Original Research Article

Prevalence of insulin resistance in cirrhosis of liver

Hardeep Singh Deep, Navida Babbar*, Devinder Singh Mahajan

Department of Medicine, Sri Guru Ram Das Institute of Medical Sciences and Research, Vallah, Amritsar, Punjab, India

*Correspondence:
Dr. Navida Babbar,
E-mail: drnav12@gmail.com

ABSTRACT

Background: Liver plays a central role in glucose homeostasis. Chronic liver disease is associated with an increased incidence of insulin resistance (IR) and Diabetes Mellitus. Diabetes that develops as a complication of cirrhosis of liver is known as 'Hepatogenous diabetes (HD)'. This study was conducted to study the prevalence of insulin resistance in liver cirrhosis.

Methods: One Hundered (100) non-diabetic patients of liver cirrhosis considering the inclusion and exclusion criteria and visiting both indoor and outpatient department of medicine, SGRDIMSAR were included in the study. All cirrhotic patients irrespective of etiology were subjected to fasting plasma glucose level and fasting plasma insulin levels and insulin resistance was calculated by HOMA-IR method. Study was statistically analyzed.

Results: 79 out of 100 patients were found to have insulin resistance and increase in prevalence with grades of child pugh score were noted.

Conclusions: Keeping in view the results of the study, we conclude that FPG and HbA1c are not sufficient in detecting glucose metabolism disorders in cirrhosis. As insulin resistance can be used as an important prognostic marker in patients with cirrhosis of liver, serum insulin levels can be recommended as routine investigation in these patients. Diabetes mellitus increases the risk of HCC in cirrhosis patients. So, by early detection of diabetes mellitus by calculating insulin resistance with HOMA-IR method we can prevent progression of disease to development into HCC.

Keywords: Hepatogenous diabetes, Insulin resistance, Liver cirrhosis

INTRODUCTION

Diabetes is a chronic disease that occurs either when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it produces. Insulin is a hormone that regulates blood sugar.[1] The prevalence of DM in patients with chronic liver disease is reportedly 18%-63%.[2,3]

Liver plays a central role in glucose homeostasis. Chronic liver disease is associated with an increased incidence of insulin resistance and diabetes. Diabetes that develops as a complication of cirrhosis of liver is known as 'Hepatogenous diabetes'.[4]

The pathophysiology of hepatogenous diabetes is complex and is not precisely known but porto-systemic shunting of insulin result in systemic hyperinsulinemia with subsequent down regulation of insulin receptors causing insulin resistance.[5] Chronic inflammation also plays a role in development of insulin resistance. Insulin resistance in peripheral tissues (adipose and muscular tissue) plays a central role in the glucose metabolism disturbance.[6]

It has also been speculated that genetic and environmental factors and some etiologic agents in liver disease such as HCV, alcohol, and iron infiltration impair the insulin secretion activity of the β-cells of the pancreas.[6,7]

Patients with alcoholic liver disease have a high relative risk of suffering from diabetes.[7] Acute alcohol ingestion produces a significant reduction of insulin mediated glucose uptake. On the other hand, patients with chronic alcoholism frequently have chronic pancreatic damage and injury of pancreatic islet β- cells resulting in DM.

HCV induces insulin resistance regardless of the body mass index and the fibrosis stage. The TNF-α phosphorylates the serine residues of insulin receptor (IRS-1 and IRS-2) and stimulates the overproduction of suppressor of cytokines (SOC3) which further inhibits the phosphorylation of protein kinase B and phosphatidylinositol 3-kinase.

All these disorders related to intracellular signals of insulin could block the transactivation of GLUT-4, which might result in the blocking of the glucose uptake at the cellular level. These mechanisms induce insulin resistance in HCV.[8]

Hepatogenous DM is less often associated with a positive family history, retinopathy and cardiovascular diseases.[9] In fact, major causes of death in cirrhotic patients with DM relate to liver disease or its complications, such as chronic liver failure, hepatocellular carcinoma (HCC) and gastrointestinal hemorrhage.[10]

The incidence of HCC has been well demonstrated to relate to DM, a major target in the management of DM should be to reduce the incidence of HCC in patients with liver cirrhosis.[11] The homeostatic model assessment (HOMA) method can be used to determine hepatogenous insulin resistance/diabetes. HOMA was first developed in 1985 by Matthews et al.[12] It is a method used to quantify insulin resistance (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. The HOMA model has been validated and widely used for determining the degree of IR in epidemiological studies. HOMA-IR strongly predicts the development of type 2 diabetes, independent of obesity, body fat distribution, and glucose tolerance status.[13,14] Value of HOMA-IR more than 1.64 implied the presence of abnormally high IR.[15,16]

METHODS

100 patients of liver cirrhosis were included in this study who visited indoor and outdoor Department of Medicine, SGRDIMSR, Amritsar as per the inclusion and exclusion criteria.

