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Study of Plasma Glucose and HbA1c in Patients with Chronic Liver Disease.

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ABSTRACT

Background: Chronic liver disease (CLD) is a major cause of morbidity. In CLD high plasma glucose and HbA1c level are independently associated with severe disease and poor prognosis. The Child Pugh scoring is still the corner stone in prognostic evaluation of CLD patients. Aims & Objectives: The aim of this study was to evaluate plasma glucose (FBS, PPBS) & glycosylated haemoglobin (HbA1c) in patients with CLD and calculate the Child-Pugh score for each patient and correlate with each other. **Methods:** It was a cross sectional,observational hospital based study consisted of 100 patients with CLD whose FBS,PPBS and HbA1C were measured & it was correlated with Child-Pugh score. **Results:** There was significant association between impaired FBS & impaired OGTT &PPBS with the severity of CLD (p - 0.0487& 0.0476). However HbA1c & its correlation with Child Pugh score showed no significance (p- 0.142) but incidence of death with raised plasma glucose & with raised HbA1c were significant (p - 0.043 & 0.042). **Conclusion:** Incidence of impaired FBS, OGTT & PPBS were more in-patient with CLD, which may be considered as prognostic marker for the severity of CLD. Impaired blood gucose may also adversely affect outcome of CLD& therefore, blood glucose should be determined in every CLD patients. Early detection & management can improve the overall outcome of CLD patients.

Keywords: Child-Pugh score, chronic liver disease, fasting blood glucose, glycoselated hemoglobin, post prandial blood glucose.

INTRODUCTION

Liver is an important organ in maintaining glucose homeostasis by means of glycogenesis and glycogenolysis. In the presence of chronic liver disease, there is insulin resistance, glucose intolerance and diabetes mellitus. On the other hand, DM-type II itself in absence of obesity and hypertriglyceridemia acts as a risk factor for development and progression of liver disease. It is necessary to perform OGTT to detect impairment of glucose metabolism. The natural course of CLD is characterized by a progressive decline in liver function that remains more than period of 6 months and requiring hospitalization. Moreover, Patients with cirrhosis of liver and diabetes mellitus suffer more frequently from complication which can cause death.

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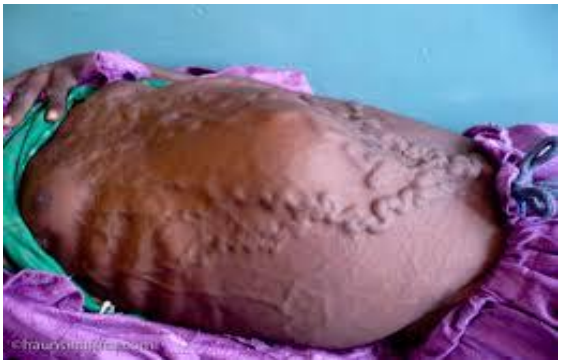
Treatment of diabetes in presence of chronic liver disease is complex due to hepatotoxicity or oral hypoglycemic drugs so close monitoring is required for the risk of hypoglycemia.



A patient with chronic liver disease

In 1964, Child and Turcotte described prognostic model for assessment of surgical risk in cirrhotic patients. Pugh at all proposed a modification of this model in 1973. At present the Child Pugh classification is by far the most widely applied and reported system as it is easy to use at bed sides.

Studies regarding the relation of plasma glucose and HbA1c level with different parameters of liver disease like Child-Pugh scoring are rare in India.We would like to select patients of CLD of any etiology.We shall evaluate plasma glucose level(FBS,PPBS, OGTT,HbA1c level)and calculate the Child-Pugh score for each patient and correlate with each other.

Liver disease may cause, be coincident with, or may occur as a result of Diabetes Mellitus (DM). The prevalence of type 1 diabetes in the United States is ~0.26%. The prevalence of type 2 diabetes is far higher, ~1–2% in Caucasian Americans and up to 40% in Pima Indians. DM and Hepatitis C may occur by chance in the same person, which would help in explaining the apparent association between DM and liver disease.[10]

A large number of clues have suggested the potential role of a common hepatotrophic virus in developing diabetes. A large prevalence of Diabetes has been reported in patients with chronic liver diseases. Both insulin resistance and impaired insulin secretion have been considered to play an important role in the pathogenesis of DM in patients with CLD.

