



## Glycemic Profile in Chronic Liver Disease

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### Abstract

*Liver has a pivotal role in glucose homeostasis and maintaining blood glucose values within strict normal limits. Chronic liver disease results in impaired glucose tolerance and diabetes, resulting in the entity called Hepatogenous Diabetes. The aetiology as well as the severity of hepatocellular dysfunction has a significant effect on carbohydrate metabolism. The reported incidence of glucose intolerance and diabetes in different studies varies from as low as 20% to as high as 80%. As the liver function worsens, diabetes manifests clinically, and thus Hepatogenous diabetes can be considered a marker of advancing liver disease. The underlying mechanisms are ill-understood. The influence of other extraneous factors like infections, old age, medications and other systemic diseases might also influence the glycemic status. Despite these findings, little attention has been paid on understanding the full spectrum of glycemic dysfunction in our population. This study on 169 patients with chronic liver disease was undertaken to clarify the frequency of occurrence of impaired glucose tolerance, with emphasis on the effect of aetiology and severity of liver dysfunction. This study concluded that of all the causes of chronic liver disease, cirrhosis was most frequently associated with impaired glucose tolerance, next being Hepatitis C (compared to Hepatitis B). Higher incidence was also noted in Child Pugh's A grading of severity, alcoholism and in the male gender patients. However, our study was limited by the lack of liver biopsy in all patients, with the diagnosis of cirrhosis resting on USG findings.*

### Materials and Methods

This study was carried out in the Dept of General Medicine, Government T D Medical College, Alappuzha, on 169 patients admitted with the diagnosis of Chronic Liver Disease during the year 2012-2013, with the following objectives:

1. To study the incidence of Diabetes and Impaired Glucose Tolerance in patients with chronic liver disease.
2. To co-relate the severity of cirrhosis, as determined by Child Pugh's criteria with the glycemic status.
3. To identify other factors that might predispose to Diabetes and Impaired Glucose Tolerance.

This observational study was carried out in the Department Of Internal Medicine, and 169 patients of either sex, admitted with the diagnosis of Chronic Liver disease were included in the study. Despite cirrhosis being a histo-pathological diagnosis, due to the invasive nature of liver biopsy and patient preference, USG proven coarse echo texture, with its 98% predictive value was used to diagnose Cirrhosis of liver.

Pregnant women, obese patients with BMI >30kg/m<sup>2</sup>, history of ingestion of drugs like corticosteroids and thiazides, those with inherited metabolic liver disease and those already known to have diabetes were excluded from the study.

All patients underwent baseline screening, including detailed personal, social and past history. Old medical records were reviewed, in-depth physical examination, estimation of BMI, and systemic examination was carried out.

Blood samples were taken for assessment of hemogram, peripheral smear, blood urea, serum creatinine, urine examination, stool examination for occult blood, prothrombin time and HBsAg / HCV virology screening was done.

In addition, detailed liver function tests, upper GI Endoscopy, Ultrasound abdomen and Oral Glucose Tolerance Tests were done. Abdominal CT and liver biopsy were done in few cases.

Diabetes Mellitus was based on the new WHO criterio-1999, with diagnosis based on one abnormal value in symptomatic individual, two values in asymptomatic individuals and glucose tolerance test in borderline cases.

Time	Blood Glucose(mmol)	Blood Glucose (mg%)
Fasting plasma glucose.	7.0	126
Random plasma glucose.	11.1	200

Oral Glucose Tolerance test (OGTT), as per the WHO criteria, was done after 12 hours overnight fasting. Blood and urine samples for estimation of reducing sugar were drawn in fasting state and subsequent to 75 gm oral glucose administration, half-hourly, for two and half hours. The results were analysed graphically, with time intervals on the abscissa and glucose values on the ordinate.

### Oral Glucose Tolerance Test

Normal	<7.0 mmol/l in Fasting <7.8 mmol/l 2h after Glucose
Impaired Glucose Tolerance	between 7.8 and 11 mmol/l at 2 hrs.
Diabetes Mellitus	11.1 mmol/l (126mg%) or more at 2 hrs.
Adult : 75 g glucose in 300 ml water. Child: 1.75g glucose/kg bodyweight.	

Although cirrhosis is a histopathological diagnosis, as per patient preference, liver biopsy was not done in all cases. USG, with its positive predictive value of 98% in detecting cirrhosis and sensitivity of 88% for detecting irregular liver surface was utilized for diagnosis of cirrhosis. Child Pugh’s scoring system was used to stage the severity of cirrhosis.

Patients were treated according to existing guidelines. SPSS software and appropriate statistical tests were applied for data analysis, associations and comparisons. A two-tailed P value of <0.05 was taken as significant.

### Results

Of the 169 patients studied, 124(73.4%) were males and 45(26.6%) were females. Of the 45 female patients, 13 (28.8%) had Impaired glucose tolerance and 9(20%) had and Diabetes. Similarly, of the 124 male patients, Impaired glucose tolerance and Diabetes was seen in 41(33.3%) and 15 (12%) cases respectively. The comparison between the two genders was statistically insignificant.(Chi square test p=0.424).

