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Diagnostic significance of diabetes in liver cirrhosis

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Abstract
Alterations in carbohydrate metabolism are frequently observed in cirrhosis, and approximately 15% to 30% of patients have overt diabetes. The aim of the present study was to examine the clinical implications and the prognostic significance of hepatogenous diabetes in patients with liver cirrhosis. In a retrospective and prospective study in cirrhosis; we analyzed the prognostic significance of diabetes, which was defined as the presence of hyperglycemia and overt glycosuria that in most cases required dietary restrictions or active treatment. The prospective cohort study was conducted in 76 patients with histologically confirmed liver cirrhosis. The examination included a history, determination of basal C-peptide and glycosylated hemoglobin (HbA1c) and, in some cases, a 3 hours oral glucose tolerance test with 100 g glucose. The clinical records of all patients with cirrhosis admitted to Govt City Hospital, Bilaspur and CIMS, Bilaspur for the period 2011 to 2016 were reviewed in 2016 and surviving patients were prospectively followed up until December 2016. Final status could be obtained in 76 (41 with diabetes); 63 were alive at the end of follow-up. The model identified, in sequence, albumin, ascites, age, bilirubin, serum Glucose and platelets as prognostic factors. The larger mortality rate in patients with diabetes was not due to complications of diabetes but to an increased risk of hepatocellular failure. Thus, the presence of diabetes, clinically detectable and often requiring adequate treatment is a risk factor for long-term survival in cirrhosis. Fifty Four percent of patients with liver cirrhosis had manifest diabetes, 41% had impaired glucose tolerance and only 5% had normal glucose tolerance. In most cases, the hepatogenous diabetes was clinically asymptomatic. The prognosis of cirrhotic patients with diabetes is more likely to be negatively affected by the underlying hepatic disease and its complications than by the diabetes. Thus, antihyperglycemic treatment of hepatogenous diabetes should always be carefully weighed up in each individual case.

Keywords: hepatogenous diabetes, liver cirrhosis, antihyperglycemic treatment, glycosylated hemoglobin

1. Introduction
In a normal individual, the liver plays a key role in maintaining glucose homeostasis. In patients with advanced cirrhosis, due to alterations in glucose metabolism, the hepatogenous diabetes has been developed in significant number of cirrhotic patients. In patients with cirrhosis, diabetes can be either a classical type 2 diabetes mellitus or the so-called hepatogenous diabetes, i.e. a consequence of liver insufficiency and portal hypertension. Cirrhosis is associated with development of porto-systemic shunts as well as reduced hepatic mass, which can both impair insulin clearance by the liver, contributing to peripheral insulin resistance through down-regulation of insulin receptors. Moreover, cirrhosis is associated with increased levels of advanced-glycation-end products and hypoxia-inducible-factors, which may play a role in the development of diabetes. [1, 2] First, diabetes is an independent factor for poor prognosis in patients with cirrhosis. Specifically, diabetes is associated with the occurrence of major complications of cirrhosis, including ascites and renal dysfunction, hepatic encephalopathy and bacterial infections. Insulin resistance in muscular and adipose tissues and resultant hyperinsulinemia seems to be the patho-physiologic bases of diabetes as liver disease driven complication [3, 4, 5]. An impaired and delayed response of the islet of β-cells of the pancreas and hepatic insulin resistance are also contributory factors. Non-alcoholic fatty liver disease, alcoholic cirrhosis, chronic hepatitis C (CHC) and hemochromatosis are more frequently associated with Diabetes. Insulin resistance increases the failure of the response to treatment in patients with CHC and enhances progression of fibrosis. [6, 7] Hepatogenous diabetes is clinically different from that of type 2 DM, since it is less frequently associated with microangiopathy and patients more frequently suffer complications of cirrhosis. [8, 9].