A larger prevalence of Diabetes has been reported in HCV infected patients in comparison with patients with other types of chronic liver diseases. Both insulin resistance and impaired insulin secretion have been considered to play an important role in the pathogenesis of DM in patients with HCV infection.

In 1994, Allison et al., first reported the association of chronic hepatitis C with DM, and gained extensive attention thereafter.[17] A number of studies have shown that 13–33% (median 25%) of patients with chronic HCV infection is diabetic.[11-13] Mason et al., performed a retrospective analysis of 1,117 patients with chronic viral hepatitis and analysed whether age, sex, race, Hepatitis B virus (HBV) infection, HCV infection, and cirrhosis were independently associated with diabetes. In this study after the exclusion of patients with conditions predisposing to hyperglycemia, Diabetes was observed in 21% of HCV-infected patients compared with 12% of HBV-infected subjects (p = .0004).[13] Another cross sectional study from Calcutta studied occurrence of Type two diabetes in patients with CLD taking all aetiologies into concern.[14]

Diabetes that develops as a complication of cirrhosis of liver is known as “hepatogenous diabetes (HD)”.[3,4] In patients with cirrhosis of liver, the prevalence of impaired glucose tolerance (IGT) is estimated to be about 60-80%, and that of overt diabetes is about 7-15%5,6. Patients acquiring diabetes as a result of cirrhosis of liver differ from typical type 2 diabetes mellitus patients by having a lower prevalence of family history of diabetes and a lower risk of macro-and micro-angiopathic complications.[3] In a point prevalence study, the prevalence of micro and peripheral macro-angiopathy and coronary heart disease in cirrhosis with diabetes mellitus was comparable to that of controls, and was significantly lower than that observed in randomly selected patients with type 2 diabetes mellitus.[7] Numerous reports in the literature have indicated that impaired glucose tolerance and diabetes mellitus frequently complicate chronic viral hepatitis and cirrhosis. Hepatitis B virus infection has been directly related to the development of glucose metabolism disorders secondary to pancreatic islets cell injury.[8] A recent study from the 3rd National Health and Nutrition Examination Survey (NHANES-III) in United States reported a three-fold greater risk of type 2 diabetes in HCV-positive more than 40 years old subjects, compared to those who were HCV-negative9.Literature is scarce regarding the occurrence of type 2 diabetes mellitus in chronic liver diseases (CLD) in Indian situation. The involvement of liver in diabetes mellitus is well-studied. But, the occurrence of diabetes mellitus in CLD patients, not known to be diabetic, has not been well-stressed. Hence, the present study was conducted in a medical college of Kolkata, West Bengal with the objectives to study the magnitude of the problem of type 2 diabetes mellitus and impaired glucose intolerance among the patients with various types of chronic liver diseases, to find out the association of diabetes mellitus and impaired glucose tolerance with the demographic and clinical characteristics of the patients.

In child Pugh classification

Grade 0 score -1
Grade 1 score -2
Grade 2 to 4 score – 3

Child Pugh Classification Of Chronic Liver Disease[1,2]

Factor	Units	1	2	3
Serum Bilirubin	mg/dl umol/liter	<2 <34	2 to 3 34 to 51	>3 >51
Serum Albumin	Gm/dl gm/liter	>3.5 >35	3 to 3.5 30 to35	<3 <30
Prothrombin Time	Seconds prolonged INR	0 to 4 <1.7	4 to 6 1.7to2.3	>6 >2.3
Ascites	……	None	Easily controlled	Poorly Controlled
Hepatic Encephalopathy	……	None	Minimal	Advanced

Note: The child Pugh score is calculated by adding the scores of the five factors and can range from 5 to 15 child Pugh class is either A(a score of 5 to 6), B (a score of 7 to 9) & C (a score of 10 or above). De compensation indicates with a child Pugh score of 7 or more (Class B & Class C). Child Pugh score employs 5 variables. Among the 5 variables 3 laboratory variables (Bilirubin, Albumin, INR) and 2 clinical variables ascites and encephalopathy.

MATERIALS AND METHODS

This study was carried out at Nilratan Sircar Medical College and Hospital, Kolkata which caters to both urban and rural population of different districts of West Bengal during the period from January 2015 to October 2016. 100 patients who presented to the

Department of Medicine, both to outdoor and indoor with signs and symptoms of CLD were included in the study. 10 normal subjects were taken as controls. All the patients had CLD confirmed by USG, some by liver biopsy.

