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Prevalence of Hepatogenous Diabetes in Cirrhotic Patients - A Cross Sectional Study

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Abstract:*Diabetes manifests clinically as liver function deteriorates which is coined as Hepatogenous Diabetes [HD]. The presence of HD in cirrhotic patients is considered as an indicator of advanced liver disease. This cross sectional study comprising of 88 Cirrhotic patients was done to assess the prevalence of HD in cirrhotic patients in a tertiary care centre in Chennai, South India. Patients were assessed for liver function, Insulin resistance was measured by fasting insulin levels and incorporating in HOMA-IR formula and DM was diagnosed by Fating plasma glucose levels. Analysis of glycemic status revealed presence of hepatogenous diabetes in 12.5% and those with glucose intolerance were 21.6 %. The above two groups totalling34.1 %, exhibits prevalence similar to the prevalence of HD observed in previous studies (20-60%).Insulin resistance calculated by HOMA-IR reveals increasing values across the groups with HOMA-IR values of 3.36 in intolerance group and 6.97 in overt Diabetic group respectively. Absence of therapeutic guidelines or recommendations for these patients present further challenges in therapy and these patients frequently encounter hypoglycemia. Hence early identification of glycemic impairement will help clinician in planning therapy and assessing prognosis. Also it is recommended that cirrhotic patients be screened for DM by OGTT as these patients may present with a normal fasting plasma glucose level and HbA1C levels, which is a limitation in the current study.*

The prevalence of Hepatogenous Diabetes is 12.5 % in cirrhotic patients, which is higher than the incidence in general population estimated at 5%.

Key words*: hepatogenic diabetes, cirrhosis, insulin resistance, HOMA-IR,*

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I.Introduction

Chronic liver disease, including cirrhosis, is a major cause of death in many areas of the world, including India[1]. Due to pandemic of obesity and metabolic syndrome, non-alcoholic steatohepatitis (NASH) is becoming a common burden to chronic liver disease leading to cirrhosis all over the world[2].Impaired glucose tolerance is frequentlyencountered in cirrhotic patients, and 20% develop diabetes mellitus overthe natural history of illness[3,4].The number of persons suffering from liver cirrhosis in India went up from 1,776 in 2007 to 2043 cases in 2008-12[5, 6].

There is strong association between liver disease and diabetes (DM) which is higher than expected .Liver diseases may occur as a result of diabetes, and the reverse is true as well. Hepatogenous diabetes is defined as "Diabetes which occurs as a complication of cirrhosis ", according to WHO. Depending on etiology, degree of liver damage and diagnostic criteria, incidence of glucose intolerance was found to be around 60 to

80% and incidence of frank diabetes was nearly 20 and 60%[7-10]. It is known that insulin resistance and glucose intolerance may be found in most of these patients, even from the early stages of chronic liver disease[11, 12].

Diabetes manifests clinically as the liver function deteriorates, consequently leading to hepatogenous diabetes which is considered as an indicator of advanced liver disease[13].The pathophysiology of hepatogenous diabetes (HD) is complex in which hyperinsulinemia and peripheral insulin resistance plays a major role[14]**.**

1. Reduced insulin extraction by the damaged liver and Porto systemic shunts result in hyperinsulinemia which is potentiated by counter regulatory hormones[15]**.**
2. Hyperinsulinism may also be produced by increased pancreatic β-cell sensitivity to glucose[16]**.**Hyperinsulinism causes dampening effects by continuous exposure of the target cells to stimulatory levels of insulin leading to reduction in number, affinity and effectiveness of the receptors in signal transduction leading to insulin resistance [17]**.**

Decompensated liver is unable to synthesize glucose by gluconeogenesis to maintain normal glucose homeostasis and the expected outcome is hypoglycaemia. But, at the same time, insulin resistance thus caused results in reduced glucose uptake by peripheral cells thereby resulting in hyperglycaemia. The net effect being increased glucose as well as insulin levels in blood leading on to diabetes mellitus.