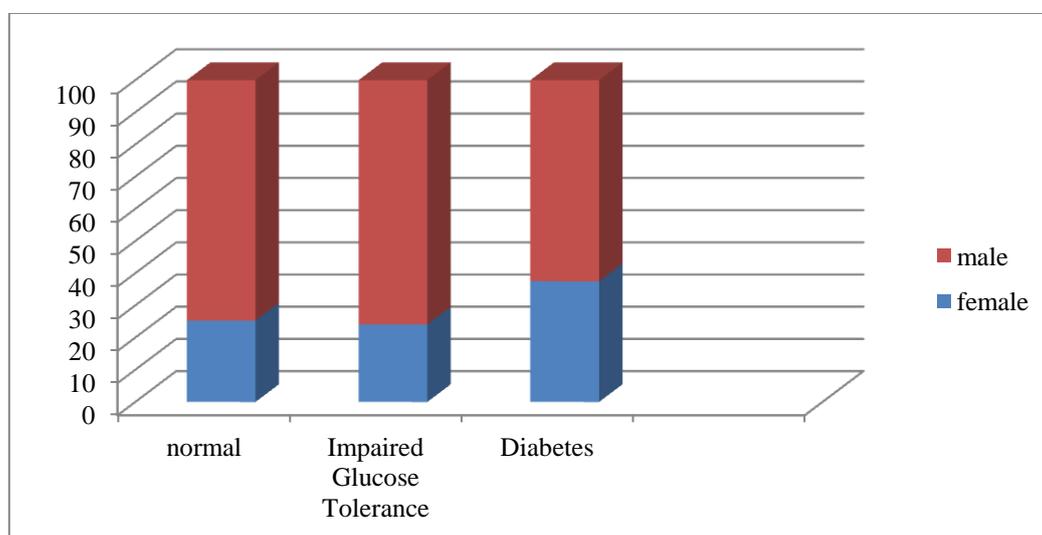
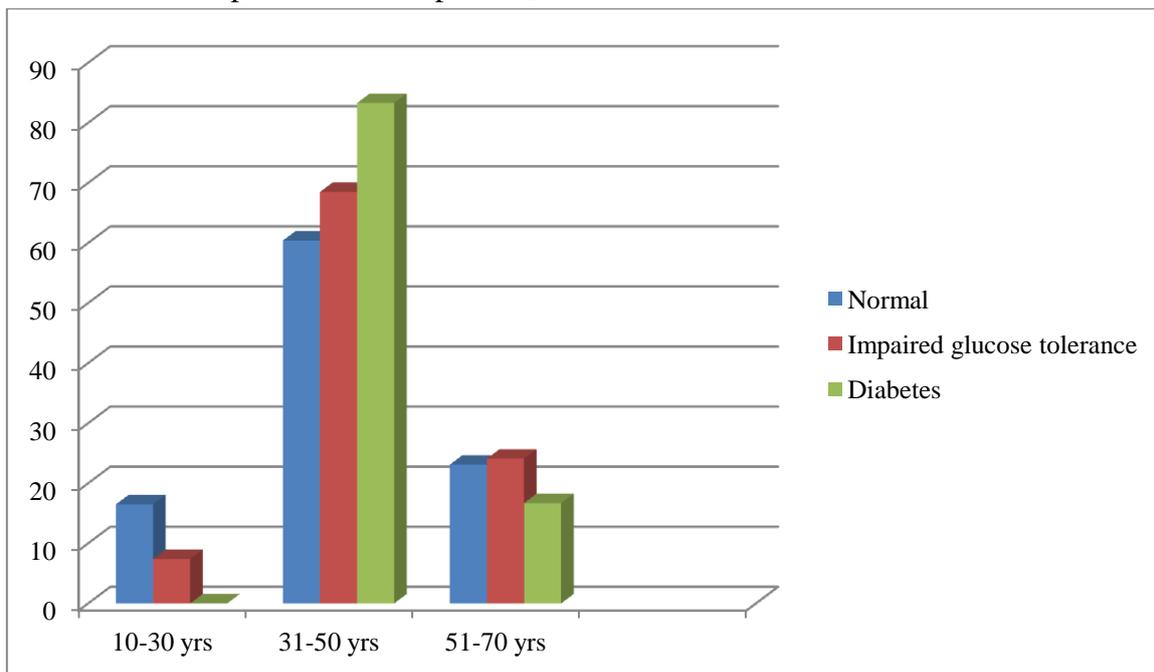


