



HYPOGLYCEMIA; PATIENTS WITH LIVER CIRRHOSIS

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ABSTRACT... Objective: To determine the frequency and severity of hypoglycemia in patients with liver cirrhosis. **Study Design:** Cross sectional case series study. **Period:** Six months. **Setting:** Liaquat University Hospital Hyderabad. **Methods:** All the patients of liver cirrhosis, of >12 years of age and of either gender were evaluated for hypoglycemia by assessing the glycemic status through random or fasting blood glucose level. The severity of liver cirrhosis was identified according to the Child-Pugh classification whereas the severity of hypoglycemia was grouped in mild, moderate and severe categories. The data was entered and saved in SPSS and frequency and percentage was calculated for hypoglycemia in patients with liver cirrhosis. The stratification was done for age, gender, hypoglycemia and severity of the disease and hypoglycemia. The chi-square test was applied between categorical variables at 95% confidence interval and p -value ≤ 0.05 was considered as statistically significant. **Results:** During six months study period, total 100 cirrhotic subjects were studied for hypoglycemia, of which 59% were males and 41% were females. The mean \pm SD for age in all (100) cirrhotic patients was 42.33 ± 8.87 while the mean \pm SD for age in male cirrhotic patients was 44.06 ± 11.45 where as in female cirrhotic subjects it was 39.92 ± 12.55 respectively. The hypoglycemia was observed in 67%, of which 45(67.2%) were males and 22(32.8%) were females. The mean random blood glucose level in male and female hypoglycemic cirrhotic patients was 67.88 ± 8.43 and 65.62 ± 6.75 while the mean fasting blood glucose level in male and female hypoglycemic cirrhotic patients was 52.93 ± 5.31 and 53.64 ± 8.73 respectively. Out of sixty seven hypoglycemic cirrhotic subjects 45(67%) were males and 22(33%) were females. Of sixty seven, 32(47.8%) had moderate hypoglycemia while 30/67(44.8%) were in Child-Pugh class B ($p < 0.05$). **Conclusions:** The hypoglycemia was detected in patients with liver cirrhosis, hence frequent blood glucose monitoring is one of the most important way to detect mild hypoglycemia and prevent serious and severe episodes.

Key words: Cirrhosis, hypoglycemia, liver, blood sugar and chronic liver disease - CLD

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INTRODUCTION

Chronic liver disease is a significant cause of mortality due to complications i.e. cirrhosis.¹⁻³ Findings of low haemoglobin, thrombocytopenia and hypoalbuminemia correspond well with advanced stages of chronic liver disease.⁴ The complication of cirrhosis other than the fibrosis includes portal hypertension, ascites, hepatic encephalopathy, and hepatorenal syndrome. Liver cirrhosis is the major cause of hospitalization in Pakistan that cost burden on health structure and chronic viral hepatitis B and hepatitis C are the most common etiological infectious agents in Pakistan, while the alcoholism is the common cause in Western countries.⁵ The history and physical examination of cirrhotic

subjects have various findings that need liver / gastrointestinal work-up and monitoring to evaluate the etiology. The prevalence of liver cirrhosis reported by Kakakhel et al, Nadeem et al and Shaikh et al was 52%, 55% and 51%.⁵⁻⁷

Hypoglycemia has various causes including severe illnesses, hepatic impairment i.e. hepatitis or liver cirrhosis can leads to hypoglycemia because of its main role in production of glucose and stability of blood glucose levels.^{8,9} The prevalence of hypoglycemia in liver cirrhosis is 58%.¹⁰ The hypoglycemia is diagnosed by taking detail history, complete physical and relevant clinical examination and measurement of serum glucose level.

The purpose of this study was to assess the hypoglycemia in subjects with liver cirrhosis because early identification and correction of hypoglycemia can prevent the patients to acquire life threatening complications.

PATIENTS AND METHODS

This cross sectional case series study of six months was conducted in department of medicine at Liaquat University Hospital Hyderabad / Jamshoro. All the patients of liver cirrhosis, had age ≥ 12 years and either gender were recruited and enrolled in the study while the known cases of diabetes mellitus, already on anti-diabetic treatment and non-cooperative patients or the patients who refused to give consent for participation in the study were considered in the exclusion criteria. The informed consent was taken according to the vital stability and orientation of the patient, if he/she was stable, cooperative, can speak / understand and well oriented then was taken from the subject else from their parents / attendants / next to kin whereas the priority was given to parents / attendants / next to kin in the subjects below 18 years of age. The serum glucose level was measured by using glucometer (a medical device for determining the approximate concentration of sugar level in the blood) or by taking 2ml venous blood sample in a disposable syringe and sent to laboratory for analysis. The hypoglycemia is grouped in three categories i.e. mild (serum glucose ≥ 55 and < 70 mg/dl), moderate (serum glucose ≥ 35 and < 55 mg/dl) and severe (serum glucose < 35 mg/dl). The frequency of hypoglycemia was assessed by serum glucose level while the severity of liver

cirrhosis was assessed by Child-Pugh score. The data of all such patients was collected on pre-designed proforma. The SPSS 16 was used to calculate the frequency (percentage) of hypoglycemia in liver cirrhosis while the mean \pm SD was calculated for numerical variables. The p-value was calculated by analyzing the categorical variables through chi-square test at 95% CI and the level of statistical significance was ≤ 0.05 .

