

PREVALENCE OF INSULIN RESISTANCE IN PATIENTS OF LIVER CIRRHOSIS AND ITS ASSOCIATION WITH SEVERITY OF CIRRHOSIS

Muskan Jindal¹, Ashish Kumar², Puneet Garg¹, Ginni³, Amandeep Singh¹, Parminder Pal Singh⁴

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Corresponding Author:

Dr. Parminder Pal Singh,

Email: drpps98@gmail.com

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¹Senior Resident, Govt medical College, Patiala, Punjab, India.

²Professor, Govt Medical college, Patiala, Punjab, India.

³Junior Resident, Govt Medical College, Patiala, Punjab, India.

⁴Assistant Professor, Govt Medical College, Patiala, Punjab, India.

Abstract

Background: Liver cirrhosis can lead to insulin resistance which can manifest as diabetes mellitus when liver functions further deteriorates. Early identification of glycemic impairment will help clinicians in planning the therapy as well as assessing the prognosis. This study was done to estimate the prevalence of insulin resistance in liver cirrhosis and finding its association with severity of liver cirrhosis. **Materials and Methods:** It was a cross sectional done on 100 patients of liver cirrhosis coming to IPD and OPD of Medicine Department at Govt. Medical College and Rajindra Hospital, Patiala. All cirrhotic patients meeting the inclusion criteria were subjected to fasting insulin levels, fasting plasma glucose levels and Insulin resistance assessment. Insulin resistance was assessed by HOMA IR method and its association with severity of liver cirrhosis was assessed by Child-Turcotte-Pugh score. **Result:** Our study found Insulin resistance in 71 % of patients using HOMA IR>1.64 which is statistically significant. This study showed a statistically significant association of HOMA IR with CTP score. Insulin resistance increases with CTP score and was found in 47.8% of CTP A, 75% of CTP B and 80.5% of CTP C patients. **Conclusion:** As the liver function deteriorates, the incidence of insulin resistance increases significantly, so that it may be seen as a marker of liver failure and should be considered as a complication of CLD.

INTRODUCTION

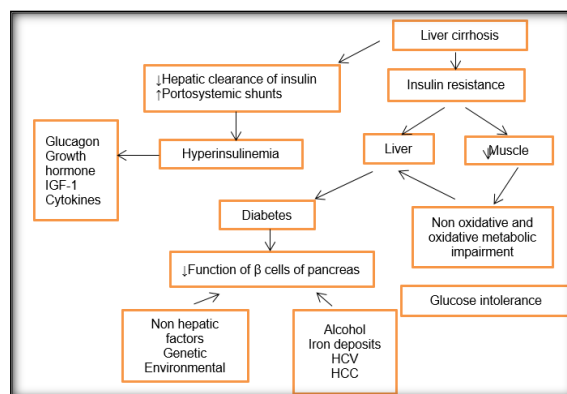
Liver is a major site for various synthetic, metabolic as well as excretory functions. Liver plays an important role in metabolic homeostasis of glucose which is impaired in cirrhosis either because of insulin resistance or impaired sensitivity of beta cells in pancreas.^[1]

The incidence of glucose intolerance and insulin resistance varies from 60-80%, and that of diabetes between 20-60% depending on etiology, the degree of liver damage and diagnostic criteria. In the early stages of chronic liver disease, IR and glucose intolerance may be found in most of these patients.^[1] Bohan et al. described about occurrence of diabetes in cirrhosis patients.^[2] The diabetes which develops as a complication of cirrhosis is known as Hepatogenous Diabetes.^[3] Insulin resistance in muscle, hepatic and adipose tissues as well as hyperinsulinemia seems to be pathophysiological basis for hepatogenous diabetes.^[1]

Pathophysiology of hepatogenous diabetes:

Insulin resistance is defined where a normal or an elevated insulin level produces an attenuated

biological response.^[3] IR in cirrhotics is more due to depressed peripheral glucose use rather than an increased endogenous production.^[4] Many factors such as hepatic parenchymal cell damage, portal systemic shunting, HCV virus, etc. are responsible for development of hepatogenous insulin resistance.^[5]



One of the major abnormalities is insulin resistance in muscle cells and liver tissue. Insulin resistance in

muscle impairs nonoxidative and oxidative glucose metabolism. Reduced insulin clearance and the presence of portosystemic shunting due to damaged liver on the one hand, and desensitization of pancreatic beta cells induced by various factors on the other hand, can lead to hyperinsulinemia. With the progression of diabetes, there is a reduction in the sensitivity of β -cells for production of insulin.[6]

MATERIALS AND METHODS

The study was conducted on 100 Outdoor and indoor patients of liver cirrhosis in the Department of Medicine, Government Medical College, Rajindra Hospital, Patiala.

Inclusion Criteria

- Already diagnosed cases of liver cirrhosis
- Patients with unequivocal clinical grounds (chronic liver disease stigmata, jaundice, ascites, esophageal varices), impaired liver function tests and ultrasonographic features consistent with cirrhosis (Nodular liver surface, coarse echopattern; heterogeneous density, hypertrophy of the left lobe and atrophy of the segment IV, hypertrophy of caudate lobe, reduction of the medial segment of left hepatic lobe, dilatation of portal vein (≥ 13 mm), splenic vein and superior mesenteric vein (≥ 11 mm), splenomegaly: diameter > 12 cm and/or area ≥ 45 cm², presence of porto-systemic collateral circulation) or Fibroscan with median stiffness > 12.5 kpa.
- Age > 18 yrs

Exclusion Criteria

- Known case of Type 2 Diabetes Mellitus or fasting blood sugar > 126 mg/dl
- Pregnancy
- Lactation
- Renal failure (CKD stage 3 and above)
- HIV patients
- Known malignancy
- Transplant patients

The data of the study was collected by patient selection as per inclusion criteria. Patients fulfilling the selection criteria were selected, and written informed consent in patient language was obtained. Then they were subjected to detailed history taking, clinical examination and relevant investigations as per case requirement using a proforma specially designed for this study.

Investigations

- Complete blood count
- Fasting blood sugar
- Liver function tests
- TSP/DSP
- Renal function tests
- Viral markers (HbsAg, HCV, HIV)
- PTI/INR
- HbA1c
- Fasting insulin level
- Ultrasonography whole abdomen

- Modified Child-Turcotte-Pugh score
- HOMA IR index
- Fibroscan (wherever possible)

Eligible patients underwent blood investigations. Venous blood samples were taken in the morning after 8 hour overnight fasting. Fasting serum insulin levels were processed by using CALBIOTECH insulin ELISA kits, considering a normal value of < 25 μ U/ml. After the processing of samples for fasting insulin levels, HOMA-IR was calculated to detect the insulin resistance by using the following formula taking IR into consideration if HOMA-IR > 1.64 .

Formula

$$\text{HOMA IR} = \frac{\text{Fasting plasma glucose (mg/dl)} \times \text{Fasting insulin } (\mu\text{U/ml})}{405}$$

Statistical Analysis

Collected data were analyzed using statistical methods such as mean, median, standard deviation (SD) per value and chi-square/Fischer exact test. The results were displayed in tables with categorical variables presented as numbers and percentages and continuous variables presented as mean \pm SD. A p-value of < 0.05 is considered statistically significant

RESULTS

The majority of patients with cirrhosis in our study were in the age group of 51- 60 years. The mean age of the study population came out to be 48.86 ± 11.12 years.

In the study population, 82% were males and 18% were females, and the male to female ratio came out to be 4.6:1.