Figure 1: Gender distribution and OGTT

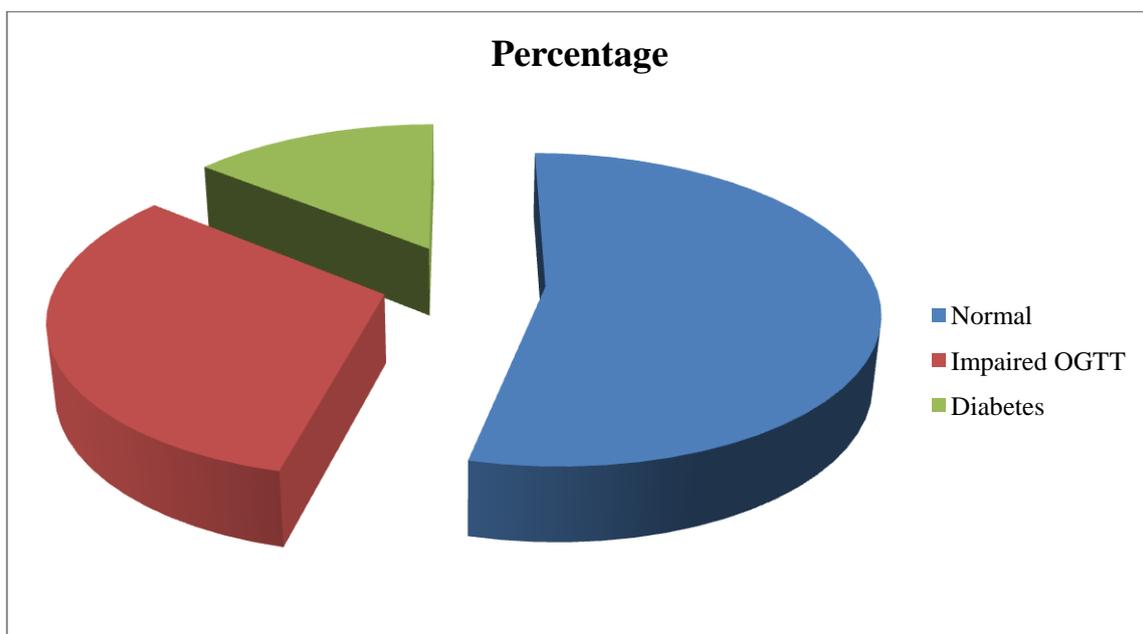
The age distribution amongst the study patients with normal glyceamic status, impaired glucose tolerance and Diabetic response was comparable,

with most of the patients belonging to the age group between 31 and 50 years.



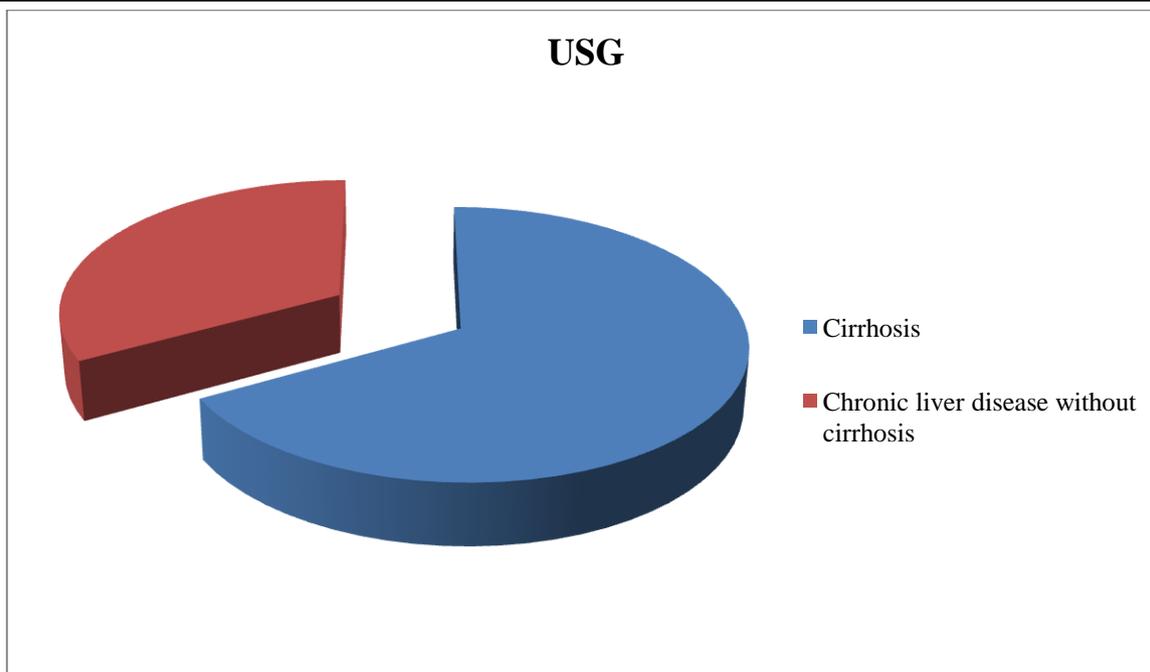
**Figure 2:** Age distribution and OGTT

Impaired GTT was seen in 54(32.2%), Diabetic Response in 24(14.2%) and Normal GTT in 91(53.8%) of the cases.



