To Study the Prevalence of Impaired Glucose Tolerance in Patients with Hepatitis C Virus Related Chronic Liver Disease

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ABSTRACT

Background: Hepatitis C infection is a major cause of Chronic Liver Disease and the prevalence of Diabetes Mellitus is also high. Diabetes has been hypothesised as one of Extrahepatic manifestations of Hepatitis C.

Aims and Objectives: The objective of our study was to study the prevalence of impaired glucose tolerance in patients with HCV related liver disease.

Study Design: The study was a prospective study conducted over a period of one and half year in Dayanand Medical College and Hospital, Ludhiana, Punjab, India.

Materials and Methods: The study was conducted taking total of 100 Hepatitis C virus positive patients above 40 years of age who had fasting blood glucose levels ≥110mg/dl on two occasions, 24 hours apart. These patients underwent an oral glucose tolerance test. Blood sugar levels were tested at 0 and 2 hours. Based on the findings, patients were classified to have impaired glucose tolerance if levels were between 140-200mg/dl and frank diabetes if the levels were ≥ 200mg/dl. These findings were further assessed according to age, gender, Body Mass Index (BMI) Child Turcott Pugh score and Ultrasonography findings.

Statistical Analysis: In our study all the statistical analysis was done using simple z-test and student t-test. The p-values were calculated and the results assessed accordingly.

Results and Conclusion: Out of 100 patients, 78 were males and rest females. The mean age of the study group was 55.89 ± 11.22 years. Mean BMI of males was higher than in females ($21.98kg/m^2$ v/s $20.13kg/m^2$). Maximum patients belonged to Child Turcott Pugh class C. Out of 100 patients, 80 had cirrhosis on ultrasound. On doing Glucose Tolerance Test, 40 patients were found to have impaired glucose tolerance and one patient to be diabetic. The prevalence increased significantly as age increased and had significant relation with gender. On assessing according to BMI, there was not much significant relation but prevalence was significantly related to severity of disease.

INTRODUCTION

Hepatitis C virus (HCV) was first described by Prince et al., in 1974 [1]. Since its discovery, it has become a major cause of chronic hepatitis, cirrhosis and even hepatocellular carcinoma. It is a global health problem affecting almost three percent of the world's population [2,3]. Hepatitis C is a small blood-borne ribonucleic acid (RNA) virus of the family Flaviviridae which has six genotypes. Latest studies have shown that genotype 1 is the most prevalent worldwide (46.2%), followed by genotype 3(30.1%). Genotypes 2, 4 and 6 cause a total of 22.8% cases worldwide. Genotype 5 is the least prevalent (<1%) [4].

An estimated number of people infected worldwide is around 150–200 million [3,5,6]. According to recent studies, about 1.8% of American population and 1.1% population of United Kingdom is Anti HCV positive. In India, the estimated prevalence has been estimated to be 1.5% which amounts to about 1.82 crore people being anti HCV positive [3].

HCV mainly affects the liver, but it can also replicate in several tissues for example peripheral blood mononuclear cells. In the first large multicentre study which involved 312 patients with chronic HCV infection, 39% of the patients came to medical attention with at least one clinical extrahepatic manifestation [7]. DM is one such extrahepatic manifestation which has gained importance in recent years and this correlation between these two chronic diseases will be a subject of speculation in the coming years.

Liver disease may cause, be coincident with, or may occur as a result of Diabetes Mellitus (DM). The prevalence of type 1 diabetes in the United States is ~0.26%. The prevalence of type 2 diabetes is far higher, ~1–2% in Caucasian Americans and up to 40% in Pima Indians. DM and Hepatitis C may occur by chance in the same person, which would help in explaining the apparent association between DM and liver disease [8].

A large number of clues have suggested the potential role of a common hepatotrophic virus in developing diabetes. As many as 80% of patients with cirrhosis show glucose intolerance, and 10–20% of them have DM [9]. A larger prevalence of Diabetes has been reported in HCV infected patients in comparison with patients with other types of chronic liver diseases. Both insulin resistance and impaired insulin secretion have been considered to play an important role in the pathogenesis of DM in patients with HCV infection.

In 1994, Allison et al., first reported the association of chronic hepatitis C with DM, and gained extensive attention thereafter [10]. A number of studies have shown that 13–33% (median 25%) of patients with chronic HCV infection is diabetic [11-13]. Mason et al., performed a retrospective analysis of 1,117 patients with chronic viral hepatitis and analysed whether age, sex, race, Hepatitis B virus (HBV) infection, HCV infection, and cirrhosis were independently associated with diabetes. In this study after the exclusion of patients with conditions predisposing to hyperglycemia, Diabetes was observed in 21% of HCV-infected patients compared with 12%

of HBV-infected subjects (p = .0004) [13]. Another cross sectional study from Calcutta studied occurrence of Type two diabetes in patients with CLD taking all aetiologies into concern [14].

