Prevalence of insulin resistance among patients with cirrhosis of liver in Government Royapettah Hospital, Chennai

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Abstract

Background: Liver is the major site for carbohydrate, protein and lipid metabolism. In liver cirrhosis, derangements in metabolic functions can happen. Liver cirrhosis can lead to insulin resistance then impaired glucose tolerance and finally diabetes. The occurrence of insulin resistance in cirrhosis has definite clinical implications like rapid progression to fibrosis and increased risk of gastrointestinal haemorrhage and hepatocellular carcinoma.

Objectives: This study was done to find the prevalence of insulin resistance in patients with cirrhosis in Government Royapettah Hospital due to varied etiology.

Materials and methods: It was a cross sectional study done on 50 subjects in Government Royapettah Hospital. Patients were selected according to the inclusion criteria. A detailed history was taken, and a thorough clinical examination was done followed by further investigations, all of which were recorded in a pre-designed, structured proforma. Insulin resistance was assessed using three indices: HOMA1 IR, HOMA2 IR calculator and TyG index.

Results: The mean age of the population was 46.18± 9.78 years. 94% of patients were males and 6% were females. Among the fifty subjects included, 34% had insulin resistance according to HOMA 1 IR (p 0.024) and 28% with HOMA2 IR (p 0.002). Insulin resistance using both HOMA 1 and 2 was significantly increased in Child Turcott Pugh C (p <0.001 for both). Insulin resistance was not demonstrated in any of subjects using TyG index. There was positive correlation between insulin resistance and fasting glucose and insulin.
Conclusion: Insulin resistance is demonstrated in liver cirrhosis which is increased with advancing disease. It can be concluded that regular monitoring of glycemic status is mandatory in these patients who would have definite bearing upon treatment strategy.

Key words
Cirrhosis, Insulin resistance, Triglycerides, Homeostatic model assessment, Child turfcott pugh.

Introduction
Liver is a major site for various metabolic, synthetic and excretory functions. Cirrhosis of liver due to varied etiology like alcohol, infections and metabolic reasons can cause derangements in all functional aspects of liver. Bohan, et al. [1] described about occurrence of diabetes in cirrhosis initially, which was later termed as hepatogenous diabetes by Megyesi, et al. [2]. It is found that 57 % of them can develop insulin resistance, 14 % go for diabetes and 60-80% develop impaired glucose tolerance [3, 4].

Insulin resistance is described as normal or elevated insulin producing attenuated insulin response [5]. Insulin resistance in cirrhosis can be due to impaired clearance of insulin by liver due to hepatocellular fibrosis or porto systemic shunting of insulin or impaired feedback regulation of insulin or increased pancreatic insulin secretion but the exact mechanism is still unclear. Many studies concluded that insulin resistance could be due to insulin receptor and post receptor defects resulting in hyperinsulinemia [6].

In AIIMS, Jain, et al. assessed glucose tolerance in euglycemic cirrhotics using insulin suppression test (Modified Hirano s method) [5]. They found that cirrhotics had higher postprandial glucose and insulin. They have higher than normal insulin to produce normal glucose homeostasis. They concluded that cirrhotics have decreased insulin sensitivity or endogenous insulin resistance that precedes impaired glucose tolerance and diabetes. A study was conducted in Italy by Nielson, et al. found that endogenous glucose release suppression was unaltered but there was a defect in uptake of glucose [6] and glucose utilisation even during physiological conditions. They concluded that carbohydrate intolerance in cirrhosis is due to insulin resistance which can be ascribed to defective glucose uptake rather than abnormalities in glucose production and beta cell function [7]. Hyperinsulinemia thus occurred has multiple adverse effects on vascular bed. Patients with cirrhosis and insulin resistance need regular glycemic monitoring as they may develop impaired glucose tolerance and diabetes in future which has definite clinical implications in the form of decrease response to treatment, rapid progression to fibrosis, hepatocellular carcinoma risk and increased complications due to cirrhosis.

Materials and methods
This study was conducted in Government Royapettah Hospital in 50 patients for duration of 1 year from July 2014 to July 2015 after getting informed consent from all the patients involved in this study. Ethical committee clearance was obtained from Kilpauk Medical College.