**Figure 3:** OGTT End-Result.

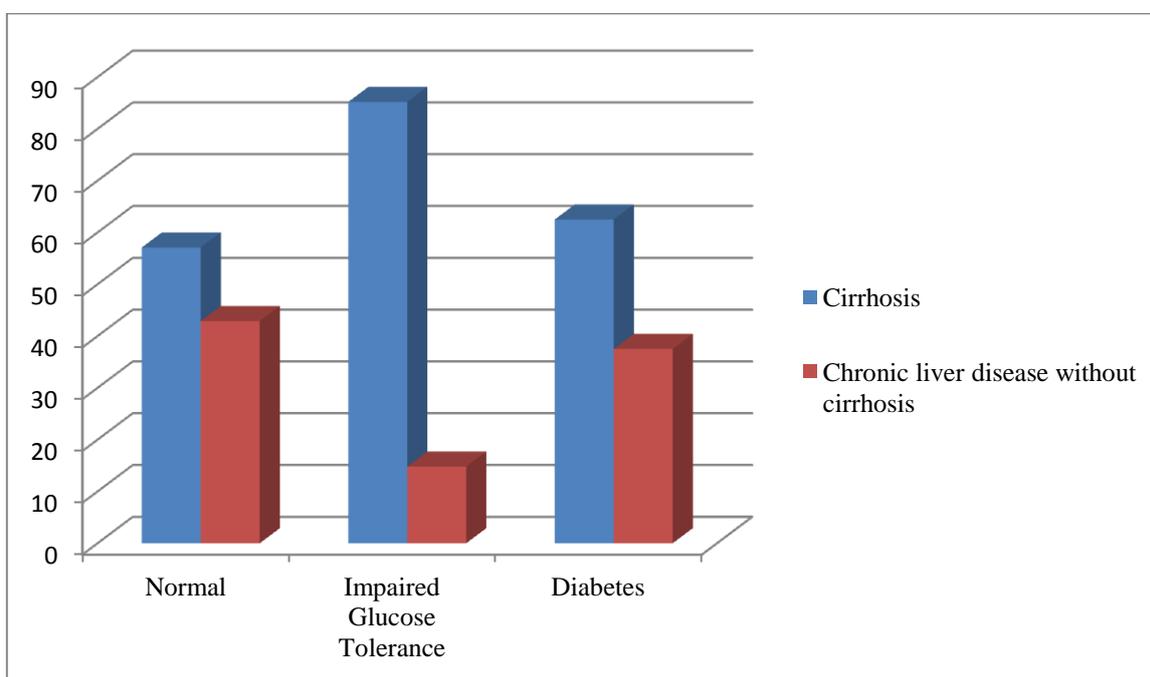
Of the 169 patients, cirrhosis was detected on USG in 113 cases (66.9%), while the rest 56(33.1%) had chronic liver disease without cirrhosis.



**Figure 4:** Cirrhosis Percentage.

Of the patients with cirrhosis, 85% had impaired glucose tolerance, compared to 14.8% in patients having CLD without cirrhosis. Similarly, in cirrhotic patients, 62.5% had diabetic response,

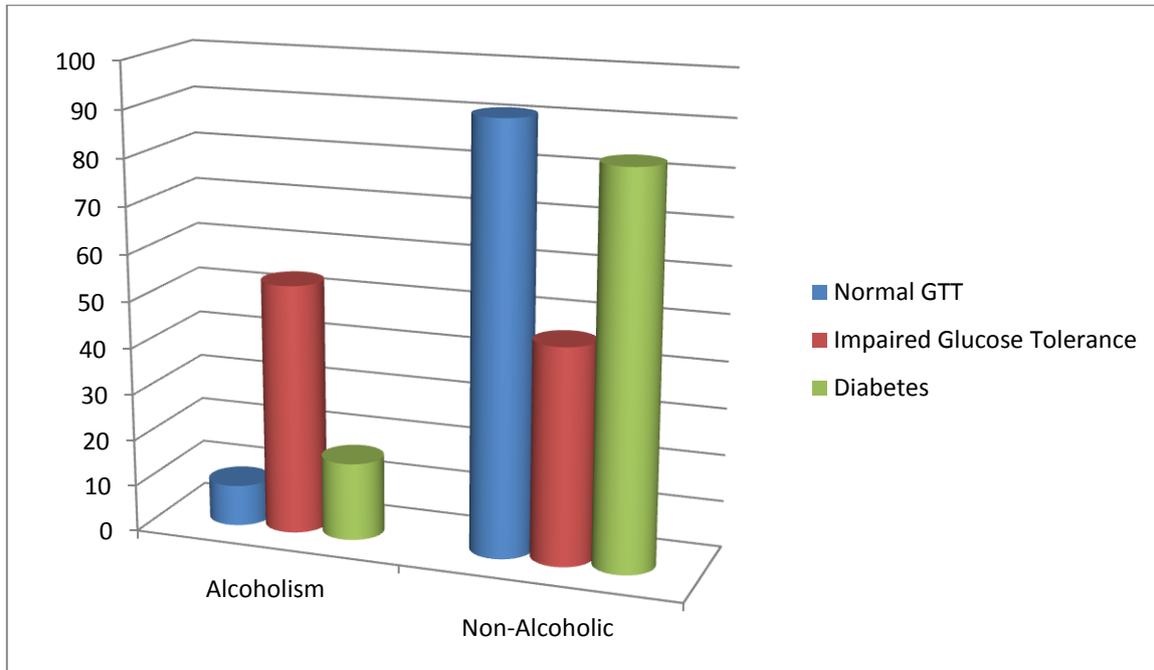
compared to 37.5% incidence in non-cirrhotic CLD patients. This incidence was significantly higher in patients with cirrhosis (p value 0.002).