The etiology of cirrhosis was alcohol in 51 % of the patients while it was hepatitis C virus in 24 % of the patients. In 15 % of the patients, etiology was both alcohol and hepatitis C virus. In 5 % of patients etiology was NASH and in 2 % of patients, etiology was hepatitis B virus. In 3% of patients, it was due to other causes (Cryptogenic, autoimmune, HBV+ HCV+ Alcohol)

According to Child-Turcotte-Pugh score, 41% of the patients belonged to Class C while 36% of the patients belonged to Class B. 23% belonged to Class A.

Mean FBS (mg/dl) was 96.33 ± 16.57 . Mean fasting insulin levels (μ U/ml) was 9.97 ± 5.06 . HOMA IR value had mean of 2.39 ± 1.37 . Mean HbA1c was 5.22 ± 0.4 . [Table 1]

Our study found Insulin resistance in 71 % of patients using HOMA IR > 1.64 which is statistically significant and mean IR in insulin resistant patients was 2.86 ± 1.35 . as shown in [Table 2].

Out of 71 patients, 33.8% were in the age group of 51-60 years, 25.4% were in age group 41-50 years, 21.1% were in age group of 31-40 years, 14.1% were of age more than 60 years, and 5.6% were in age group of 21- 30 years. However there is no significant

association observed. similarly with regard to sex of the patients, out of 71 patients having insulin resistance, 80.3% were males and 19.7 % were females and there was no association of insulin resistance with sex of the CLD patients

There is no significant association observed between etiology and insulin resistance. In our study insulin resistance in HCV positive cases was found in 79.2% of patients. and in 62.7% of alcoholic patients. In combined HCV and alcoholic patients insulin resistance was found in 80% of patients and IR increase with advancement in stage of liver disease. Insulin resistance was found in all patients of HBV

positive cases, autoimmune and cryptogenic patients. Insulin resistance was found in 60% of NAFLD patients. [Table 3]

This study showed a statistically significant association of HOMA IR with CTP score. Insulin resistance increases with CTP score and was found in 47.8% of CTP A, 75% of CTP B and 80.5% of CTP C patients. [Table 4]

In our study out of 71 patients who had insulin resistance (HOMA IR >1.64), 61 patients (86%) had HbA1c <5.7 and 36 patients (50.7%) had FBS <100 making HOMA IR a better marker for detecting insulin resistance in liver cirrhosis patients. [Table 5]

Table 1: baseline parameters of study population

Baseline Parameters	Mean	S.D	Range
FBS(mg/dl)	96.33	16.57	60 – 125
Fasting insulin(uU/ml)	9.97	5.06	2.56 – 26.50
HOMA IR	2.39	1.37	0.37 – 7.56
S.Albumin(g/dl)	2.76	0.70	1.00 – 4.60
bilirubin	3.95	5.57	0.20 – 23.00
INR	1.17	0.36	0.97 – 3.20
Hemoglobin	8.87	2.30	3.80 – 14.10
Platelet Count	1.17	0.57	0.50 – 3.60
Hba1c	5.22	0.40	4.40 – 6.30
Fibroscan	28.88	14.61	13.40 – 75.00

Table 2: Prevalence of Insulin Resistance

HOMA-IR	Number	Mean	S.D	P value
<1.64	29	1.23	0.32	<0.001
>1.64	71	2.86	1.35	

Table 3: Etiology Of Liver Cirrhosis and Insulin Resistance

Etiology of liver cirrhosis	Number of patients in each group(%)	Number of Cases with IR >1.64
HCV	24	19 (79.2)
HCV + Alcohol	15	12 (80.0)
HBV+ HCV+ Alcohol	1	1 (100.0)
Alcohol	51	32 (62.7)
HBV	2	2 (100.0)
NASH	5	3 (60.0)
Autoimmune	1	1 (100.0)
Cryptogenic	1	1 (100.0)

Table 4: Correlation Of Insulin Resistance With CTP

HOMA IR	Child-Turcotte-Pugh Score							
	A		B		C		Total	
	Number	%	Number	%	Number	%	Number	%
<1.64	12	52.2	9	25.0	8	19.5	29	29.0
>1.64	11	47.8	27	75.0	33	80.5	71	71.0
Total	23	100.0	36	100.0	41	100.0	100	100.0
Chi Square	8.071							
P value	0.018							

DISCUSSION

The present study was conducted to know whether cirrhosis is an insulin resistant state or not because in future it may lead to impaired glucose tolerance and frank diabetes.