Some studies have speculated that genetic, environmental factors and etiologic agents such asHCV, alcohol, and iron infiltration impair the insulin secretion activity of the β-cells of the pancreas[18]**.**HD unlike the hereditary type 2 DM, is less frequently associated with risk factors such as age, body mass index, and family history of diabetes, also retinopathy, cardiovascular and renal complications.

The treatment of DM of cirrhotic patients has particular characteristics that make it different from type 2 DM without liver disease: about half the patients have malnutrition; when clinical DM is diagnosed. Also the patient has advanced liver disease and most of the oral hypoglycemic agents(OHA) are metabolized in the liverchallenging therapy with OHAs; Patients often have episodes of hypoglycemia.

The role of DM as a prognostic factor of morbidity and mortality in cirrhotic patients has been scarcely studied. In addition, the impact of early diagnosis and treatment of DM on the clinical course of cirrhosis is unknown.

Hence the objective of this study is to estimate the prevalence of diabetes and insulin resistance in cirrhotic patients.

II. Materials and Methods

This cross – sectional study was conducted in the Departments of Medicine &Biochemistry of Govt. Kilpauk Medical College, Chennai-10.

Study design: cross – sectional study.

Study location: Departments of Medicine & Biochemistry of Govt. Kilpauk Medical College, Chennai-10.

Study duration: July, 2014 – October, 2014**.**

Sample size: 80

Sample size calculation: The study required 80 cases with the assumption that the expected proportion of hepatogenous diabetes mellitus in the population was 0.30, with an absolute error of 10%.

Subjects and selection method: Patients attending Medicine OP and those admitted in Medicine wards with a diagnosis of decompensated liver disease were enrolled sequentially in the study after obtaining informed consent. Patients who were not willing were excluded from the study. It was a convenient sampling technique. 88 patients were recruited to make up for haemolysed samples, but all samples were included for analysis as none were lysed.

Inclusion criteria: all patients with clinically diagnosed decompensated liver disease.

Exclusion criteria: patients who were known diabetics with cirrhosis.

Procedure methodology: The Institutional Ethics Committee of Govt. Kilpauk Medical College, Chennai-10, approved the study. 5ml of fasting venous sample was drawn from the antecubital vein under aseptic conditions after obtaining informed consent from all the study participants.

Serum was separated by centrifugation at 3000 rpm for 10 minutes, aliquoted into eppendorf and stored at -20 º C for further analysis. The samples were assayed for fasting blood glucose, urea, creatinine, fasting insulin levels and Liver function tests which included Bilirubin-total and direct, AST, ALT, ALP , GGT, Serum protein & albumin. Insulin was assayed by ELISA with kit from Omega and biochemical investigations were done using kits from Bio-systems in automated clinical chemistry analyser (ROBONIK AUTORA) with due calibration and control checks.

HOMA-IR was calculated using the formula:

HOMA-IR= fasting insulin X fasting Glucose (mg/dl) / 408.3.

A value >2.5 is considered as insulin resistance.

Statistical analysis: Statistical analysis was performed using SPSS package version17. Mean, Standard deviation and percentage were calculated. The values were also presented from 25th to 75th percentiles.

III. Results

Table :1 Age and blood pressure of study population

	N	Minimum	Maximum	Mean	Median	SD	RSD	25 - 75 P
Age in years	88	25.000	70.000	45.955	45.000	10.6490	0.2317	39.500 to 53.500
SBP mmHg	88	90.000	150.000	111.159	110.000	12.6008	0.1134	100.000 to 110.000
DBP mmHg	88	60.000	100.000	75.273	70.000	8.0868	0.1074	70.000 to 80.000

Age, blood pressure and biochemical characteristics of study population are presented as mean and SD with 25th to 75th percentiles. Mean age of the study population was 45.95 years. The mean systolic and diastolic blood pressures were 11.15 mmHg and 75.27 mmHg respectively.

Table :2 Gender distribution

Variable Gender	N	%
F	4	4.5%
M	84	95.5%
Total	88	100.0%

The study population comprised of 95.5% males and only 4.5 % were females.