**Figure 5:** Cirrhosis and OGTT

Increased association was noted between alcohol intake and incidence of impaired glucose response. Of the 41 patients with alcoholism, 53.7% had impaired glucose tolerance, 16.7% had

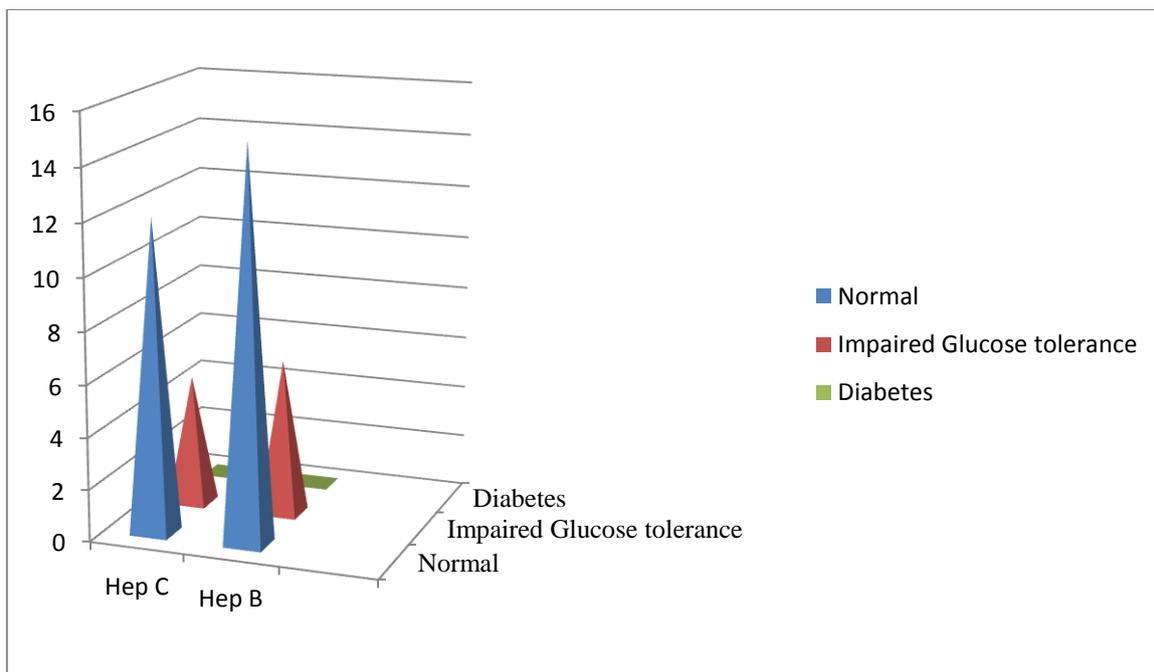
diabetic response and only 8.8% had normal glucose tolerance. This was found to be statistically significant (p<0.001).



**Figure 6:** Alcohol and OGTT.

However, Hepatitis B or Hepatitis C was not found to have a statistically significant effect on glycemic status. 5 out of the 12 Hepatitis C cases

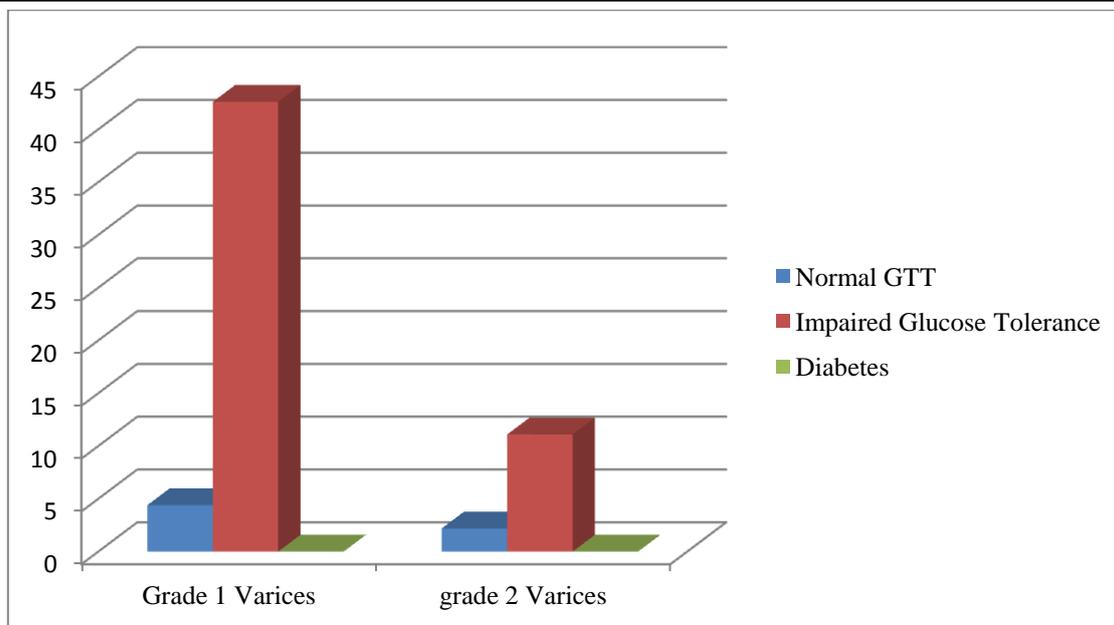
( $p=0.157$ ) and 6 out of 15 Hepatitis B cases ( $p=0.08$ ) had impaired glucose response