Inclusion criteria
Patients with cirrhosis already proven by imaging, who was regularly attending Medicine and Medical Gastroenterology outpatient clinic and inpatients in medical ward were included.

Exclusion criteria
- Diabetes mellitus as defined by ADA with fasting blood glucose >126 mg/dl
- Hepatitis C virus infection
- Pregnancy
- Lactation
- Cardiac failure
- Renal failure
- Respiratory failure
- Hepatocellular carcinoma
• Presence of infection and acute decompensation in the prior 2 week
• Prescription of hypolipidemic drugs, antihypertensives, corticosteroid, bronchodilator, vasoactive, or hypoglycemic agents within 1 month.

Methodology
Patients who were already diagnosed to have cirrhosis and attending medical or medical gastroenterology outpatient clinics and inpatients in medical ward were taken into study. The sample size was set to be 50. The procedures to be employed were explained to the patients, and written consent was obtained from all patients included in the study. A detailed history was taken, and a thorough clinical examination was done followed by further investigations, all of which were recorded in a pre-designed, structured proforma. Height and weight were measured. Presence of ascites and pedal edema were noted. After getting consent from the patients following investigations were done:

- Fasting insulin
- Fasting blood glucose
- Blood urea, Serum creatinine.
- Serum triglycerides
- Liver function tests- bilirubin, AST, ALT, ALP, serum total protein, serum albumin
- Prothrombin Time/ International Normalised Ratio (INR)
- Ultrasound abdomen

Child Pugh Scores were calculated by adding the scores of the five factors (serum bilirubin, serum albumin, prothrombin time, grade of ascites and hepatic encephalopathy) in order to classify patients according to severity of CLD into Child-Pugh class A (a score of 5-6), B (7-9), or C (10 or above). Body mass index was calculated using the formula weight (kg)/ height* height (m). If ascites was present, then correction of 4 was given for weight.

Insulin resistance
HOMA 1R [8, 9]

\[
\text{Insulin resistance} = \frac{\text{fasting insulin (}\mu\text{U/dl}) \times \text{fasting glucose (mmol/L))}}{22.5}.
\]

A value >2.7 is taken as insulin resistance.

HOMA2R
Programmed calculator downloaded from university of oxford. http://www.dtu.ox.ac.uk/.
Value of >1.8 is taken as insulin resistance.

TyGINDEX [10]
The formula is \{ln (fasting triglycerides mg/dl)* fasting glucose (mg/dl) /2 \}. The cut off value is 4.6.

Statistical analysis
The data obtained was analysed using SSPS software. Chi square test was used for comparison of dichotomous variables. A p value of <0.05 was taken as statistically significant value. Pearson correlation coefficient was used to compare the regression coefficient between two groups.

Results
In our study, 18 patients in the age group 41-50 years were major contributors. All the patients were more than 30 years and maximum age in our study was 75 and minimum was 31. The mean age of study population was 46.18 ± 9.78 years. Out of fifty cases, 47 cases were male and only 3 were female (Table – 1).

Table – 1: Age wise distribution of cases.

<table>
<thead>
<tr>
<th>Age (Years)</th>
<th>Frequency</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-40</td>
<td>16</td>
<td>32</td>
</tr>
<tr>
<td>41-50</td>
<td>18</td>
<td>36</td>
</tr>
<tr>
<td>51-60</td>
<td>13</td>
<td>26</td>
</tr>
<tr>
<td>&gt;60</td>
<td>3</td>
<td>6</td>
</tr>
</tbody>
</table>

In our study, 17 patients out of 50 had insulin resistance by HOMA 1 which accounted for 34% of patients which was statistically significant with p value < 0.001. Out of 17 patients who had insulin resistance, 3 patients (17.6%) were in the age group of 30-40 years, 8 patients (47.1%) were in 41-50 years, 4 patients (23.5%) were in 51-60 years and 2 patients (11.8%) were in more than 60 years age group.
In our study, out of 50 patients, 14 patients (28%) had insulin resistance according to HOMA 2IR score (p value of 0.002). Out of 14 patients, 3 patients (21.4%) were in age group 30-40 years, 8 patients (57.1%) in 41-50 years group, 3 patients (21.4%) in 51-60 years age group and no one were above 60 years group.

