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Insulin resistance in euglycemic cirrhosis

Amitava Goswami, Narendra Bhargava, Sunil Dadhich, Ganaraj Kulamarva

Dr Sampurnanand Medical College, Jodhpur, India

Abstract

Background Insulin resistance (IR) is associated with hepatic fibrosis and cirrhosis, regardless of its etiology but the mechanism of hyperinsulinemia in cirrhosis is still unclear. The current study was designed to assess hyperinsulinemia and pancreatic β-cell function in euglycemic cirrhosis of varied etiology.

Methods A cross sectional case control study of 100 subjects. IR was assessed by the Homeostasis Model Assessment (HOMA) and quantitative insulin sensitivity check index in euglycemic cirrhosis of varied etiology and in different stages of cirrhosis. HOMA-β was calculated for insulin secretion ability of pancreatic β-cells in different stages of cirrhosis.

Results Overall IR in euglycemic cirrhosis was seen in 68.5%. IR was seen in the order hepatitis C (100%), non-alcoholic fatty liver disease (100%), autoimmune hepatitis (100%), hepatocellular carcinoma (80%), alcoholic liver disease (72%) and hepatitis B (45%). HOMA-IR value was raised in Child Turcotte Pugh (CTP) score >9 (P value 0.0004) and model of end stage liver disease (MELD) score >15 (P value 0.02). HOMA-β was raised in CTP score >9 (P value 0.02) and MELD score >15 (P value 0.0003). HOMA-β level among diabetic controls was 27.1±7.7 compared to 154.6±80.7 in euglycemic cases (P value <0.0001).

Conclusion IR is common in euglycemic cirrhosis and with advancement of liver disease; there is a compensatory increase in pancreatic β-cell insulin secretion to overcome the IR. However, over a period of time with fall in β-cell function development of hepatogenous diabetes may occur.

Keywords Homeostatic model assessment, quantitative insulin sensitivity check index, Child Turcotte Pugh, model of end stage liver disease, hepatocellular carcinoma

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Introduction

An association between diabetes mellitus and liver cirrhosis was first described by Bohan [1] and named as hepatogenous diabetes by Megyesi *et al*, in which 57% of cirrhotic patients showed increased insulin resistance (IR) [2]. Currently, it is still unclear whether type 2 diabetes mellitus, in the absence of other risk factors contributing to metabolic syndrome (obesity and hypertriglyceridemia), could be a risk factor for the development and progression of liver disease [3-5]. On the other hand, the diabetes which develops as a complication of cirrhosis is known as "hepatogenous diabetes" and is not recognized by the American Diabetes Association and the World Health Organization as a specific independent entity [6]. IR is defined where a normal or elevated insulin level produces an attenuated biological response [7]; classically this refers to impaired sensitivity to insulin-mediated glucose disposal [8]. Compensatory hyperinsulinemia occurs when pancreatic β-cell secretion increases to maintain normal blood glucose levels in the setting of peripheral IR in muscle and adipose tissue. IR results from defects either at the receptor level or in insulin receptor substrates molecules [9]. However, whether the hyperinsulinaemia in cirrhosis is a consequence of increased pancreatic insulin secretion, decreased hepatic insulin removal, or impaired feedback regulation of insulin secretion is still doubtful. So the current study was designed with a hypothesis that IR progressively increases with advancement of liver disease and identification of IR may access the risk for development of hepatogenous diabetes and hepatocellular carcinoma (HCC).

The aim of the study was to investigate: 1) IR in euglycemic cirrhosis of varied etiology. 2) IR in different stages of cirrhosis. 3) Pancreatic β-cell Insulin secretions in relation to stages of cirrhosis.

Department of Gastroenterology, Dr Sampurnanand Medical College, Jodhpur, India

Conflict of Interest: None

Correspondence to: Amitava Goswami, Department of Gastroenterology, S.N.M.C. Jodhpur 342001, Rajasthan, India, Tel.: +91 87699 47345, e-mail: amitavagoswami77@gmail.com

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Patients and methods

A cross sectional case control study of one hundred patients. The study was conducted in the Department of Gastroenterology (Dr Sampurnanand Medical College) over a period of 6 months (April-September 2013). The study was approved by the ethics committee of the medical college. After written consent, subjects were counselled and explained about the objectives of the study by a qualified medical doctor. Detailed personal history was taken using a standard questionnaire and 5 mL of fasting blood sample was collected.