All patients have been interviewed as per the proforma and a complete clinical examination was done.

- Diagnosis of cirrhosis of liver was made by thorough clinical evaluation, biochemical investigations (PTI, LFTs, TSP/DSP) and USG abdomen.
- All cirrhotic patients irrespective of etiology were subjected to all routine investigations, fasting plasma glucose level and fasting plasma insulin levels and insulin resistance was calculated by HOMA-IR formula.

Fasting is defined as no caloric intake for at least 8 hours.

HOMA-IR formula = (fasting plasma glucose) × (fasting plasma insulin) / 22.5

Insulin concentration is reported in μU/L and fasting plasma glucose in mmol/L.

The constant of 22.5 is a normalizing factor. The product of normal fasting plasma insulin of 5 μU/mL, and the normal fasting plasma glucose of 4.5 mmol/L (4.5 × 18 = 405 mg/dl) typical of a "normal" healthy individual = 22.5 mg/dl). Results were analyzed by student's t test.

Inclusion criteria

Patients with liver cirrhosis visiting indoor and outdoor of Sri Guru Ram Das Institute of medical sciences and Research, Vallah, Sri Amritsar.

Exclusion criteria

- HbA1c >6.5
- Fasting plasma glucose ≥126mg/dl
- Known case of Diabetes mellitus.
- Patients receiving insulin and drugs like oral hypoglycemics, corticosteroids, Thiazides and Phenytoin.
- Pregnant women

All the patient have been subjected to following tests

- Complete hemogram
- PTI
- TSP/DSP
- HbA1c
- Liver function tests
- Ultrasonography of the abdomen
- Fasting plasma glucose level
- Fasting plasma insulin level
- Hbs Ag, HCV
- Serum ammonia
- Modified child Pugh score

Child Pugh classification of cirrhosis[24]

The Child Pugh score was originally developed by Child and Turcotte in 1964. Factors used included serum bilirubin, albumin, clinically apparent encephalopathy, ascites and malnutrition. Nearly ten years later, a modification of this score was proposed by Child-Pugh.

Nutritional status was replaced by the prothrombin time or international normalized ratio (INR) (Table 1).

Table 1: Modified child Pugh score.

Factor	Units	Points toward total score		
		1	2	3
Serum bilirubin	μmol/L	<34	34-51	>51
		<2.0	2.0-3.0	>3.0
Serum albumin	g/L	>35	30-35	<30
	g/Dl	>3.5	3.0-3.5	<3.0
Prothrombin time	seconds prolonged	<4	4-6	>6
	INR	<1.7	1.7-2.3	>2.3
Ascites		None	Easily Controlled	Poorly Controlled
Hepatic encephalopathy		None	Minimal	Advanced

Class A: child Pugh score 5-6; Class B: child Pugh score 7-9; Class C: child Pugh score 10-15

RESULTS

Insulin resistance was found in 79 cases out of 100. The p value is <0.001 which is highly significant (Table 2).

Table 2: Showing insulin resistance.

Insulin resistance	No. of cases	Mean IR	±S.D.
<1.64	21	0.74	0.53
>1.64	79	6.01	5.51

P value <0.001 (Highly significant)

Insulin resistance in HCV positive cases was found in 88% of patients with a mean IR of 5.64±5.24 (Table 3).

Insulin Resistance among alcoholic patients was found in 75.86% of patients with a mean IR of 5.63±5.03 (Table 3). In combined HCV + ALCOHLIC cases, IR was found in all patients and with a mean of 8.29 + 8.11 (Table 3).

Table 3: No. of cases with insulin resistance in different parameters.