**Figure 7:** Hepatitis B and Hepatitis C and OGTT.

Grade 1 varices were found in 16% and grade 2 in 4.7% of the cases. 42.6% of patients with Grade 1 varices had Impaired Glucose Tolerance Test, compared to 11.1% in patients with Grade 2

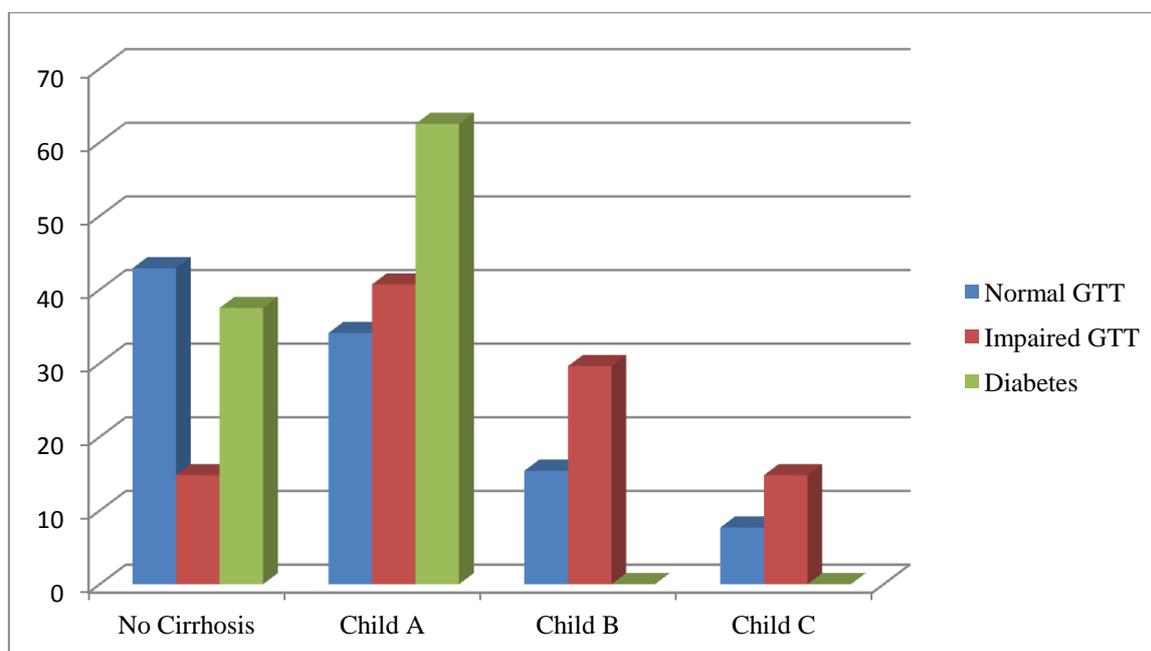
Varices. ( $p<0.001$ ). Patients with Grade 1 varices had higher incidence of Impaired Glucose Tolerance, which may be indirectly related to cirrhosis.



**Figure 8:** Varices and OGTT.

Child Pugh Staging was Grade A in 60% patients with cirrhosis, Grade B in 27.1% cases and Grade C in the rest. 48.8% of patients with Child Pugh

A, 35% in Child B and 17% in Child C had Impaired Glucose Tolerance.



**Figure 9:** Child Pugh Grading and OGTT.

**Table 1:** Association between Age and OGTT

Age	Normal OGTT		Impaired GTT		Diabetes		Total	
	N	%	N	%	N	%	N	%
10-30	15	16.5	4	7.4	0	0	19	11.2
31-50	55	60.4	37	68.5	20	83.3	112	66.3
51-70	21	23.1	13	24.1	4	16.7	38	22.5
Total	91	100	54	100	24	100	169	100

$\chi^2 = 7.627$      $df=4$      $p=0.106$

Patients within age group of 31-50 years had most incidence of abnormal OGTT.

**Table 2: Gender Distribution and OGTT**

Sex	Normal OGTT		Impaired GTT		Diabetes		Total	
	N	%	N	%	N	%	N	%
Female	23	25.3	13	24.1	9	37.5	45	26.6
Male	68	74.7	41	75.9	15	62.5	124	73.4
Total	91	100	54	100	24	100	169	100

$\chi^2 = 1.718$  df=2 p=0.424

Abnormal OGTT was more common in males when compared to females.

**Table 3: OGTT and Cirrhosis**

USG Findings	Normal OGTT		Impaired GTT		Diabetes		Total	
	N	%	N	%	N	%	N	%
CLD without Cirrhosis	39	42.9	8	14.8	9	37.5	56	33.1
Cirrhosis	52	57.1	46	85.2	15	62.5	113	66.9
Total	91	100	54	100	24	100	169	100

$\chi^2 = 12.269$  df=2 p=0.002

Impaired Glucose Tolerance was seen more in patients with Cirrhosis compared to those with CLD but no cirrhosis.

**Table 4: Oesophageal Varices and OGTT**

OGD Findings	Normal OGTT		Impaired GTT		Diabetes		Total	
	N	%	N	%	N	%	N	%
Grade 1 Varices	4	4.4	23	42.6	0	0	27	16
Grade 2 Varices	2	2.2	6	11.1	0	0	8	4.7
Total	91	100	54	100	24	100	169	100

$\chi^2 = 53.429$  df=4 p=0.001

Impaired Glucose Tolerance was seen more in patients with Grade 1 varices and may be indirectly related to occurrence of cirrhosis.