Table :3 Biochemical characteristics of study population

	N	Minimum	Maximum	Mean	Median	SD	RSD	25 - 75 P
Glucose mgs/dl	88	41.800	257.660	96.293	88.430	32.6003	0.3386	75.400 to 104.980
Urea mgs/dl	88	0.510	193.570	32.816	22.495	29.2796	0.8922	16.555 to 40.000
Creatinine mgs/dl	88	0.0200	5.200	1.136	0.875	0.7413	0.6528	0.765 to 1.190

Mean blood glucose concentration was 96.39 mg/dl with mean urea and creatinine levels in normal range.

Table :4 Liver Function tests of study population

	N	Minimum	Maximum	Mean	Median	SD	RSD	25 - 75 P
Total_Bilirubin mgs/dl	88	0.0800	25.270	4.326	2.760	4.8586	1.1230	1.485 to 4.615
Direct_Bilirubin mgs/dl	88	0.0300	10.090	1.708	1.155	1.9046	1.1150	0.625 to 1.755
SGOT IU/L	88	0.670	442.810	77.337	63.820	53.2315	0.6883	49.515 to 93.435
SGPT IU/L	88	3.770	235.110	32.271	27.160	25.1538	0.7795	20.610 to 35.975
ALP IU/L	88	24.250	358.780	105.079	85.370	57.8292	0.5503	70.590 to 124.245
GGT IU/L	88	13.800	34028.000	477.337	56.550	3618.8045	7.5812	29.905 to 109.615
Total_Protein Gms/dl	88	1.020	8.020	6.071	6.145	0.9150	0.1507	5.640 to 6.545
Albumin gm/dl	88	1.630	4.400	2.826	2.820	0.5102	0.1805	2.530 to 3.160

Liver function tests were abnormal with elevated mean levels of total and direct bilirubin. Aspartate amino transferase was elevated and GGT levels showed a mean of 477.337 IU/l , which is elevated. All patients exhibited hypoalbuminemia with mean albumin levels of 2.826 gm/dl.

Table :5 Parameters of Insulin resistance in study population

	N	Minimum	Maximum	Mean	Median	SD	RSD	25 - 75 P
Glucose mgs/dl	88	41.800	257.660	96.293	88.430	32.6003	0.3386	75.400 to 104.980
HOMA_IR	88	0.000	30.906	2.413	0.000	5.6093	2.3250	0.000 to 2.491
Insulin µIU/L	88	0.000	80.740	9.091	0.000	18.5038	2.0354	0.000 to 12.820

Values of insulin, Glucose and HOMA-IR are presented as mean and Sd with 25th to 75th percentiles. As mean values are in normal range and we need interpretation based on glycemic status disaggregation data are presented for interpretation.

Table :6 Segregation of study population based on glycemic status

Variable glycemic_status	N	%
Normoglycemic	58	65.9%
Glucose intolerant	19	21.6%
overt diabetes	11	12.5%
Total	88	100.0%

Analysis of glycemic status revealed that 65.9% were normoglycemic with fasting blood glucose levels ≤ 100 mgs/dl, 21.6% were glucose intolerant with fasting blood glucose values between 101mgs/dl and 125mgs/dl and 12.5% had overt diabetes with fasting blood glucose values ≥126 mgs/dl.

Table: 7 Insulin levels based on glycemia in study population

S.No:	Glycemic status	Mean insulin levels µIU/L	SD
1.	Normoglycemia	6.058	13.628
2.	Impaired Glucose tolerance	12.377	17.792
3.	Overt diabetes	19.406	34.048

Insulin levels in the study population revealed an increasing trend depending on the glycemic status . Normoglycemics had values in the normal range- 6.058 µIU/L, while patients in the intolerance group had higher levels-12.377 µIU/L while those of overt diabetes had markedly elevated levels – 19.406 µIU/L of insulin.