Parameters	No of cases in each group	Total No. of cases with IR (>1.64)	%	Mean±SD
HCV	25	22	88.00	5.64±5.24
HCV + Alcoholic	11	9	81.81	8.29±8.11
HBS+HCV	1	1	100.00	16.24
Alcoholic	58	44	75.86	5.63±5.03

62.5% of child Pugh class A patients had IR with Mean insulin resistance of 5.82±4.28 (Table 4).

Table 4: CPS v/s insulin resistance.

CPS	Total no. of patients	No. of cases with IR (>1.64)	Percentage	Mean±S.D.	Correlation
5-6 Class A	8	5	62.50	5.82±4.28	P <0.05
7-9 Class B	45	36	80.00	6.37±5.32	P <0.05
>10 Class C	47	38	80.80	5.69 ± 5.92	P <0.05

80% of Child Pugh Class B patients had IR and mean was 6.37+5.32 (Table 4). 80.80% of Chuld Pugh Class C had IR with a mean of 5.69 + 5.92 (Table 4).

Prevalence of Insulin resistance increased with increasing grades of child Pugh score. As Insulin Resistance was detected in 64 out of 79 patients who even had HbA1c levels below 5.7 and in 38 out of 79 had FPG levels

below 100 which makes IR a better predictor of impending Diabetes mellitus.

DISCUSSION

The present study was conducted on 100 patients admitted in medical wards of Sri Guru Ram Das Institute of Medical Science and Research, Amritsar. All cirrhotic patients irrespective of etiology were subjected to all routine investigations, fasting plasma glucose level, HbA1c and fasting plasma insulin levels. Insulin resistance was calculated by HOMA-IR formula.

- Prevalence of insulin resistance in patients of liver cirrhosis was calculated.
- Insulin resistance was correlated with severity of liver cirrhosis as assessed by child Pugh score.

The age of all patients included in this study varied between 24-95 years. The most common age group studied was between 41-60 years with a mean age of 51.03±12.39.

As per the present study insulin resistance was found in 79 out of 100 cases. The p value is <0.001 which is highly significant.

A study conducted in Spain by Erice E et al on-insulin resistance in patients of cirrhosis with portal hypertension also showed that insulin resistance was present in 60 % of his studied population which supports our study.[17]

In a study conducted by Goswami et al from Medical College Jodhpur, India in the year 2014, Insulin resistance was present in 68.5% of euglycemic cirrhotic patients which nearly match the present study results.[18]

Present study is also supported by Holstein who did a prospective cohort study on 52 histologically confirmed patients of liver cirrhosis.[4] 44% of his patients had child Pugh score A, 37% score B and 19% score C. Seventy-one percent (71%) of his patients with liver cirrhosis had manifest diabetes, 25% impaired glucose tolerance and only 4% normal glucose tolerance.

A cross sectional study by Mukherjee et al done in Calcutta showed the prevalence of impaired glucose tolerance in about 60-80% and overt diabetes in 7- 15% which also supports the present study.[19]

In the present study, 62.5 % of child Pugh class A (5-6) patients had insulin resistance with a mean of 5.82 +4.28. 80% of child pugh Class B (7-9) patients had IR with a mean of 6.37±5.32 and 80.80% of Class C (10-15) had insulin resistance with a mean of 5.69±5.92. There is a significant increase in IR in patients with increased child pugh score and advanced disease.

A study from Jodhpur, India by Goswami et al also showed significant increase in insulin resistance in

patients with child Turcott Pugh score >10 which matched our study results.[18]

Similar to the present study, Gharvi et al also found that the prevalence of insulin resistance for groups A, B, and C of Child-Pugh classification were 31.6%, 66.7% and 74.1% respectively and the relationship between IR and severity of liver cirrhosis was significant statistically (p=0.01).[20,7]

CONCLUSION

64 out of 79 patients with IR had HbA1c levels below 5.7 and 38 out of 79 had FPG levels below 100 which makes IR a better predictor of impending diabetes mellites. Keeping in view the results of the study, we conclude that FPG and HbA1c are not sufficient in detecting glucose metabolism disorders in cirrhosis. As insulin resistance can be used as an important prognostic marker in patients with cirrhosis of liver, serum insulin levels can be recommended as routine investigation in these patients. Moreover, as there is an increase in complications in patients detected to have insulin resistance and diabetes in cirrhosis, early intervention for control of diabetes in such cases may prevent/reduce the occurrence of complications. Insulin resistance developing in cirrhotic patients if detected early can help in preventing overt diabetes and thus progression to HCC.