In this study, out of fifty patients taken in to study, 18 were in CTP A, 19 in B and 13 in CTP C score. By HOMA1-IR, among 18 CTP A patients, 1 had insulin resistance, among 19 CTP B patients, 4 had insulin resistance and among 13 CTP C patients, 12 had insulin resistance. As the CTP grade increases, insulin resistance among the patients increases which was statistically significant (p value <0.001).

Out of 18 patients in CTP A score, only 1 had insulin resistance according to HOMA 2IR and out of 19 patients in CTP B score 1 had insulin resistance and out of 13 patients in CTP C score, 12 had insulin resistance. It was found to be statistically very significant p<0.001.

Number and percentage of our study group showing insulin resistance according to HOMA1 IR and statistical significance was as per Table – 2. Number and percentage of our study group showing insulin resistance according to HOMA2 IR score was as per Table – 3. Correlation with HOMA 1-IR was as per Table – 4 and correlation with HOMA 2 IR was as per Table – 5.

**Table – 2: HOMA 1**

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Percent</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IR -</td>
<td>33</td>
<td>66.0</td>
</tr>
<tr>
<td>IR +</td>
<td>17</td>
<td>34.0</td>
</tr>
<tr>
<td>Total</td>
<td>50</td>
<td>100.0</td>
</tr>
</tbody>
</table>

**Table – 3: HOMA 2**

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Percent</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IR -</td>
<td>36</td>
<td>72.0</td>
</tr>
<tr>
<td>IR +</td>
<td>14</td>
<td>28.0</td>
</tr>
<tr>
<td>Total</td>
<td>50</td>
<td>100.0</td>
</tr>
</tbody>
</table>

**Table – 4: Correlation with HOMA 1-IR**

<table>
<thead>
<tr>
<th>BMI</th>
<th>HOMA1-IR</th>
<th>Pearson coefficient</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0.422</td>
<td>0.002</td>
</tr>
<tr>
<td>FBS</td>
<td>HOMA1-IR</td>
<td>0.461</td>
<td>0.001</td>
</tr>
<tr>
<td>Fasting TGL</td>
<td>HOMA1-IR</td>
<td>-0.144</td>
<td>0.320</td>
</tr>
<tr>
<td>Fasting Insulin (µg/dl)</td>
<td>HOMA1-IR</td>
<td>0.968</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Table – 5: Correlation with HOMA 2 IR**

<table>
<thead>
<tr>
<th>BMI</th>
<th>HOMA 2</th>
<th>Pearson coefficient</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0.422</td>
<td>0.002</td>
</tr>
<tr>
<td>FBS</td>
<td>HOMA 2</td>
<td>0.351</td>
<td>0.013</td>
</tr>
<tr>
<td>Fasting TGL</td>
<td>HOMA 2</td>
<td>-0.101</td>
<td>0.485</td>
</tr>
<tr>
<td>Fasting Insulin (µg/dl)</td>
<td>HOMA 2</td>
<td>0.935</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Discussion**

Diabetes can lead to non alcoholic fatty liver disease and non alcoholic steatohepatitis and ultimately cirrhosis. But conversely cirrhosis can lead to impaired glucose tolerance and diabetes. Diabetes occurring in the setting of cirrhosis is called hepatogenous diabetes. Hepatogenous diabetes has little micro and macrovascular complications [11]. 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.

