycogen nuclei in a patient with fatty liver is useful confirmatory evidence that the fatty liver is secondary to diabetes even if the glucose tolerance test is normal. However, some previous experiments

have reported the combination also in obese patients.

- Patients showing solely excessive glycogen deposition may exhibit hepatomegaly and liver enzyme abnormalities and may have abdominal pain and even nausea and vomiting and rarely ascites. All these abnormalities may improve with sustained glucose control.
- Fatty Liver, Steatohepatitis-Hepatic fat accumulation is a well-recognized complication of diabetes with a reported frequency of 40–70%. Unfortunately, associated obesity is a frequently occurring confounding variable. Type 1 diabetes is not associated with fat accumulation if glycemia is well controlled, but type 2 diabetes may have a 70% correlation regardless of blood glucose control.
- Fat is stored in the form of triglyceride and may be a manifestation of increased fat transport to the liver, enhanced hepatic fat synthesis, and decreased oxidation or removal of fat from the liver. The steatosis may be micro-vesicular or macro-vesicular and may progress to fibrosis and cirrhosis. The degree of glycaemic control does not correlate with the presence or absence of fat. The most common clinical presentation is hepatomegaly, and most patients have normal or only mildly abnormal transaminases and normal bilirubin.

Complications of Diabetes Therapy: Insulin therapy may increase patients' risk of acquiring viral hepatitis because of the exposure to needles. Adhering to good infection-control practices should significantly reduce this risk.

- The biguanide metformin (Glucophage) does not undergo hepatic metabolism and, like chlorpropamide (Diabinese), is excreted unchanged in the urine. In contrast, the sulfonylurea glyburide (Micronase, Glynase, Diabeta) is excreted in bile and urine in a 50/50 ratio. The sulfonylurea glipizide (Glucotrol, Glucotrol XL) is metabolized mainly by the liver, and, in theory, hepatic disease may result in increased blood levels.

- There is a rare association between the use of oral hypoglycemics and hepatic injury, but sulfonylureas can cause chronic hepatitis with necroinflammatory changes. Granulomatous changes can also be seen. They are described as having a well-circumscribed cellular infiltrate comprised of acidophilic histiocytes and eosinophils surrounding necrotic hepatocytes. The mechanism of liver injury is not known.
- Chlorpropamide appears to be the most hepatotoxic of these drugs, with cholestatic hepatitis occurring in 0.5% of people on the drug. Jaundice develops over 2–5 weeks and resolves in virtually all patients when the drug is stopped. Hepatic disease is very rare with tolbutamide (Orinase and generics), and tolazamide (Tolinase and generics). Although very uncommon, acetohexamide and glyburide can cause acute hepatocellular necrosis, and fatalities have been reported. At least two cases of granulomatous hepatitis thought secondary to glyburide have been reported in the literature.
- The biguanides, such as metformin hydrochloride, have not been associated with liver injury. Lactic acidosis can be associated with the use of metformin to treat diabetes, but it is reported to occur occasionally and usually in patients with major contraindications to the drug. "Chronic liver disease" is one of the conditions that may predispose patients taking metformin to developing lactic acidosis, probably due to a reduced ability of the liver to clear lactate. It is therefore listed as a contraindication.
- Troglitazone (Rezulin) is an oral antihyperglycemic agent that acts primarily by decreasing insulin resistance. Its package insert carries a warning that severe idiosyncratic hepatocellular injury, usually reversible but possibly leading to death or liver transplantation, has been reported in patients using the medication, usually during the early months of therapy.

Hypothesis: Based on these finding I designed a research to assess the presence and severity of

Hepatic Steatosis in Diabetics and non diabetics. I have selected Diabetic patients who have been diagnosed as diabetic at least 2-3 years age, by contacting personally and also by contacting in various diabetic clinics in Bilaspur. The controls were selected randomly from the societies, who were demographically matched with the subjects. Study Area- Bilaspur city and outskirt area Study duration-November 2015-June 2016 Sample Size-30 Subjects, 30 controls. I have not included the persons who are having High Blood Pressure or hyperlipidemias of non-diabetic origin, women having PCOs were also dropped from the study. The patients having Hepatitis were also not included in the study.

Objectives-The following objects were set to conduct this research-

- The demographic data of all the subjects and controls were collected.
- The blood sugar of all the related persons were analyzed by using NYCOCARD.
- The Blood tests were done to assess the serum level of the following enzymes-
 - Aspartate aminotransferase (AST or SGOT)
 - Alanine aminotransferase (ALT or SGPT)
 - Alkaline phosphatase, 5' nucleotidase,
 - Gamma-glutamyl transpeptidase (GGT)
 - LDH (Lactate dehydrogenase)

Biochemical Auto-analyzer Star 21 was used for the serum level analysis of these enzymes. The estimation kits of Span Diagnostics were used for the quantative analysis.

- Estimation of Coagulation panel (prothrombin time or PT), it was done by using Ink Spot method.
- Estimation of Albumin level by using Autoanalyser –Star 21 model.
- Estimation of serum Bilirubin level was done by using Autoanalyser –Star 21 model.
- Platelet count was done, by using Total Hematology chamber, DT 5000 of Mindrey company.

Imaging procedures: Imaging procedures used to diagnose fatty liver disease include ultrasound, computerized tomography (CT) scan and

magnetic resonance imaging (MRI). Out of 30 patients only 5 were followed CT Procedure, one patient followed MRI and 11 were followed scanning procedure on my request.

Liver tissue testing: If it's suspected that you have a more serious form of nonalcoholic fatty liver disease, your doctor may recommend a procedure to remove a sample of tissue from your

liver (liver biopsy). The tissue sample is examined in a laboratory to look for signs of inflammation and scarring. Only 3 patients followed this procedure on my request.