**Table 5: Alcoholism and OGTT**

Alcohol	Normal OGTT		Impaired GTT		Diabetes		Total	
	N	%	N	%	N	%	N	%
No	83	91.2	25	46.3	20	83.3	128	75.7
yes	8	8.8	29	53.7	4	16.7	41	24.3
Total	91	100	54	100	24	100	169	100

$\chi^2 = 38.081$  df=2 p<0.001

Alcoholism was associated with higher incidence of cirrhosis as well as impaired glucose response on OGTT.

**Table 6: Hepatitis C and OGTT**

Hepatitis C	Normal OGTT		Impaired GTT		Diabetes		Total	
	N	%	N	%	N	%	N	%
Absent	79	86.8	49	90.7	24	100	152	89.9
Present	12	13.2	5	9.3	0	0	17	10.1
Total	91	100	54	100	24	100	169	100

$\chi^2 = 3.706$  df=2 p=0.157

Impaired glucose tolerance was noted in 41% of patients with Hepatitis C.

**Table 7: Hepatitis B and OGTT**

Hepatitis B	Normal OGTT		Impaired GTT		Diabetes		Total	
	N	%	N	%	N	%	N	%
Absent	76	83.5	48	88.9	24	100	148	87.6
Present	15	16.5	6	11.1	0	0	21	12.4
Total	91	100	54	100	24	100	169	100

$\chi^2 = 4.64$  df=2 p<0.088

40% of patients with Hepatitis B had Impaired glucose tolerance, compared to 63% in patients not having Hepatitis B.

**Table 8:** Child Pugh Grading and OGTT

Child Pugh Grading	Normal OGTT		Impaired GTT		Diabetes		Total	
	N	%	N	%	N	%	N	%
No Cirrhosis	39	42.9	8	14.8	9	37.5	56	33.1
Child A	31	34.1	22	40.7	15	62.5	68	40.2
Child B	14	15.4	16	29.6	0	0	30	17.8
Child C	7	7.7	8	14.8	0	0	15	8.9
Total	91	100	54	100	24	100	169	100

$$x^2 = 25.284 \quad df=2 \quad p<0.001$$

*Child Pughs A stage was more frequently associated with Impaired glucose tolerance in patients with cirrhosis, when compared to other stages.*

## Discussion

The reported incidence of glucose intolerance varies from 60 to 80%, and that of diabetes between 20 to 60%, dependent on the diagnostic criteria, aetiology and degree of liver damage.<sup>1-4</sup>

Insulin resistance and glucose intolerance may be found right from the very early stages of chronic liver disease. As the liver function deteriorates, the diabetes starts manifesting itself clinically, and thus Hepatogenous diabetes indicates advanced liver disease.<sup>5</sup>

The aetiology behind chronic liver disease is crucial to the degree of development of hepatogenous diabetes. Type 2 DM is found in about 30-45% patients with NASH, and its association with visceral obesity, hypertriglyceridemia and insulin resistance is well known.<sup>6</sup> On the other hand, obesity with its state of adipokine mediated chronic inflammation is itself a risk factor to severe liver disease.<sup>7,8</sup>

The National Health and Nutrition Examination Survey identified a 3-fold higher risk of DM in patients with Chronic Hepatitis C infection.<sup>9</sup> Acute alcohol intake reduces insulin mediated glucose uptake, while chronic alcoholism produces chronic pancreatic  $\beta$  cell damage, resulting in Diabetes.<sup>10-11</sup>

With this background, this study was carried out in the Department of General Medicine, Government TD Medical College, Alappuzha over a period of one year. 169 patients admitted in TD Medical college Hospital with chronic liver disease and meeting the inclusion criteria were subjected to OGTT and specifically evaluated for impaired glucose tolerance. The results of OGTT

was tabulated and evaluated statistically against various variables.

Of the 169 patients enrolled, 73% were of male gender and most belonged to 31-50 years age group. The mean age in our study was 43.5 yrs and comparable to studies by Majumdar et al (42.5 yrs).<sup>12</sup> The male to female ratio in our study was 2.75:1 and comparable to the ratio of 2.63:1 in the study by Majumdar et al and Sarkar et al<sup>12-13</sup>

The male preponderance can be probably attributed to alcohol consumption, IV drug abuse and other high risk behaviour.

In our study, 32% patients had impaired glucose tolerance, 14% had Diabetes, and 53.8% had normal response to OGTT. This correlates with the incidence of 34%, 15% and 50% respectively reported by Suri KR et al<sup>11-13</sup>. The study by Majumdar et al reported values of 22.5%, 20% and 57.5% respectively for IGT, Diabetes and normal response.

Evidence of cirrhosis was found on USG Abdomen in 69.9% cases of chronic liver disease. Of the 54 patients with impaired glucose tolerance, 46(85.2%) were found to have cirrhosis. Similarly, of the 24 patients with Diabetes, 15(62.5%) had cirrhosis. Amongst all our patients with Impaired GTT, 40.7% were in Child Pugh Stage A disease, 30% in Child Pugh B and 15% in Child Pugh C. This was different from the 14% in stage A, 46% in stage B and 32% in stage C reported by Sarkar et al. Further, in our group, Grade 1 varices(42.6%) were more common than Grade 2 varices(11.1%) in patients with impaired GTT.