Our study looked specifically into correlation of HCV related liver disease with prevalence of Impaired Glucose Tolerance (IGT) and also considered factors like age, gender, BMI, severity of liver disease(based on CTP score and USG findings) and their influence on the occurrence of IGT in these patients.

AIMS AND OBJECTIVES

The aim of this prospective study was to look for prevalence of impaired Glucose tolerance test in patients with HCV related liver disease.

MATERIALS AND METHODS

This study was a prospective study carried out in the Department of Internal Medicine at Dayanand Medical College and Hospital, Ludhiana, Punjab; conducted over a period of one and half year from June 2007 to December 2008. Approval from the Ethical Committee and written informed consent from the patients was taken before conducting the study. A total of 100 patients above 40 y of age were taken in this study. All patients were anti HCV positive and had evidence of either cirrhosis diagnosed on the basis of Ultrasonography (USG), endoscopic findings and liver biopsy wherever available. Patients who were diagnosed cases of DM were excluded from the study. All patients underwent Fasting Blood Sugar (FBS) examination at two separate occasions 24h apart. All those patients who had FBS values<110 milligrams/decilitre (mg/dl) were included in the study and underwent an oral Glucose Tolerance Test (GTT). An oral glucose load of 75g was given and blood sugar levels were tested at zero and two hours. Based on the findings of test, patients were classified to have impaired glucose tolerance if the two hour blood sugar levels were between 140-200mg/dl and frank DM if the blood sugar level were >=200mg/dl. All these patients were further assessed according to age, gender, and the prevalence of IGT was correlated with Body Mass Index (BMI). Patients were further divided according to severity of liver disease according to Child Turcott Pugh (CTP) score and USG findings. According to CTP score the patients were classified into class A, B or C and the prevalence of IGT was studied according to the class. According to USG findings patients were divided into those having just hepatosplenomegaly, cirrhosis or hepatic Space occupying lesions (SOL's). Based on these the prevalence of IGT was studied.

STATISTICAL ANALYSIS

In our study all the statistical analysis was done using simple z-test and student t-test. The p-values were calculated and the results assessed accordingly.

OBSERVATIONS AND RESULTS

Of the total patients, 78 were males and 22 were females. It was observed that the mean age of the study group was 55.89±11.22 y, out of which mean age of males was 55.94±11.32 y and females was 55.73±11.13y. Our study included patients from all ranges of BMI from 16-29.13 kilograms/meter² (kg/m²). Mean BMI of the study group was 21.51 kg/m². Maximum number of patients belonged to BMI range 20-24.99kg/m² (44 patients). On further distribution according to sex, males had an overall higher mean BMI than females (21.98kg/m² v/s 20.13kg/m²). The demographic profile based on these parameters is listed in [Table/Fig-1].

CTP scores were calculated for all patients. Out of 100 patients, 22 patients belonged to CTP class A, 38 to class B and 40 to class C. When further distributed according to gender, it was found that

Number of patients	Total	100
	Males	78
	Females	22
Mean Age (years)	Total	55.89±11.22
	Males	55.94±11.32
	Females	55.73±11.13
Mean BMI (Kg/m²)	Total	21.51±3.62
	Males	21.98±2.82
	Females	20.13±4.72
Distribution of patients according to USG findings (No. of Patients)	Cirrhosis	80
	Hepatosplenomegaly	7
	SOL liver	7
Distribution of patients according to CTP class (No. of Patients)	A	22
	B	38
	C	40
Mean CTP score	Total	8.85
	Males	9.18
	Females	7.68

[Table/Fig-1]: Demographic profile of patients in study group

among males, the maximum number of patients were in class C (35 patients), whereas in females the maximum number of patients were in class A (10 patients). The mean CTP score of study group was 8.85 and was found to be higher in males than in females (9.18 v/s 7.68).

According to USG findings, it was found that maximum number of patients were those with cirrhosis (80 patients) followed by those with hepatoslenomegaly (7 patients) as well as with cirrhosis and hepatic SOL's (7 patients) which could have been Hepatocellular carcinoma (HCC). All patients underwent an Oral GTT out of which 40 were found to have impaired glucose tolerance and one patient was found to have frank diabetes. Rest 59 patients were having normal blood sugar levels. These findings were further assessed in relation to age, gender, BMI, CTP and USG.

When analysed according to age and gender, it was found maximum patients with impaired glucose tolerance belonged to the age group 60-69 y (13 patients) followed by age group 50-59 y (12 patients). With increasing age, the prevalence of impaired GTT was found to increase. Out of 78 males, 26 were found to have impaired GTT and out of 22 females, 14 were having impaired GTT and one had frank DM. One female with frank DM belonged to age group 40-49 y. On statistical analysis, the p-values were found to be significant on assessing the patients according to both age and gender(0.0056 and 0.0043, respectively), suggesting that increasing age and female gender both increase the prevalence of impaired GTT in patients with HCV related liver disease [Table/Fig-2].