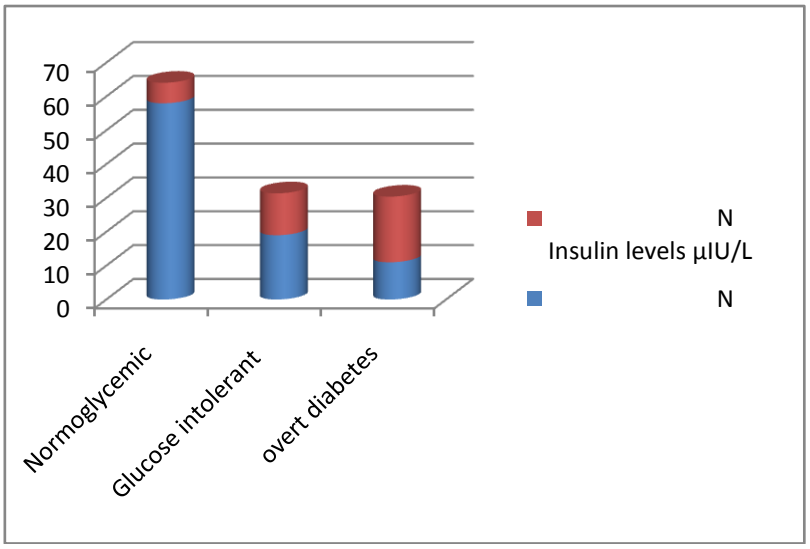
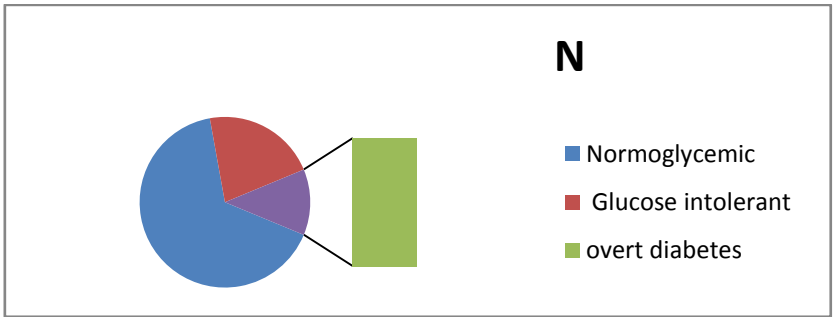


Table :8 Mean HOMA-IR levels in the study population based on glycemic status

Factor	n	Mean	SD
(1) 1. Normoglycemic	58	1.20	2.734
(2) 2. Glucose intolerant	19	3.36	4.922
(3) 3. overt diabetes	11	6.97	12.253

HOMA-IR values showed an increasing trend through normoglycemics (1.20) to glucose intolerant(3.36)to overt diabetics(6.97) in the study population. Values >2.5 are considered as insulin resistance.



IV. Discussion

The association of diabetes and liver cirrhosis was described forty years ago. Thelow frequency of risk factors of type 2 DM, higher incidence in viral, alcoholic and cryptogenic etiology and it's association with increased rate of liver complications and hepatocellular carcinoma, and decreased 5-year survival rate presents a challenging situation in hepatogenous diabetes.

The aim of this study was to estimatethe prevalence of diabetes and level of insulin resistance in cirrhotic patients of our population. Our study predominantly included males (95.5 %), because the commonest cause of decompensated liver disease (DLD) in our population is alcoholic liver disease, which is more common in males.

The present study was done on 88 cirrhotic patients. Prevalence of diabetes among cirrhotic patients in our study was 12.5%, and those with glucose intolerance were 21.6 %, The above two groups totals 34.1 %, which is similar to the prevalence of HD observed in previous studies (20-60%).Insulin resistance calculated by HOMA-IR reveals increasing values across the groups with HOMA-IR values of 3.36 in intolerance group and 6.97 in overt Diabetic group respectively. Both groups showing HOMA- IR values >2.5 indicating insulin resistance[7,9].