REFERENCES

1. WHO. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: Diagnosis and classification of diabetes mellitus. Geneva, World Health Organization. 1999. Available at http://whqlibdoc.who.int/hq/1999/WHO_NCD_NCS_99.2.pdf
2. Blanco DVC, Gentile S, Marmo R, Carbone L, Coltorti M. Alterations of glucose metabolism in chronic liver disease. Diabetes Res Clin Pract. 1990;8(1):29-36.
3. Pazhanivel M, Jayanthi V. Diabetes mellitus and cirrhosis liver. Minerva Gastroenterol Dietol. 2010;56(1):7-11.
4. Holstein A, Hinze S, Thiessen E, Plaschke A, Egberts EH. Clinical implications of hepatogenous diabetes in liver cirrhosis. J Gastroenterol Hepatol. 2002;17(6):677-81.

5. Hickman IJ, Macdonald GA. Impact of diabetes on the severity of liver disease. Am J Med. 2007;120(10):829-34.
6. Barthel A, Schmoll D. Novel concepts in insulin regulation of hepatic gluconeogenesis. Am J Physiol Endocrinol Metab. 2003;285:E685-92.
7. Zein NN, Abdulkarim AS, Wiesner RH, Egan KS, Persing DH. Prevalence of diabetes mellitus in patients with end-stage liver cirrhosis due to hepatitis C, alcohol or cholestatic disease. J Hepatol. 2000;32(2):209-17.
8. Romero-Gómez M. Insulin resistance and hepatitis C. World J Gastroenterol. 2006;12(44):7075-80.
9. Fujiwara F, Ishii M, Taneichi H, Miura M, Toshihiro M, Takebe N, et al. Low incidence of vascular complications in patients with diabetes mellitus associated with liver cirrhosis as compared with type 2 diabetes mellitus. Tohoku J Exp Med. 2005;205(4):327-34.
10. Bianchi G, Marchesini G, Zoli M, Bugianesi E, Fabbri A, Pisi E. Prognostic significance of diabetes in patients with cirrhosis. Hepatol. 1994;20(1):119-25.
11. Hassan MM, Curley SA, Li D, Kaseb A, Davila M, Abdalla EK, et al. Association of diabetes duration and diabetes treatment with the risk of hepatocellular carcinoma. Cancer. 2010;116(8):1938-46.
12. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia. 1985;28(7):412-9.
13. Chitturi S, Abeygunasekera S, Farrell GC. NASH and insulin resistance: insulin hypersecretion and specific association with the insulin resistance syndrome. Hepatol. 2002;35(2):373-9.
14. Hickman IJ, Macdonald GA. Impact of diabetes on the severity of liver disease. Is J Med. 2007;120(10): 829-34.
15. Barthel A, Schmoll D. Novel concepts in insulin regulation of hepatic gluconeogenesis. Am J Physiol Endocrinol Metab. 2003;285(4):E685-92.
16. Hui JM. Insulin resistance is associated with chronic hepatitis C and virus infection fibrosis progression Gastroenterol. 2003;125(6):1695-704.
17. Erice E, Llop E, Berzigotti A, Abraldes JG, Conget I, Seijo S. Insulin resistance in patients with cirrhosis and portal hypertension. Am J Physiol Gastrointest Liver Physiol. 2012;302(12):G1458-65.
18. Goswami A, Bhargava N, Dadhich S, Kulamarva G. Insulin resistance in euglycemic cirrhosis. Dr Sampurnanand Medical College, Jodhpur, India Ann Gastroenterol. 2014;27(3):1-7
19. Mukherjee S, Sarkar BS, Das KK, Banerjee A. A cross-sectional study on occurrence of type 2 diabetes among patients admitted with chronic liver diseases in a Medical College in Kolkata. Int J Med Pub Health. 2013;3(1):44-7.
20. Gharavi A, Mohammadi AHA, Ziaee A, Sarookhani MR, Javadi A, Haghazali S. Investigation of insulin resistance in patients with liver cirrhosis and its relationship with severity of disease. J Qazvin Univ Med Sci. 2008;12(1):27-34.