In our study, maximum patients were in the 51-60 years of age group, i.e. 34% and mean age was 48.86 ± 11.12 years. According to study conducted by Mukherjee et al,^[7] from Calcutta National Medical College, the mean age of cirrhotic population was 44 ± 10.2 years which is similar to the present study. A study conducted by Goswami et al,^[8] from Jodhpur

found the mean age of cirrhotic population was 52.3 ± 13.7 years. Similarly study conducted by Deep hs et al,^[9] found the mean age of 51.03 ± 12.39 years. Therefore, previous studies reported nearly the same mean age group compared to our study.

Cirrhosis of liver was common among male population with male to female ratio of 4.5:1. A study done by Mukherjee et al,^[7] showed that 86% were males and 14% were females. Another study by Kalaichelvi et al,^[10] also showed that 94% of cases of cirrhosis were males and 6% were females

In our study, majority of patients are in CTP C(41%), followed by CTP B (36%), followed by CTP A (

23%). A study done by Deep HS et al,^[9] also showed majority of patients in CTP C (47%) followed by CTP B (45%) and then CTP A (8%).

In our study, insulin resistance by HOMA- IR (HOMA IR >1.64) was present in 71 patients out of 100, which constitutes about 71% and is statistically highly significant (p value < 0.001). There was a study conducted by Goswami. et al,^[8] which showed that insulin resistance was present in 68.5% of euglycemic cirrhotics and universally present in all cirrhotics with recent diabetes. A study conducted by Eva Erice et al,^[11] on insulin resistance in patients with cirrhosis and portal hypertension showed that insulin resistance was present in 60 % of the study population. They concluded that insulin resistance prevalence might increase upto 70 % if the patients had concomitant portal hypertension with HVPBG > 10mmHg. similarly study done by Mukherjee et al,^[7] showed the prevalence of impaired glucose tolerance to be about 58.1%.

We found no association between age and insulin resistance in cirrhotic patients. The correlation of HOMA-IR with age came out to be statistically non-significant, p value=0.867. Similarly, there is no significant association observed between gender and insulin resistance in patients of cirrhosis. The correlation of HOMA-IR with gender came out to be statistically not significant (p-value 0.577).

There is no significant association observed between etiology of cirrhosis and insulin resistance. On statistical analysis, p-value comes out to be non-significant (0.699), suggesting no correlation of HOMA-IR with the etiology of liver cirrhosis.

This study showed a statistically significant association of HOMA-IR with severity of cirrhosis (CTP score). Insulin resistance increases with severity of cirrhosis. Insulin resistance was observed in 47.8% of CTP A, 75% of CTP B and 80.5% of CTP C patients (p value= 0.018), which is statistically significant.

We observed insulin resistance even in patients with normal blood glucose (FBS <100 and HbA1c <5.7). In our study, out of 71 patients who had insulin resistance (HOMA-IR >1.64), 61 patients (86%) had HbA1c <5.7 and 36 patients (50.7%) had FBS <100 making HOMA-IR a better marker for detecting insulin resistance in liver cirrhosis patients.

CONCLUSION

As the liver function deteriorates, the incidence of insulin resistance increases significantly, so that it may be seen as a marker of liver failure and should be considered as a complication of CLD in the same way as hepatic encephalopathy, ascites, portal hypertension or hepatorenal syndrome. However there is need of further research and studies which would clarify the impact of hepatogenous diabetes and insulin resistance in the natural history of cirrhosis, and the benefits of its early diagnosis and treatment for reduction of morbidity and mortality.

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