1.1 Etiopathology
The liver plays a pivotal role in glucose homeostasis. It stores glycogen in the fed state and produces glucose through glycogenolysis and gluconeogenesis in the fasting state. There are close relationships between liver diseases and disorders of glucose metabolism. 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 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.
- 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.
- In a chronically injured liver, hepatic stellate cells promote liver fibrosis through excessive extra-cellular matrix production and reduced extra-cellular matrix degradation. [10] Glucose and insulin have profibrogenic properties on hepatic stellate cells. Inflammation is a major player in the development of liver fibrosis. [13] The link between diabetes and inflammation is now well established and type 2 diabetes is viewed as an auto-inflammatory disease. [14] Inflammation plays a crucial role in the pathogenesis of diabetes-related complications. For instance, inflammation and subsequent extracellular matrix expansion play a key role in the development and progression of diabetic nephropathy. [15] Regarding the liver, indirect data suggest that systemic inflammation associated with insulin-resistance and diabetes might contribute to progression of liver fibrosis. In patients with hepatitis C, insulin resistance and diabetes are associated with liver fibrosis progression as well as with necroinflammatory activity [16, 17].
- Apoptosis. Apoptosis is a type of cell death characterized by the fragmentation of the dying cell into membrane-bound vesicles, called apoptotic bodies. Apoptosis is a key player in the progression of liver fibrosis. [18] Engulfment of apoptotic bodies by hepatic stellate cells stimulates their fibrogenic activity and may be one mechanism by which hepatocyte apoptosis promotes fibrosis. [19] Angiogenesis consists in the formation of new vascular structures from pre-existing blood vessels. [20, 21] Excessive angiogenesis in cirrhotic liver plays a major role in the patho-physiology of diabetic complications including nephropathy, retinopathy as well as macrovascular diseases. [22, 23] Pathological angiogenesis has also been described in chronic liver diseases, First, it has been shown that leptin-mediated neovascularisation, coordinated by vascular endothelial growth factor (VEGF), plays an important role in the development of liver fibrosis. [24, 25, 26] More recently, the same group showed that CD34 expression, a marker of neovascularisation, was overexpressed in the liver of patients. Furthermore, there was a positive correlation between neovascularisation and insulin resistance as well as with liver fibrosis. [27, 28, 29] Thus, this suggests that insulin resistance and fibrosis as in other tissues, promote diabetes through angiogenesis. Hepatic Sinusoidal Capillarization. - refers to the loss of endothelial cell fenestration, associated with the deposition of collagen and other extracellular matrix proteins in the space of hepatic sinosides. [30, 31, 32] All these factors related to liver diseases, specially cirrhosis precipitates Diabetes. [33]

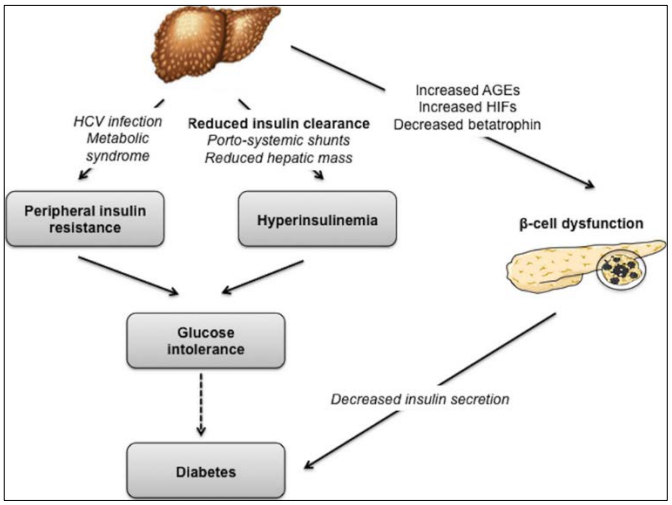

Fig 1

1.2 Hypothesis

Based on these findings, research work was designed to assess the effect of Hepatic diseases as precipitating cause for diabetes. It is a case-control study including patients of liver cirrhosis and healthy controls. I have selected Cirrhosis patients who have been diagnosed as having cirrhosis at least 1-2 years age, by contacting personally and also by contacting in various clinics in Bilaspur. The controls were selected randomly from the society, who were demographically matched with the subjects.

Study Area- Bilaspur city and outskirt area

Study duration-Jan 2011-December 2016

Sample Size-76 Subjects, 30 controls. (Demographically matched healthy persons). We 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.

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 NYCO CARD.
- Analyzing serum C- Peptide levels. Measuring C-peptide can help to determine how much of their own natural insulin a person is producing as C-peptide is secreted in equimolar amounts to insulin. C-peptide levels are

measured instead of insulin levels because C-peptide can assess a person's own insulin secretion even if they receive insulin injections, and because the liver metabolizes a large and variable amount of insulin secreted into the portal vein but does not metabolize C-peptide, meaning blood C-peptide may be a better measure of portal insulin secretion than insulin itself. A very low C-peptide confirms Type 1 diabetes and insulin dependence and is associated with high glucose variability, hyperglycaemia and increased complications. The test may be less helpful close to diagnosis, particularly where a patient is overweight and insulin resistant, as levels close to diagnosis in Type 1 diabetes may be high and overlap with those seen in type 2 diabetes. This estimation was done by Akita Abay Method.

- Oral Blood Glucose Testing- the al subjects and controls were given 100 gms of glucose (Glucose Loading) and after 3 hours of incubation, their serum glucose level was assessed to know the glucose managing capacity of the persons.
- 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)

The AST and ALT readings in such cases are usually between twice the upper limits of normal and several hundred units/liter. One of the most common causes of mild to moderate elevations of these liver tests is a condition referred to as fatty liver (steatohepatitis or hepatic steatosis).