The mean age of our study population is 46.18 years and majority are in the age group of 41-50 years. According to study conducted by Mukherjee, et al. from Calcutta National Medical College, the mean age of cirrhotic population was 44 ± 10.2 years [12]. A study conducted by Goswami, et al. from Jodhpur found the mean
age of cirrhotic population was 52.3 ± 13.7 years [13]. There was a cross sectional study conducted in a teaching hospital in Assam by Jyotiprakash, et al. to find the lipid profile abnormalities in alcoholic cirrhosis showed mean age group of alcoholic cirrhosis was 41- 50 years [14]. According to Doud’s, et al., the mean age of alcoholic cirrhosis in South Asian male was 44 years [15]. According to our study, cirrhosis of liver was common among male population with male female ratio of 15:1. A study by Bhargava, et al., the male female ratio was found as 6:1. Another study by Douds A.C., et al., also showed that 86% of cases of cirrhosis were males and 14% were females. The male preponderance of cirrhosis in South India is due to its etiology alcohol which is more common in males [15]. In Western population the most common cause of cirrhosis is due to HCV because of high prevalence of intravenous drug abuse. A study by Bellentani S., et al., found that 99 % of cirrhotics in their study were male. The Dionysos study group found a male: Female ratio of 9:1 in alcoholic cirrhosis [16]. In our study, majority of patients are in CTP B (38%) followed by CTP A (36%).

In our study, we used three scores to assess insulin resistance and then association of insulin resistance with serum triglycerides was assessed. We took the reference values according to Bruno Geloneze, et al., where the cut off value for diagnosing insulin resistance using HOMA1 was >2.7 and using HOMA 2 IR it was > 1.8 [8]. In our study, insulin resistance by HOMA-1 IR was present in 17 patients out of 50, which constitutes about 34 % which is statistically significant ( p value < 0.05). The common age group showing insulin resistance by HOMA1-IR in our study is 41-50 years (36%) followed by 30 - 40 years (32%). Insulin resistance was found in 14 patients out of 50 by HOMA 2 contributing to 28% which is statistically highly significant (p value 0.002). The common age group showing insulin resistance by HOMA 2 in our study is 41-50 years (36%) followed by 30-40 years (32%).There was a study conducted by Goswami, et al. [13] from Jodhpur, India 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 in Spain by Eva Erice, et al. [7] on insulin resistance in patients with cirrhosis and portal hypertension showed that insulin resistance was present in 60 % of the study population. Insulin resistance in this group was assessed by HOMA 2 index. They concluded that IR prevalence might increase up to 70% if the patients had concomitant portal hypertension with HVPG >10 mmHg [7]. A cross sectional study done in Kolkata by Mukherjee, et al. showed the prevalence of impaired glucose tolerance is estimated to about 60- 80% and overt diabetes in 7- 15% [12]. This study also showed IGT and diabetes were frequently higher in patients aged >45 years. But etiology had not influenced IGT and diabetes according to their study. A study conducted by Bonora, et al. showed inverse correlation between clamp mediated glucose disposal and HOMA estimated insulin sensitivity. They also validated the study for use in large epidemiological purposes [17]. A study from Mexico showed TyG index and HOMA were almost similar in assessing IR. But in our study, even patients who showed insulin resistance by HOMA 1 and HOMA 2 index, failed to show values above the cut off for TyG index which was taken as 4.6. Insulin resistance was found mostly in CTP C patients by both HOMA 1IR and HOMA2 IR which contributed to about 92 % and 92.3% of cases with HOMA 1 IR and HOMA 2 IR respectively. This is consistent with study from Jodhpur, India by Goswami and Bhargava, et al. [13] where they showed significant increase in insulin resistance in patients with CTP> 10 and MELD > 15. However, another Indian study by Mukherjee, et al. [12] from Calcutta showed no correlation with CTP score or with duration of illness.

**Conclusion**

The majority of patients with cirrhosis in our study are in the age group of 41- 50 years. About 94% of patients included are males. Majority of population included are in CTP B followed by
CTP C. Insulin resistance is found in 34% of patients using HOMA 1IR and 28% of patients using HOMA 2 IR. TyG index failed to show insulin resistance in those shown by HOMA model. Insulin resistance is significantly higher in patients with CTP C by both HOMA 1 and HOMA 2. Advancement of liver disease as indicated by CTP C shows increase in insulin resistance and compensatory increase in pancreatic beta cell function as indicated by HOMA 2. So, occurrence of impaired glucose tolerance and diabetes is a major concern in these patients which could definitely have bearing upon treatment strategy as they have increased risk of deaths related to complications of liver cirrhosis like gastrointestinal haemorrhage and hepatocellular carcinoma.

References

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