Inclusion criteria comprised: 1) euglycemic cirrhotic patients (fasting blood sugar <126 mg/dL), diagnosis of cirrhosis was based on histopathological evidence (liver biopsy) or unequivocal clinical grounds (chronic liver disease stigmata, jaundice, ascites, esophageal varices), impaired liver function tests and ultrasonographic features consistent with cirrhosis (diffuse alteration and nodular transformation of liver parenchyma, and signs of portal hypertension); 2) patients with HCC, diagnosed by cytological or histological examination of hepatic focal lesions or according to the following established criteria: ultrasound examination, α-fetoprotein >400 ng/mL, computed tomography scan and/or magnetic resonance imaging of the upper abdomen; 3) body mass index (BMI) ≤25 kg/m^2; 4) diseased controls were cirrhotic patients with recently diagnosed diabetes mellitus. The patients selected for diseased controls were cirrhotic patients of varied etiology, who had a recent onset of diabetes mellitus within a period of 2 years.

Exclusion Criteria: 1) Known type 2 diabetes mellitus or fasting blood sugar >126 mg/dL (except controls); 2) BMI >25 kg/m^2 (except controls); 3) renal failure; 4) pregnancy; 5) thyroid dysfunction.

Laboratory assessment

Venous blood samples were taken in the morning after 8-h overnight fasting. Hepatitis B surface antigen (HBsAg), anti-HBV surface antigen (anti-HBs), anti-HBV core antigen (anti-HBc), and hepatitis B "e" antigen (HBeAg) were determined by using commercial assays (Abbott Diagnostic Division, Wiesbaden; Germany). Antibodies against hepatitis C (anti-HCV) were determined using a sensitive commercial ELISA (Xcyton, Bangalore, India). Serum HCV-RNA were tested using the Roche Amplicor version 2.0 (Roche Molecular System, Pleasenton, CA). Insulin was measured by chemiluminescence immunoassay on an Advia Centaur analyzer (Bayer AG, Germany). Because pancreatic insulin secretion is pulsatile, for each subject we used the mean of three samples taken at 5-min intervals. diabetes mellitus was diagnosed using the American Diabetes Association criteria [10]: fasting plasma glucose >126 mg/dL (confirmed on a subsequent day in the absence of unequivocal hyperglycemia) or symptoms of hyperglycemia and casual plasma glucose >200 mg/dL.

IR measurement

IR was assessed by the Homeostasis Model Assessment method for the evaluation of IR (HOMA-IR). HOMA was first developed in 1985 by Matthews *et al* [11]. It is a method used to quantify IR and β-cell function from basal (fasting) glucose and insulin concentrations. HOMA is a model of the relationship of glucose and insulin dynamics that predicts fasting steady-state glucose and insulin concentrations for a wide range of possible combinations of IR and β-cell function. HOMA-IR = (glucose × insulin)/22.5; insulin concentration is reported in μU/L and glucose in mmol/L. The constant of 22.5 is a normalizing factor; i.e, the product of normal fasting plasma insulin of 5 μU/mL, and the normal fasting plasma glucose of 4.5 mmol/L typical of a "normal" healthy individual=22.5. Value of HOMA-IR more than 1.64 implied the presence of abnormally high IR [12]. Quantitative insulin sensitivity check index (QUICKI), as an alternative surrogate marker of IR, computed as 1/ [log insulin (μU/mL) + log fasting blood sugar (FBS) (mg/dL)]. Value <0.35 is suggestive for IR. QUICKI is an empirically-derived mathematical transformation of FBS and plasma insulin concentrations that provides a consistent and precise index of insulin sensitivity with better positive predictive power [13]. HOMA-β a parameter reflecting the insulin secretion ability of pancreatic β-cells, was calculated as [360 × insulin (μU/mL)]/FBS (mg/dL) -63]. Estimation with the help of HOMA-β model parallels equally with that of the euglycemic clamp method (r = 0.88) [14].

Statistical analysis

HOMA calculator 2.2 was used to calculate the HOMA IR and HOMA-β values while QUICKI values were calculated with a scientific calculator. Parametric data are expressed as mean values ± standard deviation (SD) and categorical variables as percentages. Chi-square test or Fisher's exact test were used for the comparison of dichotomous variables and Student's t test for continuous variables. Whenever more than 2 continuous variables were present, ANOVA one-way analysis was used for calculating the P values. A P value <0.05 was considered statistically significant. Spearman and Pearson's coefficient correlation were used to compare the regression coefficient between the two groups. All data were analyzed using the SAS 8.0 statistical package.