RESULTS

During six months study period, total 100 cirrhotic subjects were studied for hypoglycemia. The identified cause of liver cirrhosis was viral hepatitis i.e. hepatitis C in 78% patients, hepatitis B in 10% patients while 04% patients had concurrent hepatitis B and C infection. Eight percent had non viral cirrhosis i.e. 03% patients had history of alcoholism, Wilson disease was identified in 01% patient whereas no cause was detected in 04 cirrhotic subjects. The age and gender distribution of subjects is shown in Table: 08. The mean \pm SD for age in all (100) cirrhotic patients was 42.33 ± 8.87 while the mean \pm SD for age in male cirrhotic patients was 44.06 ± 11.45 where as in female cirrhotic subjects it was 39.92 ± 12.55 respectively. The hypoglycemia was observed in 67% of which 45(67.2%) were males and 22(32.8%) were females. The hypoglycemia in relation to age and gender distribution is shown in Table-I while the gender distribution in relation to severity of hypoglycemia is shown in Table-II whereas the severity of hypoglycemia in relation to severity of liver cirrhosis is shown in Table-III.

Age (in years)	Hypoglycemia		Total	P-value
	Male	Female		
12-19	06(13.3%)	02(9.1%)	08(11.9%)	0.68*
20-29	07(15.6%)	04(18.2%)	11(16.4%)	
30-39	13(28.9%)	06(27.3%)	19(28.4%)	
40-49	12(26.7%)	07(31.8%)	19(28.4%)	
50-59	02(4.4%)	01(4.5%)	03(4.5%)	
60-69	04(8.9%)	01(4.5%)	05(7.5%)	
≥ 70	01(2.2%)	01(4.5%)	02(2.0%)	
Total	45(100%)	22(100%)	67(100%)	

Table-I. The hypoglycemia in relation to age and gender distribution in patients with liver cirrhosis

*P-value is statistically non-significant

Pearson Chi-square value = 1.08; df = 6

Hypoglycemia	Gender		Total	P-value
	Male	Female		
Mild	07(15.6%)	08(36.4%)	15(22.4%)	0.04*
Moderate	26(57.8%)	06(27.3%)	32(47.8%)	
Severe	12(26.7%)	08(36.4%)	20(29.9%)	
Total	45(100%)	22(100%)	67(100%)	

Table-II. The gender distribution in relation to severity of hypoglycemia

*P-value is statistically significant Pearson Chi-square value = 6.20; df = 2

Child-Pugh class	Hypoglycemia			Total	P-value
	Mild	Moderate	Severe		
A	06(40.0%)	02(6.3%)	08(40.0%)	16(23.9%)	0.02*
B	05(33.3%)	17(53.1%)	08(40.0%)	30(44.8%)	
C	04(26.7%)	13(40.6%)	04(20.0%)	21(31.3%)	
Total	15(100%)	32(100%)	20(100%)	67(100%)	

Table-III. The severity of hypoglycemia in relation to severity of liver cirrhosis

*P-value is statistically significant Pearson Chi-square value = 10.81; df = 4

The mean random blood glucose level in overall population was 95.85 ± 7.53 while it is 65.75 ± 5.52 in hypoglycemia cirrhotic subjects. The mean random blood glucose level in male and female hypoglycemic cirrhotic patients was 67.88 ± 8.43 and 65.62 ± 6.75 . The mean fasting blood glucose level in overall population was 84.67 ± 7.63 while it is 54.83 ± 7.43 in hypoglycemic cirrhotic subjects. The mean fasting blood glucose level in male and female hypoglycemic cirrhotic patients was 52.93 ± 5.31 and 53.64 ± 8.73 . Majority of cirrhotic subjects (78%) were belonged to rural areas.