- Estimation of Coagulation panel (prothrombin time or PT), Because in liver malfunctioning, the Prothrombin time is prolonged, because of lesser production of Fibrinigen, Prothrombin and other clotting factors.
- Estimation of Albumin level by using Autoanalyser –Star 21 model. In liver diseases, the production and hence the blood level of Albumin is reduced significantly.
- Estimation of serum Bilirubin level was done by using Autoanalyser –Star 21 model. In Liver diseases, the conversion and clearance of Mono and Di Bilirubin Glucuronoid hampers significantly, thus serum level of free and conjugated Bilirubin is elevated.
- Platelet count was done, because in liver diseases due to diminution of platelet factors, specially I & III, the count decreases.
- Imaging procedures-Imaging procedures used to diagnose cirrhosis disease include ultrasound, computerized tomography (CT) scan and magnetic resonance imaging (MRI).Out of 30 patients only 9 were followed CT Procedure, one patient followed MRI and 11 were followed scanning procedure on request.

1.3 Observation

Table 1

S. No	Parameters	Patients	Participated	Controls	Participated	Significant Difference
1	Age	61± 6.4	76	60 ± 3.9	30	0.21
2	BMI	25.7± 3.9	76	25.6 ± 4.1	30	6.03
3	Male	35(76)	76	23(30)	30	0.53
4	Serum Glucose	402 mg %	76	79 mg %	30	5.48
5	C-Peptide Level	4.014 ng/mL	30	0.6 ng/mL	30	3.232
6	Aspartate Amino transferase (AST or SGOT)	131 Units /L	30	13 units /L	30	1.594
7	Alanine aminotransferase (ALT or SGPT)	303 Units/L	30	26 /L	30	3.310
8	Alkaline phosphatase	237 U/L	30	53 U/L.	30	3.058
9	Gamma-glutamyl transpeptidase (GGT)	88 U/L	30	25 U/L.	30	3.65
10	LDH (Lactate dehydrogenase)	247 U/L	30	124 U/L	30	7.73
11	Oral Glucose Tolrence Teat	209 mg%	30	69 mg%	30	1.313
12	Prothrombin time	31 Seconds	30	8.6 seconds.	30	1.287
13	Total Albumin	2.03 g / dL	30	3.10 g/dL	30	0.0041
14	serum Bilirubin	7.88 mg/dL	30	0.16 mg/dL	30	1.55
15	Total Platelet Count	121,084 /µL	30	288,000 /µL	30	2.173
16	CT	computed tomography showed cirrhosis	5	Not shown	5	--
17	Ultra sound	Grade -3 to 4cirrhosis	11	Normal Liver	9	--
18	MRI	Diffuse surface irregularity was most often seen in a cirrhotic liver.	9	Normal MRI	8	--
19	Biopsy	Deposition of Excess Fibroid material	6	Not seen	5	--

2. Discussion

Cirrhosis may contribute to the development of DM through numerous factors. With the development of portal hypertension, blood shunting redirects blood away from hepatocytes and results in reduced insulin clearance with peripheral hyperinsulinemia [16]. This systemic hyperinsulinemia may contribute to the development of insulin resistance through the down regulation of insulin receptors [17]. This finding supported the previous observation that hepatogenous diabetes differs from type 2 diabetes in that there is less association with traditional risk factors such as body mass index and family history of diabetes In studied subjects with proved cirrhosis, a previously un diagnosed Diabetes was traced, with all biochemical parameters significantly associated with frank diabetes. Also a strong correlation was found with the occurrence and severity of cirrhosis with occurrence and degree of severity of complications of Diabetes. A hyperinsulaenemia state was observed in significant number (73%) of cirrhosis patients, showing that a condition of insulin resistance was developed in them with lesser hepatic clearance of formed insulin, but it was observed that most of the patients (88%) have no family history of

Diabetes or presence of other precipitating factors like obesity, thus it can be concluded that the origin of their diabetes was hepatic.

3. Conclusion

Enough data exists to justify a concrete relationship, between diabetes and the liver. The changes seen in a Diabetic patient's liver include fatty liver, reduction in glycogen, reduction in gluconeogenesis, increased risk of liver and biliary tract cancers. There could be many other liver problems associated with diabetes mellitus. Yet this work can serve as a good modality to learn about the fact that diabetes and liver have a pathological relationship. It is quite evident from the discussion above, that either liver problems lead to diabetes or vice-versa. These results indicate that chronic hyperinsulinemia causes insulin resistance in cirrhosis and therefore plays a central role in the etiology of the hepatogenous diabetes.

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