Results

From April 2013 to September 2013, 70 patients of euglycemic cirrhosis were included in the study group and another 30 diseased controls (recent onset diabetes mellitus) were also enrolled.

Patient characteristics

Euglycemic cirrhosis cases: The mean age of cases of euglycemic cirrhosis was 52.3±13.7 yrs with M: F 6:1. Mean

BMI was 22.6±2.4 kg/m². Alcoholic liver disease (ALD) (51%) was the most common etiology followed by hepatitis B (HBV) (31%), HCV (6%), non-alcoholic fatty liver disease (NAFLD) (6%) and autoimmune hepatitis (AIH) (6%) respectively (Table 1). Ten cases of euglycemic HCC were present among which 8 cases were due to HBV-related cirrhosis and only 2 cases due to HCV-related cirrhosis. Most of the patients had advanced liver disease; that is Child Turcotte Pugh's score (CTP) ≥10 (60%), CTP score 7-9 (31%), and CTP score 5-6 (9%). Likewise, 63% of cases had model of end-stage liver disease (MELD) score >15; 26% had MELD score 10-15; and 11% had MELD score <10. The mean FBS level was 84.7±20.2 mg/dL, and the mean fasting insulin was 11.8±6.7 μU/mL. The overall IR in the euglycemic cirrhotic patients was 68.5%. The mean levels of HOMA-IR, QUICKI and HOMA - β were 2.54±1.71, 0.34±0.01 and 154.6±80.7 respectively.

Diabetic (diseased) controls: The mean age group and M: F ratio was comparable with the cases, 52.2±8.1 yrs and 13:2 respectively (P>0.05). The etiology of cirrhosis was different from the cases; NAFLD (53%) was the most common etiology followed by ALD (27%), HBV (13%) and HCV (7%) respectively. There were 4 diseased controls with HCC and diabetes mellitus; all were caused by HBV-related cirrhosis. The mean FBS and fasting insulin were 198±47.3 mg/dL and 9.9±2.5 μU/mL respectively. IR was universal among the diseased diabetic controls with mean HOMA-IR and QUICKI levels of 4.9±1.9 and 0.31±0.01 respectively (P<0.0001). IR was much higher among the diabetic controls than the euglycemic cirrhotic cases. There was a significant difference in the HOMA-β levels between the diabetic controls and euglycemic cirrhotic cases (P<0.0001). The mean HOMA-β level in the diseased controls was 27.1±7.7 as compared to 154.6±80.7 in the cases.

Table 1 Baseline characteristics

Variables n=100	Cases n=70 (%)	Diseased controls n=30 (%)	P value
Etiology			
Alcohol	36 (51)	8 (27)	0.01
HBV	22 (31)	4 (13)	0.03[a]
HCV	4 (6)	2 (7)	0.13
NAFLD	4 (6)	16 (53)	0.001[b]
AIH	4 (6)	0 (0)	0.20
HCC	10 (14)	4 (13)	0.16
Age (years)			0.49
Mean±SD	52.3±13.7	52.2±8.1	
Range	(23-75)	(41-67)	
M:F	6:1	13:2	0.27
BMI (kg/m²)			0.005[b]
Mean±SD	22.6±2.4	24.1±2.3	
Range	(19.2-31.6)	(19-28.6)	
CTP Score	9.9±2.1	7.4±1.8	<0.001[b]
A	6 (9)	12 (40)	
B	22 (31)	14 (47)	
C	42 (60)	4 (13)	
MELD Score	19±8.3	11.5±5.1	<0.0001[b]
<10	8 (11)	14 (47)	
10-15	18 (26)	10 (33)	
>15	44 (63)	6 (20)	
FBS (mg/dL)			<0.0001[b]
Mean±SD	84.7±20.2	198±47.3	
Range	(53-125)	(145-342)	
Fasting Serum Insulin (μU/mL)			0.03[a]
Mean±SD	11.8±6.7	9.9±2.5	
Range	(2.7-33.3)	(6.1-16)	
HOMA-IR			<0.0001[b]
Mean±SD	2.54±1.71	4.9±1.9	
Range	(0.5-7.02)	(2.72-8.59)	
QUICKI			<0.0001[b]
Mean±SD	0.34±0.04	0.31±0.01	
Range	(0.29-0.44)	(0.28-0.33)	
HOMA-β			<0.0001[b]
Mean±SD	154.6±80.7	27.1±7.7	
Range	(37.4-384)	(7.4-37.4)	

[a]*P* value <0.05, [b]*P* value <0.01; *P* value were determined using the chi-square test or Fisher's exact test for the dichotomous variables and Student's *t* test for continuous variables.