DISCUSSION

The present study evaluates the hypoglycemia and outcome in patients with liver cirrhosis and observed 67% cirrhotic patients had hypoglycemic status, the finding are coexist with the study by Tanveer S, et al.¹⁰ Fischer et al¹¹ was reported the hypoglycaemic episodes due to hepatic and kidney insufficiency.¹¹ Any disruption of liver metabolism, structural integrity, or intracellular dynamics may impair the hepatic ability to stabilize normal glucose homeostasis.¹¹⁻¹⁴ When such interruption affects hepatic glucose output, hypoglycemia may eventuate. Multiple drugs including alcohol may impair the intrahepatic pathways that are vital for normal glucose production by the liver.¹⁵ The liver is an important organ for glucose homeostasis.¹⁶ Nouel

O, et al observed hypoglycaemia in 50% subjects with hepatic cirrhosis and sepsis.¹⁶

In present study the 64(96%) patients had clinical symptoms of hypoglycemia whereas 4% patients were free from symptoms and had asymptomatic hypoglycemia, the findings are consistent with the study by Nouel O et al and observed that hypoglycemia is a common feature of sepsis in patients with liver cirrhosis.¹⁶ Hypoglycemia, also identified in acute fulminant hepatitis and end stage liver disease.¹⁶ Liver cirrhosis can leads to hepatoma which is also a risk factor for hypoglycemia. The hypoglycemia in HCC is of two types: type A and B respectively.¹⁷ In type A patients, the tumor grows at rapid pace, appetite is reduced and muscle wasting and weakness is marked. Hypoglycemia, if present is usually mild and occurs as a terminal event within hours to 2 weeks of death. It results from infiltration by the tumor and cirrhotic subjects to satisfy the demands for glucose by both i.e. rapidly growing tumor and other normal tissues.^{16,18} In contrast, type B patients have a slow and gradual growing tumor with little or no muscle wasting and weakness. The type B hypoglycemia is believed to be resulting from the defective processing by malignant hepatocytes of the precursor to the insulin-like growth factor II (pro-IGF-II).^{16,18,19}

In present series, 04(6%) of hypoglycemic cirrhotic subjects were expired, however mortality in hypoglycemia was observed from 04% to 27% in former literature.¹⁹⁻²² Guven M, et al²³ found a mortality rate of 7%, other features seen were behavioral features, psychiatric problems, neurologic sequelae, aphasia, paresis and convulsions. When giving treatments to cirrhotic subjects, it is necessary to give attention to the alteration of their blood glucose levels, especially for those patients who have fallen into a coma. When considering about liver cirrhosis complicated with hepatic encephalopathy, it is necessary to consider that whether the coma is induced by the decrease of blood glucose and physicians should do relevant and specific examinations and also to evaluate blood glucose and treatments. Meanwhile, when facing patients with abnormalities in glucose metabolism, healthcare provider should also consider that if there is complication of liver cirrhosis (hepatoma) and should adopt specific accessory examinations to precisely diagnose the disease and avoid treatment delays.²⁴

In present study, the mean \pm SD for age in all (100) cirrhotic patients was 42.33 ± 8.87 while the mean \pm SD for age in male cirrhotic patients was 44.06 ± 11.45 where as in female cirrhotic subjects it was 39.92 ± 12.55 respectively, however the male gender is predominant in present series correlates with the study by Bartolomeo N, et al and Schuppan D, et al.^{25, 26} High carbohydrate meal is the available tool to treat hypoglycemia.^{27,28} Continuous glucagon infusion may be beneficial and glucagon stimulation test may also be useful to predict treatment responsiveness.^{29,30} There are various theories regarding the hypoglycemia in liver cirrhosis, the hepatocytes convert arriving glucose to the starch glycogen, glycogen is then broken back down into glucose as needed. When breakdown is impaired, hypoglycemia occurs especially in severe acute liver disease or in advanced cirrhosis. So in clinical practice, it is necessary to understand that cirrhotic patients may have low blood glucose level. Therefore, besides treating the liver cirrhosis, physicians should also

give attention to replenish adequate amount of glucose and monitor the blood glucose level to avoid the repeated occurrence of hypoglycemia and even some irreversible complications, which could lead to the loss and burden on individuals, families and the society.

CONCLUSIONS

The hypoglycemia was observed in 67% patients with liver cirrhosis, therefore proper education, awareness, accurate diagnosis and early treatment may save the patients from various complications. The particular attention should be given and early warning signs of hypoglycemia should be recognized and treat low blood glucose immediately, appropriately and on priority basis.

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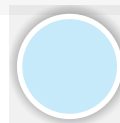
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“In the end,
it's not the years in your life that count.
It's the life in your years.”

Abraham Lincoln



AUTHORSHIP AND CONTRIBUTION DECLARATION

Sr. #	Author-s Full Name	Contribution to the paper	Author=s Signature
1	Dr. Dolat Singh	Contriubtion to conception and deisng, acquisition of data, analysis and terpretation of data	
2	Dr. Hamid Nawaz Ali Memon	Drafting the article and shares its expert research opinion and experience in finalizing the manuscript	
3	Dr. Tariq Zaffar Shaikh	Contributed in conection and interpretation fo data and give his expert view for manuscript designing	
4	Dr. Syed Zulfiqar Ali Shah	Analysis and interpretation of data, contributed in conception and shares its expert research opinion	