24% had history of alcoholism and all of them were males. Alcoholism was associated with

higher incidence of both impaired glucose tolerance (54%) and Diabetes (16.7%). Of the 41 patients with alcoholism, 26 had cirrhosis. Similar findings have been reported by Zein et al and Wei et al.<sup>10-11</sup>

Hepatitis B was positive in 12.4% and Hepatitis C in 10% of the study group. However, a higher incidence of abnormal GTT was seen in patients with Hepatitis C, with 41% showing impaired glucose tolerance. Knobler et al reported a 33% prevalence rate of Diabetes in patients with Hepatitis C infection<sup>9,15</sup>.

The liver has a pivotal role in Glucose homeostasis.<sup>16</sup> Thus, it is not surprising that irrespective of the aetiology, patients with advanced liver disease have significant metabolic derangements.<sup>17</sup> However, the data regarding correlation between nutritional status of patient, severity of liver disease and severity of insulin resistance is conflicting.

The liver affects glucose homeostasis by combination of gluconeogenesis, glycogenolysis and glycogenesis. The metabolic derangements are complex and ill-understood.

In cirrhotic liver, impaired release of hepatic glucose and reduced glycogen reserve causes carbohydrate mediated energy production to fall from 38% of normal state to 2%<sup>18</sup>. Defects develop in both Insulin receptor function and post-receptor cascade in hepatocytes of patients with cirrhosis. Further, insulin resistance might affect ability of liver to metabolise glucose, causing post-prandial hyperglycemia. Elevated serum lactate levels also suggest an inability of the cirrhotic liver to utilize lactate for gluconeogenesis<sup>19</sup>.

NASH, a severe manifestation of NAFLD is associated with obesity, hyper-triglyceridemia and insulin resistance. About 30-45% of patients with NASH have type 2 Diabetes.<sup>6</sup> Obesity is itself a state of chronic inflammation and elevated adipokines have deleterious effect on lipid metabolism in the liver.<sup>8</sup> TNF- $\alpha$  is a cytokine stimulating liver stellate cells and induces hepatic fibrosis.<sup>20</sup>

Chronic Hepatitis C infection is associated with high incidence of fatty liver<sup>21</sup> (30-70%), glucose intolerance<sup>9,15</sup> (40%) and Diabetes in more than 17%. Further, an association is noted between severity of fibrosis, insulin resistance and steatosis.<sup>9,15,21,22</sup>. The mechanism is ill-understood, but studies on transgenic animal models showed that HCV core protein can induce insulin resistance, steatosis and DM by amplifying production of TNF- $\alpha$ .<sup>8</sup>

TNF  $\alpha$  phosphorylates serine residues of Insulin Receptor (IRS1 and IRS 2) and stimulates SOC-3 (suppressor of cytokine-3). These block the transactivation of GLUT-4, and inhibit cellular uptake of glucose. Further, CHC patients show a linear relation between poor interferon response and a faster progression of fibrosis and levels of TNF  $\alpha$ .<sup>8</sup> Studies have also reported a poorer response to peg interferon and ribavarin in patients with CHC and insulin resistance as compared to those with only CHC.<sup>8,23</sup>. Our study also detected a 41% incidence of impaired glucose tolerance in patients with CHC

Acute alcohol consumption reduces insulin mediated glucose uptake. Chronic alcoholism causes pancreatic islet beta cell damage. Amount of ingested alcohol also affects degree of impaired GTT.<sup>10,11</sup>. Of the 41 patients with alcoholism in our study, 29 had impaired glucose tolerance and 4 had impaired diabetic response.

The data is scant regarding treatment of diabetes in patients with cirrhosis. Decisions regarding management depend on degree of hyperglycemia and recommended measures include diet control, sulphonyureas and insulin. Biguanides such as metformin should be avoided to prevent lactic acidosis. In absence of strict guidelines, short acting insulin before meals and intermediate acting insulin at night may be attempted. Good control in these patients is often difficult to attain. So, from our study, we presumed that cirrhosis is the most common cause of chronic liver disease. As liver biopsy couldn't be done in all cases, underlying aetiology was undetermined in some cases and cirrhosis was diagnosed based on USG

abdomen findings. Impaired glucose tolerance and impaired diabetic response were seen more in patients with cirrhosis when compared to those without cirrhosis. Further, Child Pugh's A stage of cirrhosis, male gender and Hepatitis C associated cirrhosis was more frequently associated with impaired GTT.

### Conclusions

- Incidence of Chronic liver disease was higher in male patients.
- Most common cause of chronic liver disease was cirrhosis. Impaired glucose tolerance and Diabetes were more frequent in cirrhotic patients with chronic liver disease as compared to those without cirrhosis.
- Amongst cirrhosis patients, higher incidence of impaired glucose response was seen in male gender, Child Pugh Grade A and Hepatitis C associated cirrhosis.
- Alcoholism associated chronic liver disease was associated with higher incidence of impaired glucose response.

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