Observations: As serum analysis and imaging procedures were, the following observations were found-

Table 1

Sr	Parameters	Patients	Participated	Controls	Participated	Significant Difference
1.	Serum Glucose	206mg %	30	96 mg %	30	1.98
2.	Aspartate aminotransferase (AST or SGOT)	126 Units /L	30	15 units /L	30	1.322
3.	Alanine aminotransferase (ALT or SGPT)	243 Units/L	30	29 /L	30	8.066
4.	ALT/AST Ratio	1.73 ± 1.31	30	0.84 ± 0.17	30	2.09
5.	Alkaline phosphatase	209 U/L	30	56 U/L.	30	1.81
6.	gamma-glutamyl transpeptidase (GGT)	81 U/L	30	29 U/L.	30	4.41
7.	LDH (Lactate dehydrogenase)	218 U/L	30	122 U/L	30	1.005
8.	Prothrombin time	31 Seconds	30	9.8 seconds.	30	6.93
9.	Total Albumin	2.1 g / dL	30	3.9 g/dL	30	4.56
10.	serum Bilirubin	3.4 mg/dL	30	0.18 mg/dL	30	1.90
11.	Total Platelet Count	128,000 /µL	30	267,000 /µL	30	2.09
12.	CT	computed tomography showed Fatty Liver	5	Not shown	5	--
13.	Ultra sound	Grade -3 to 4 Fatty Liver	11	Normal Liver	9	--
14.	MRI	On in-phase GRE images or T1- or T2-weighted echo-train spin-echo images, Higher than normal liver suggests fat deposition in liver	1	Normal MRI	2	--
15.	Biopsy	steatohepatitis	3	Not seen	1	--

Table 2: Correlation among serum Glucose Level and different factors related to Fatty Liver Disease

Serial	Factors	Degree of correlation
1.	Serum Level of SGPT	0.8039
2.	GGT	0.1057
3.	Serum Albumin Level	-0.70951
4.	Serum Bilirubin	0.9012
5.	Platelet count	-0.1033
6.	Prothrombin time	-0.863

Discussion

AST (SGOT) and ALT (SGPT) are reasonably sensitive indicators of liver damage or injury from different types of diseases or conditions, and collectively they are termed liver tests. However, it must be emphasized that higher-than-normal levels of these liver enzymes should not be automatically equated with liver disease. The interpretation of elevated AST and ALT results depends upon the entire clinical evaluation of an individual, and so it is best done by physicians experienced in evaluating liver disease and muscle disease. The serum levels of both hepatic enzymes were significantly higher in diabetics in comparison to demographically matched controls, thus this showed a strong positive correlation between elevated blood sugar level and liver damage. Other related enzymes as GGT, LDH and Alkaline Phosphatase showed many fold increase in the serum of patients, as due to uncontrolled diabetes the hepatic cells are damaged and the stored enzymes are released in extracellular cells and hence the serum level of these enzymes is increased indicating the damage of hepatic cells. A very strong correlation was observed among serum Glucose level and elevated serum levels of these enzymes. The damaged liver produce little or even no Albumin, thus a very significantly reduced serum Albumin level was observed in patients, but in controls the level was near normal. A negative correlation was observed between these two parameters- serum glucose level and serum Albumin level. The liver with reduced functioning capacity can not handle the bilirubin produced in the body, thus the un-excreted bilirubin remained in blood, so the

serum of patients had higher level of it. Also the prothrombin time and the platelet count were critically lower in patients, because of lesser production of prothrombin protein and platelet factors by liver.

- ALT (SGPT) is, by contrast, normally found largely in the liver. This is not to say that it is exclusively located in the liver, but that is where it is most concentrated. It is released into the bloodstream as the result of liver injury. Thus, it serves as a fairly specific indicator of liver status. Coagulation panel (prothrombin time or PT, and international normalized ratio or INR): These tests measure blood's ability for normal clotting and prevention of bleeding and bruising. This is the function of certain proteins called clotting factors that normally are produced in the liver. Normal values are about 9.5 to 13.8 seconds.
- Albumin level (hypoalbuminemia): Albumin is a very common protein found in the blood with a variety of functions. It also is produced only in the liver, and if its levels are lower than normal it can be suggestive of chronic liver disease or liver cirrhosis. Of note, many conditions other than liver disease also may cause low albumin levels. Normal values are about 3.5 to 5 g/dL.
- Bilirubin: This molecule is a byproduct of the routine destruction of red blood cells occurring in the liver. It is normally released as bile in the feces. Elevation of the bilirubin can suggest liver dysfunction. However, other conditions with increased destruction of red blood cells also can cause elevated bilirubin levels despite normal liver function. Normal values are about 0.1 to 1.0 mg/dL.

A strong positive correlation was observed among increasing level of serum Glucose and serum level of SGPT, Serum level of Bilirubin and also serum level of GGT, Thus it can be concluded that uncontrolled Diabetes with high blood Glucose level has hepato-damaging effect. There is significant negative correlation between Serum Glucose level and total Albumin levels. also with serum glucose level and total platelet

count, thus this showed the reduced functioning capacity of liver due to uncontrolled diabetes, also a prominent negative correlation was observed among glucose level and prothrombin time, which may precipitate hemophilic picture. Thus a single univariate association is found between Chronic Diabetes and occurrence of Fatty liver disease.

Suggestions: Diabetics, specially type –II diabetics should regularly monitored their hepatic health as they are prone to develop Fatty Liver Disease and further other hepatic diseases.

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