CTP, Child pugh turcotte; MELD, Model of end-stage liver disease; HBV, Hepatitis B virus; HCV, Hepatitis C virus; NAFLD, Non-alcoholic fatty liver disease; AIH, Autoimmune hepatitis; HCC, Hepatocellular carcinoma; FBS, Fasting blood sugar; HOMA, Homeostatic model assessment; QUICKI, Quantitative insulin sensitivity check index

IR of varied etiology in euglycemic cirrhosis

The Spearman coefficient correlation between IR and varied euglycemic cirrhosis was very significant (R=1). Pearson regression coefficient was 0.96. IR was seen in all cases of NAFLD, AIH and HCV (genotype 3) related euglycemic cirrhosis (Table 2). Eighty percent of cases of euglycemic HCC and 72% with alcoholic cirrhosis had IR, while least among cases of HBV-related cirrhosis (45%). HOMA-IR was highest among HCV (5.7±0.7) and least among HBV-related euglycemic cirrhosis (1.9±1.5) (Fig. 1). Cases of HCV cirrhosis, alcoholic cirrhosis and NAFLD-related cirrhosis had advanced liver disease with high CTP and MELD score while most of the cases with HCC had lower mean CTP and MELD score (8.8, 11.4 respectively), suggesting that IR occurs early in HCC.

IR in different stages of cirrhosis

CTP score: An increasing trend in IR was seen from CTP-A to CTP-B (33%, 54%; P=0.08), though statistically nonsignificant. The advanced cirrhotics with CTP ≥10 had

Table 2 Insulin resistance of varied etiology in euglycemic cirrhosis

Etiology	N (%)	CTP	MELD	IR (%)	Pearson/spearman coefficient (r/R)	HOMA-IR	QUICKI	HOMA-β
ALD Mean±SD	36 (51)	10.1±2.3	21.1±8.9	26 (72)		2.4±1.3	0.34±0.03	160.1±96.4
HBV Mean±SD	22 (31)	9.2±1.8	16±7.9	10 (45)	r=0.96 R=1	1.9±1.5	0.37±0.05	143.4±65.5
HCV Mean±SD	4 (6)	12±2.3	18.5±2.9	4 (100)		5.7±0.7	0.29±0.01	114.4±27.8
NAFLD Mean±SD	4 (6)	10.5±0.6	20±4.6	4 (100)		4.9±2.4	0.30±0.02	185.9±71.3
AIH Mean±SD	4 (6)	9.5±2.5	16±7	4 (100)		2±0.2	0.34±0.01	175.5±1.7
HCC Mean±SD	10 (14)	8.8±2	11.4±3	8 (80)		3.5±1.6	0.32±0.04	117.9±55.6

R, Spearman coefficient correlation; r, Pearson coefficient correlation; CTP, Child Turcotte Pugh; MELD, Model of end-stage liver disease; HOMA, Homeostatic model assessment; IR, Insulin resistance; QUICKI, Quantitative insulin sensitivity check index; ALD, Alcoholic liver disease; HBV, Hepatitis B virus; HCV, Hepatitis C virus; NAFLD, Non-alcoholic liver disease; AIH, Autoimmune hepatitis; HCC, Hepatocellular carcinoma