Inclusion Criteria

Patient more than 18 years male and female having 2 out of 3 criteria

(i) Signs and symptoms – jaundice, ascites, Hematemesis, Malena for duration > 6month
(ii) USG whole abdomen- liver with coarse echotexture
(iii) Splenomegaly and Portal vein dia meter- > 13mm

Exclusion Criteria

(i) Known diabetic before development of CLD
(ii) CLD patients given autologous blood transfusion
(iii) CLD patients with altered hemoglobin (hemoglobinopathies)
(iv) Known renal disease
(v) Significant respiratory or cardiac dysfunction
(vi) Untreated thyroid dysfunction
(vii) Patients with recent surgery and trauma.

All the CLD patients were classified in three classes A, B and C according to Child Pugh classification and 2 groups compensated CLD (class A) and decompensated CLD (class B and C).
All the subjects were between 18 to 65 years and some have history of chronic alcoholism. They are all not known to have Diabetes Mellitus. They completed questionnaires about symptoms, Gastro Intestinal like Ascites, jaundice and hematemesis/or melena. Patients with known diagnosis of diabetes Mellitus or impaired glucose tolerance as evidence by blood report before diagnosis of CLD, were not included in the study. All patients underwent relavant investigations which are given below:

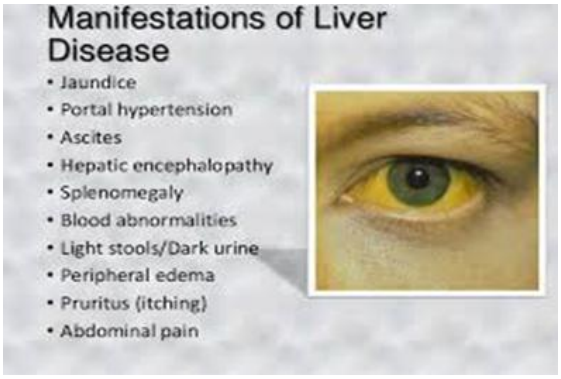
Method of data analysis and interpretation

The data were presented in the form of tables, graphs and diagrams & analyzed by using proper statistical tests. For demographic profile, frequency distribution and percentage were used. Chi-square test was used to determine the association between plasma glucose level and HbA1C level with severity of CLD and outcome using 'Graph Pad Prism 6' software.

RESULTS

This hospital based cross sectional and observational study was done in the Department of General Medicine, Nilratan Sircar Medical College and Hospital from January 2015 to October 2016. A total of 100 patients of Chronic Liver Disease were selected of which 70 were male and 30 were female who were satisfying the inclusion criteria through simple random selection. Most of them were in the age group of 51-60 year & 62 patients were alcoholic .

Ascites was the most common presenting symptoms followed by hematemesis/or melena & jaundice. 92% of the patients presents with Hepatic Encephalopathy (Gr-1-4) & 82% of patients in this study have oesophageal varices. Majority of them are II and III degree. Serum albumin is an excellent marker of hepatic synthetic function in patients with chronic liver disease and cirrhosis.[1]



Clinical presentation of chronic liver disease the results of the present study are analyzed through the following tables and charts.

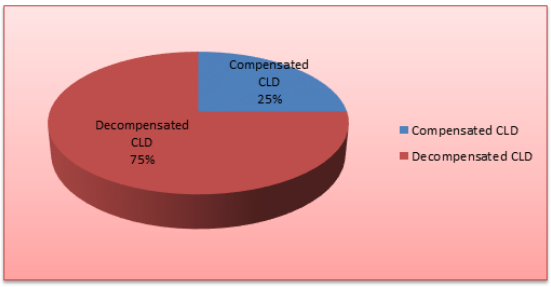


Figure 1: Pie chart showing percentage of compensated and de-compensated CLD

In this study patients were classified into A (5-6), B(7-9) and C(10 or above) according to Child Pugh classification,
And also compensated (Score<7 or classA) and decompensated (score 7 or more/ class B and C) CLD category.
Among all CLD patients, majority of patients (75%) were decompensate CLD & 25% were compensated CLD.