Insulin resistance has been identified in many studies on cirrhotic patients. Though the mechanism is not clearly understood, there are several studies that explain a number of alterations at different levels. Many studies state that in cirrhotic patients the first phase of hepatic uptake of glucose is reduced and also insulin mediated glucose uptake is reduced in peripheral tissues due to insulin resistance. The elevated level of HOMA – IR score shows a hyperinsulinemic status in cirrhotic patients. It has been proposed that, insulin that is being degraded by the liver is increased in cirrhotic patients due to reduced hepatic extraction starting from the early stages of the disease. The increased level of peripherally circulating insulin leads to downregulation of insulin receptors in the target cells leading to poor glucose tolerance[15,16,17] .

Values of HOMA-IR in DLD patients with Overt diabetes had a mean of 6.97 and those with glucose intolerance had a mean HOMA-IR of 3.36, indicating insulin resistance in this set of patients.Normoglycemic individuals had HOMA-IR of 1.2, well within normal range. Values >2.5 favour insulin resistance which is clearly documented in patients of DLD with diabetes and glucose intolerance.

Disaggregation data for glycemic status and insulin levels indicate increasing levels of insulin as we proceed from normoglycemia to intolerance to Diabetes.

Diagnosis of HD is challenging as clinical manifestations are absent in the early stages of liver disease and fasting plasma glucose may be normal[19]. About 80% to 85% of these patients, even those with normal fasting glucose levels, may have glucose intolerance or DM[20,21]. Hence HD should be considered as a complication of DLD in the same way as hepatic encephalopathy, ascites, portalhypertension or hepatorenal syndrome. This is a limitation for the current study as DM was identified by fasting glucose levels. In a study by Jeon HK in Korea,HD was observed in 55.4 %of the patients. Among them, 62.0 % required OGTT for diagnosis because they did not show an abnormal fasting plasma glucose level[24].

Patients with hepatogenous diabetes usually present with normal fasting glucose and haemoglobin A1c levels and abnormal response to an oral glucose tolerance test, which is the diagnostic tool in these patients

in contrast to fasting glucose and haemoglobin A1c levels, which remain the gold standard for diagnosing type 2 DM[25] .

Diagnosis can only be made by measuring glucose intolerance unmasked by OGTT and Insulin resistance by HOMA-IR index. Clinical manifestation of Diabetes occurs as liver disease progresses.Hence Overt HD is considered as a marker of liver function deterioration[19].

When diabetes isovert, discrimination between HD and type 2 DM is difficult. HD is suspected in lean patientswithout family history of diabetes, hyperlipidemia orarterial hypertension. A recent study discriminated HD and type 2 DM based on the ratios of postprandial plasma glucose to fasting plasma glucose, fasting insulin and HOMA-Insulin ResistanceIndex and found theses values to be significantly higher in patients with HD as compared with type 2 DM[22].

Absence of therapeutic guidelines or recommendations for these patients present further challenges in therapy as only few studies have assessed the long term safety of antidiabetic drugs in patients with severe liver failure[23].

In spite of lack of information, it is recommended that adequate control of plasma glucose levels through diet and lifestyle changes be undertakenonceHD is detected. Also it is recommended that Decompensated liver disease patients be screened for DM by OGTT as these patients may present with a normal fasting plasma glucose level.

V.Conclusion

The prevalence of hepatogenous diabetes was studied in this cross sectional analysis of 88 previously non diabetic cirrhotic patients, and it was found to be 12.5%and those with glucose intolerance were 21.6 %. The above two groups totals 34.1 %, which is similar to the prevalence of HD observed in previous studies (20-60%).Insulin resistance calculated by HOMA-IR reveals increasing values across the groups with HOMA-IR values of 3.36 in intolerance group and 6.97 in overt Diabetic group respectively. As liver function deteriorates, the incidence of diabetes increases so that clinical diabetes is seen as a marker of liver failure. Therapy of DM in liver failure is challenging as OHAs are metabolized in the Liver and these patients frequently encounter hypoglycemia. Hence early identification of glycemic impairement will help clinician in planning therapy and assessing prognosis. Also it is recommended that DLD patients be screened for DM by OGTT as these patients may present with a normal fasting plasma glucose level.

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Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards."

Informed consent

Informed consent was obtained from all individual participants included in the study.

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