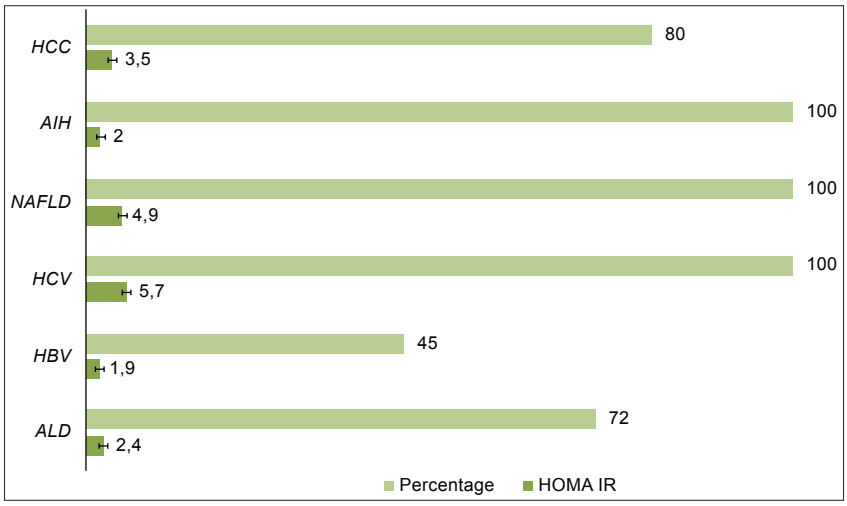

Figure 1 Insulin resistance in varied etiology of euglycemic cirrhosis
HCC, hepatocellular carcinoma; AIH, autoimmune hepatitis; NAFLD, non-alcoholic fatty liver disease; HCV, hepatitis C virus; HBV, hepatitis B virus; ALD, alcoholic liver disease

a statistically significant IR as compared to other groups (P=0.05). HOMA-IR is significantly higher (3.08±1.92) in cases with CTP ≥10 as compared to CTP-A and B (Table 3). QUICKI as a surrogate marker of IR showed similar correlation with HOMA-IR, it was significantly lower in advanced cirrhosis with CTP-C (P=0.02). Diseased controls with recent onset of diabetes mellitus had higher IR value than its euglycemic counterpart (Fig. 2). A significant fall in QUICKI in diseased controls with CTP score >9 was seen as compared to CTP score <9 (P=0.004), but no significant rise in HOMA-IR was seen among the diseased controls with CTP-C status (P=0.22).

MELD score was divided into three groups, i.e., <10; 10-15; and >15, which correlated well with CTP score. Similar to CTP score, the IR is most commonly seen in cases with advanced cirrhosis with MELD score >15 (82%, P=0.03). HOMA-IR and QUICKI correlated well, and a higher IR was seen in MELD score >15 as compared to MELD score 10-15 and less than 10 (P value 0.02 and 0.01, respectively). Controls (diseased) had a higher HOMA-IR value, but no significant alteration was seen among the three different groups of MELD score (Table 4).

Pancreatic β-cell insulin secretions correlation with stages of cirrhosis (HOMA-β)

HOMA-β a parameter reflecting the insulin secretion ability of pancreatic β-cells was evaluated in euglycemic cirrhotic with different CTP score and MELD score. HOMA-β is seen significantly elevated in patients with CTP-C and MELD score >15 (P values 0.02 and 0.0003, respectively). HOMA-β

Table 3 HOMA-IR and HOMA-β correlation with CTP score

N=100	Cases (n=70)				Diseased controls (n=30)			
CTP score	A (6)	B (22)	C (42)	P value	A (12)	B (14)	C (4)	P value
HOMA-IR Mean±SD	2.05±1.39	1.66±0.75	3.08±1.92	0.004	4.84±2.04	4.55±1.83	6.45±1.44	0.22
QUICKI Mean±SD	0.35±0.04	0.36±0.04	0.33±0.04	0.02	0.31±0.01	0.31±0.01	0.29±0.01	0.004
HOMA-β Mean±SD	121.6±64.8	123.1±60.6	175.8±86.1	0.02	27.7±10.8	25.9±3.3	29.5±9.1	0.69

P values were calculated using the ANOVA one way test for continuous variables.
HOMA-IR, homeostatic model assessment of insulin resistance; QUICKI, quantitative insulin sensitivity check index; HOMA-β, homeostatic model assessment of β-cell sensitivity; CTP, Child Turcotte Pugh

Table 4 HOMA-IR and HOMA β correlation with MELD score

N=100	Cases (n=70)				Diseased controls (n=30)			
MELD score	<10 (8)	10-15 (18)	>15 (44)	P value	<10 (14)	10-15 (10)	>15 (6)	P value
HOMA-IR Mean±SD	1.99±1.24	1.92±1.39	2.94±1.83	0.02	5.26±2.39	4.5±1.76	4.79±0.50	0.64
QUICKI Mean±SD	0.35±0.03	0.36±0.05	0.33±0.03	0.01	0.30±0.01	0.31±0.01	0.30±0.01	0.05
HOMA-β Mean±SD	134.7±61.5	97.2±45.6	181.7±82.5	0.0003	26.32±9.97	29.74±5.75	24.7±2.5	0.4