Table 1: Measurement of plasma glucose level (FBS) in CLD patient & its correlation with Chid Pugh classification (n=100)

FBS(mg/dl)	Total	In Compensated (CLD)	In Decompensate (CLD)	P Value
Normal FBS (<100)	42	15	27	0.0487
Impaired fasting (100-125)	30	5	25	
Diabetes type –II ≥126	28	5	23	
Total	100	25	75	

Result shows p≤ 0.05(0.0487) which revealed significant association between impaired FBS & type II Diabetes with the severity of CLD.

Table 2: Measurement of Plasma glucose Level (PPBS & OGTT) in CLD patient & its correlation with CP classification. (n=100)

PPBS(mg/dl)	Total	In Compensated (CLD)	In Decompensate (CLD)	P Value
Normal PPBS (<140)	27	7	20	0.0476
Impaired PPBS(140-200)	28	10	18	
Diabetes type –II > 200	45	8	37	
Total	100	25	75	

Result shows p≤ 0.05 (0.0476) which revealed significant association between impaired glucose tolerance & type II Diabetes with the severity of CLD.

Table 3: Association between Death with Raised Plasma glucose & type of CLD.

Type of CLD	Death with Raised plasma glucose	Death with Normal Plasma Glucose	Total Death	P. Value
Compensated CLD	2	0	2	0.043
Decompensated CLD	15	2	17	
Total	17	2	19	

Association between raised plasma glucose (FBS or PPBS) and death due to CLD is statistically significant (Pvalue<0.05) and that is 0.043.

Table 4: Association with HbA1c Level and outcome of CLD.

Outcome	With Raised HbA1c	With Normal HbA1c	Total	P. Value
Died	11	8	19	0.042
Survived	29	52	81	
Total	40	60	100	

Study shows there is significant association between HbA1c level and death due to CLD(P value<0.05) and that is 0.042. So death with raised HbA1c is more common than normal HbA1c.

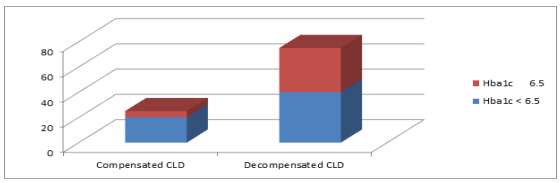


Figure 2: Showing measurement of HbA1c level in CLD patient encountered in this study.

P value is 0.142

Result shows P≥0.05 which revealed no significant association between HbA1c level with severity of CLD.

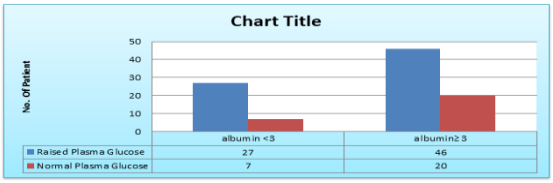


Figure 3: Association of serum albumin and raised glucose (FBS or PPBS) in CLD patient.

P value is 0.072

Result shows P value >0.05(0.072) so there is no significant association

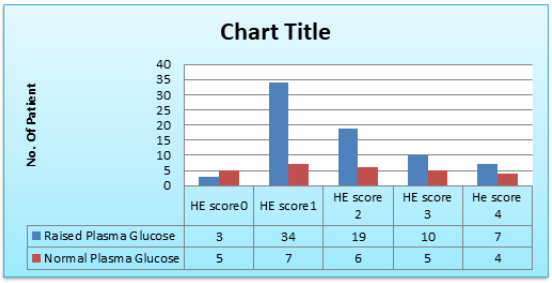


Figure 4: Association of Hepatic Encephalopathy (HE) & raised plasma glucose (FBS or PPBS) in CLD Patient.

92% of the patients presents with Hepatic Encephalopathy (Gr-1-4). Remaining 8% of the patient had no signs of HE.

DISCUSSION

In this study total 100 cases of Chronic liver Disease were evaluated, out of them 25 were with compensated CLD and 75 were with decompensated CLD [Figure 1] & the number of male & female patients were 70 and 30 respectively since the samples were not taken randomly from general population, the prevalence rate in male and female could not be calculated. A similar study done by Nishida et al.[11] had 72% male and 28% female.Mean age of the present study was 52.5 years. This finding were in accordance with other international studies where mean age of Nishida et al study was 51years.[11] Among 75% patient with decompensated CLD, 37% have diabetes mellitus, 18 % have impaired glucose tolerance, 25 % have impaired fasting glucose & 27% have normal fasting plasma glucose.Nishida et al found among 56% patients of CLD a total 38% diagnosed with diabetes,[9] 23% with glucose intolerance and 39% were normal.