P values were calculated using the ANOVA one-way test for continuous variables.
HOMA-IR, Homeostatic model assessment of insulin resistance; QUICKI, Quantitative insulin sensitivity check index; HOMA-β, Homeostatic model assessment of β-cell sensitivity; CTP, Child Turcotte Pugh; MELD, Model of end-stage liver disease

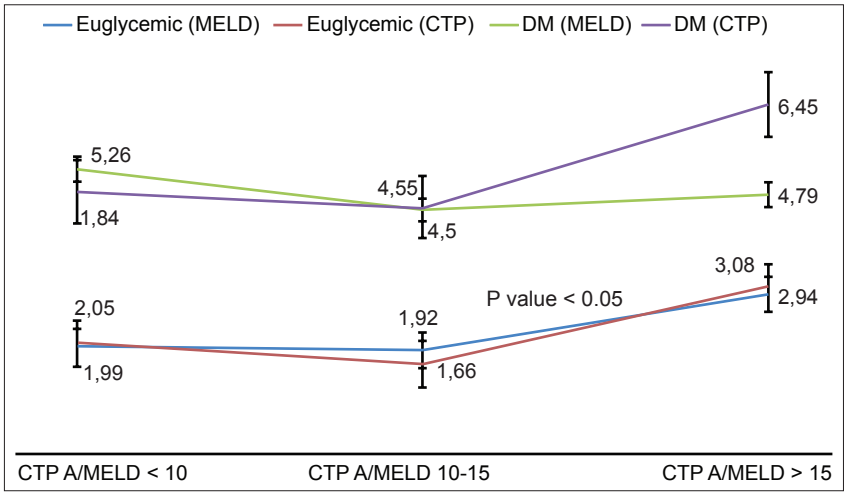

Figure 2 HOMA-IR in euglycemic and diabetic cirrhosis
CTP, Child Turcotte Pugh; MELD, model for end-stage liver disease; DM, diabetes mellitus

level is lower in MELD score 10-15 than in MELD score <10, but patients with MELD score >15 have a much higher value as compared to other groups; likewise, HOMA-β levels were comparable between patients with CTP A and B but significantly elevated in CTP C (Fig. 3). HOMA-β values were the lowest in the diabetic controls (27.1±7.7), with no significant change in the three different groups of CTP or MELD scores.

Discussion

In our study, IR in euglycemic cirrhosis was seen in 68.5%, whereas it was universally present in cirrhotic patients with recent onset diabetes. The cut off of IR was taken with HOMA-IR value >1.64 and QUICKI <0.35 which has been validated in many studies [12,15]. Our study shows that

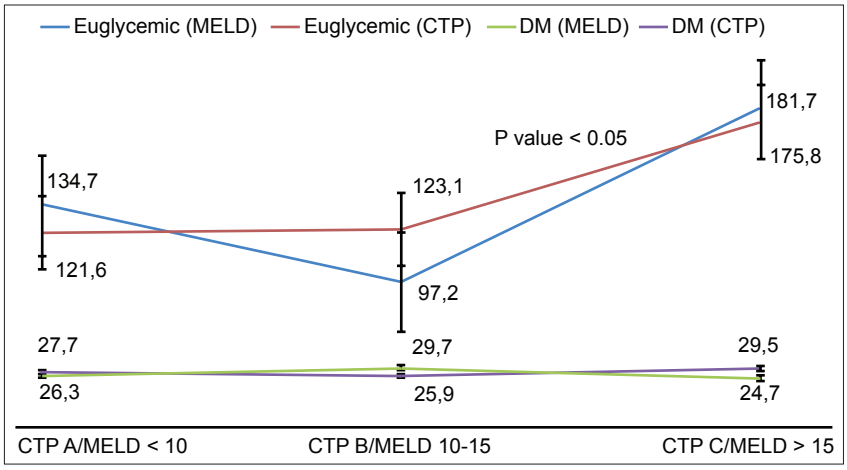

Figure 3 HOMA-β values in euglycemic and diabetic cirrhosis
CTP, Child Turcotte Pugh; MELD, model for end-stage liver disease; DM, diabetes mellitus

HOMA-IR in euglycemic cirrhosis is minimally elevated in CTP <10 and MELD <15, but it significantly rises with CTP score ≥10 or MELD score >15.