Recent study report by Greco et al that in patient with child Pugh B grade liver cirrhosis, the hyperinsulinism may be produced by an increase of pancreatic beta cell sensitivity to glucose.[16]

There was significant association between impaired FBS and diabetes mellitus with the severity of CLD with P value 0.0487 [Table 1]. Petrides AS et al showed insulin resistance is common in patient with CLD and is possibly associated with impairment of nutritional status. A elevated post prandial insulin concentration has been proposed as a factor that induces satiety and subsequent impaired glucose tolerance.[12,13]

[Table 2] showed P value<0.05(0.0476) which revealed significant association between impaired glucose tolerance and diabetes mellitus with the severity of CLD.

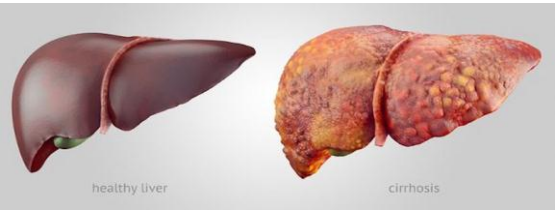
As per Picardi A et al, the presence of CLD is associated with significant impairment in glucose

homeostasis. As seen in glucose intolerance up to 80% patients with CLD and frank diabetes is present in 30 to 60%14. We found among patients with decompensated CLD 40% have HbA1C < 6.5g/dl & 35% have HbA1C ≥ 6.5g/dl ,however HbA1c level & its correlation with Child Pugh score showed no significance (p value 0.142) [Figure 2]. As RBC in the human body survive for 8 to 12 weeks before renewal, measuring HbA1C can be used to reflect average blood glucose level over that duration providing a useful longer term blood glucose control2. Hemoglobin A1c is an inaccurate marker of assessment and management of hepatogenous diabetes. Moreover, exogenous insulin or sulfonylureas may be harmful because these agents may promote hepatocarcinogenesis. Thus, pathogenesis, cause of death, assessment and therapeutic strategy for hepatogenous insulin resistance/diabetes differ from those for lifestyle related type 2 diabetes.[15]

Association between raised plasma glucose (FBS or PPBS) and death due to CLD is statistically significant (Pvalue 0.043) [Table 3]. Study showed there is significant association between HbA1c level and death due to CLD(P value 0.042). So death with raised HbA1c is more common than normal HbA1c [Table 4]. This study is similar with study of Nishida et al,[11] they performed OGTT on group of 56 patients with cirrhosis and normal fasting blood glucose.

A total 38% diagnosed with diabetic, 23% with glucose intolerance and 39% were normal.

After 5year follow up patients with diabetes and glucose intolerance had significantly higher mortality than normal patients (44% and 32% vs 5% respectively).[11] There is no significant association [Figure 3] between plasma glucose (FBS or PPBS) & serum albumin as P value is 0.072 .



Chronic liver disease-- progressive destruction and regeneration of the liver parenchyma leading to fibrosis and cirrhosis.

CONCLUSION

After analyzing the results of the present study it appears that incidence of impaired fasting glucose, impaired glucose tolerance and frank diabetes mellitus is more in patient with decompensated CLD than patient with compensated CLD. So the impaired fasting glucose, impaired glucose tolerance and diabetes mellitus may be considered as a prognostic marker for the severity of CLD patients and to assess the possibility of responding to treatment.

The study shows there was strong association between raised plasma glucose and outcome of CLD.The study also shows that death with raised HbA1c level is more common than normal HbA1c level.

So,glucose intolerance, diabetes may adversely affect outcome of CLD.Therefore, plasma glucose(FBS,PPBS) and HbA1c level should be determined in every CLD patients .Early detection & management can improve the overall outcome of CLD patients.

Limitations of The Study

1) Cross sectional design of the study posed difficulty in assessing the mortality and morbidity of decompensated CLD patients.
2) Unrecognized impaired fasting glucose, glucose intolerance or diabetes mellitus might have present in some patients.

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