HCV *per se* is an important factor for the development of IR. IR parallels the liver fibrosis stage [16,17] and is associated with a reduced level of sustained virological response to treatment. HCV genotypes 1, 3 and 4 are associated with more severe IR [17]. In the present study all the patients with HCV were of genotype 3, and IR was seen universally.

Chronic ALD is mediated by combined effects of IR and toxic injury. Hepatic IR is caused by defects in intracellular signaling, including impairments in receptor binding and receptor tyrosine kinase activation. Ethanol also inhibits tyrosine phosphorylation of insulin receptor substrate proteins, needed to transmit insulin and insulin-like growth factor receptor signals [18-20]. In the present study IR in ALD were seen 72% cases, but IR occurred mainly with advancement in liver disease that is CTP-C status or MELD score >15. IR is a very common phenomenon in NAFLD [21]. This is believed to be responsible for the 'first hit' in NAFLD, leading to increased lipolysis and hepatic steatosis [22]. Almost all patients with NAFLD had IR in our study, which is in agreement to the concept that IR is the primary event in NAFLD. We also stated that IR was least commonly associated with HBV-related liver disease and HOMA-IR rises only after advancement in the stage of liver disease. The main limitation of our study was that we did not measure the vitamin D levels of the patients. There is increasing belief that with fall in vitamin D levels there may be an increase in IR among cirrhotic patients.

Several studies suggest that type 2 diabetes mellitus may have an etiological role in chronic liver disease and HCC regardless of alcohol and viruses [5]. In a recent case-control study that included 465 patients, diabetes mellitus prevalence was higher in patients with HCC than in controls (31.2% *vs* 12.7%, OR 3.12, 95% CI: 2.22-4.43). The diabetes mellitus had been diagnosed prior to the occurrence of HCC in 84% of cases with an average duration of 181.4 months indicating that it was type 2 diabetes mellitus in most cases [23]. The above data suggests that type 2 diabetes mellitus itself might be a risk factor for the occurrence of HCC. In the present study IR was found in 80% of cases of HCC, and most of the cases had low MELD and CTP score. It is therefore suggested that IR, primarily seen in type 2 diabetes mellitus, might have a role in hepatic carcinogenesis. IR with compensatory hyperinsulinemia has been implicated in the etiology of certain cancers, including colon, endometrial, possibly pancreatic, renal-cell cancers and breast cancer [8,24].

A decrease in islet mass and/or β-cell dysfunction is a pathogenetic mechanism for type 2 diabetes mellitus [25]. In the present study we found a significant fall in β-cell function

Summary Box

What is already known:

- Insulin resistance is common in cirrhosis due to hepatitis C (HCV), non-alcoholic fatty liver disease (NAFLD), autoimmune hepatitis (AIH) but unclear in hepatitis B (HBV) and alcoholic liver diease (ALD)
- Hyperinsulinemia in cirrhosis is a consequence of increased pancreatic insulin secretion or decreased hepatic insulin removal is unclear

What the new findings are:

- Insulin resistance in varied euglycemic cirrhosis is HCV (100%), NAFLD (100%), AIH (100%), hepatocellular carcinoma (80%), ALD (72%) and HBV (45%)
- Insulin resistance and pancreatic β-cell function is raised in Child Turcotte Pugh score >9 and model for end-stage liver disease score >15
- β-Cell function loss is associated with development of hepatogenous diabetes

(HOMA-β) in diabetic controls as compared to the euglycemic cirrhotic patients (P<0.0001) and no rise in β-cell function was seen with rise in CTP or MELD score. The study conducted by Greco *et al* suggested that hyperinsulinemia, at least in CTP grade B cirrhotic patients is the consequence of increased β-cell sensitivity to glucose, while hepatic insulin extraction does not seem to play a significant part [26]. In the current study we found a significant increase in pancreatic β-cell function with increase in IR in cirrhotic patients with CTP ≥10 and MELD score >15.

In conclusion, our study justifies the hypothesis that with advancement of liver disease there is progressive increase in IR and also compensatory increase in pancreatic β-cell function occurs which counteracts IR at the receptor level. However, with prolonged or sustained IR pancreatic β-cell function loss occurs, which may result in the development of hepatogenous diabetes.

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