According to BMI, it was found that amongst males, maximum number of patients with impaired GTT had BMI ranging between 20-24.99kg/m² (12 patients). None of the males had frank Diabetes. Amongst females, maximum number of patients with impaired GTT belonged to the group of BMI 16-19.99kg/m² (9 patients). The lone diabetic female belonged to BMI > 25kg/m². On analysing statistically, the p-value in males was 0.05 which was borderline in statistical significance implying that in males though increasing BMI influences the prevalence of impaired glucose tolerance, it is not the sole predictor. In females, the overall correlation was not statistically significant (p-value 0.1728). The reason could be that maximum number of females had BMI ranging from 16-19.99kg/m². This clearly shows that in females, BMI itself is not a significant contributory factor in development of diabetes and other factors also play a role [Table/Fig-3].

Age group	Normal Number (%age)			Impaired Number (%age)			≥200mg% Number (%age)		
	Total	Males	Females	Total	Males	Female	Total	Males	Females
40-49	23 (71.88)	22 (95.65)	1 (4.35)	8 (25.00)	3 (37.5)	5 (62.5)	1 (3.13)	0 (0.00)	1 (100.00)
50-59	17 (58.62)	15 (88.24)	2 (11.76)	12 (41.38)	8 (66.67)	4 (33.33)	0 (0.00)	0 (0.00)	0 (0.00)
60-69	10 (43.48)	8 (80.00)	2 (20.00)	13 (50.52)	8 (61.54)	5 (38.46)	0 (0.00)	0 (0.00)	0 (0.00)
70-79	8 (57.14)	7 (87.50)	1 (12.50)	6 (42.86)	6 (100.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
80-89	1 (50.00)	0 (0.00)	1 (100.00)	1 (50.00)	1 (100.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Total	59			40			1		

[Table/Fig-2]: Showing assessment of GTT in relation to age and gender

p-value   0.005647(according to age)
p-value   0.004312(according to gender)

On assessing the prevalence of impaired glucose tolerance in accordance with CTP class of patients, maximum number of patients who had impaired GTT belonged to class C (17 patients). However, the calculated p-value was 0.323 suggesting that there was no significant correlation of CTP class with occurrence of DM or impaired GTT. This implies that though increasing CTP score did influence the development of diabetes, it did not make any statistical significant difference [Table/Fig-4].

Lastly, on taking into account the USG findings in correlation with impaired GTT, it was found that maximum number of patients with impaired GTT belonged to the group having cirrhosis (29 patients) followed by those with hepatic SOL's that is HCC (6 patients). However, the lone patient with frank DM had fatty liver on USG. But since this female with frank DM had high BMI, it could be conferred that there were other factors too contributing to development of DM in her. On statistically analysing the patients according to the severity of the disease based on USG findings, the p-value was highly significant (0.000528). This clearly shows that the severity of

the grade of liver involvement does greatly influence the development of diabetes in patients with HCV related liver disease [Table/Fig-5].

DISCUSSION

HCV mainly affects liver, but it can have extrahepatic manifestations also. In the first large multicentre study which involved 312 patients with chronic HCV infection, 39% of the patients had at least one clinical Extrahepatic manifestation [7]. Some like Cryoglobulinemia, Membrano Proliferative Glomerulonephritis and Prophyria Cutanea Tarda are definitely associated with HCV infection [15]. However, the role of HCV is still under debate for manifestation such as Lichen Planus, Autoimmune thyroiditis, Sjogren's syndrome and Low grade B-cell lymphoma. During the last decade, due to large number of cases of IGT/DM, it has been hypothesized that diabetes could be one more of these extrahepatic conditions attributable to HCV [9]. Our study was conducted to find the prevalence of IGT/ DM in patients with HCV related Liver disease that had normal FBS values.

BMI (kg/m²)	Males number of patients (%age)				Females number of patients(%age)			
	Total	Normal	Impaired	≥200mg%	Total	Normal	Impaired	>=200mg%
<16.00	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
16.00-19.99	23 (29.49)	16 (69.56)	7 (30.46)	0 (0.00)	16 (72.73)	7 (43.75)	9 (56.25)	0 (0.00)
20.00-24.99	43 (55.13)	31 (72.09)	12 (27.91)	0 (0.00)	1 (4.54)	0 (0.00)	1 (100.00)	0 (0.00)
25.00-29.99	12 (15.38)	5 (41.67)	7 (58.33)	0 (0.00)	5 (22.73)	0 (0.00)	4 (80.00)	1 (20.00)
>30.00	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
p-value	0.05000				0.172855			

[Table/Fig-3]: Showing assessment of GTT in relation to BMI

CTP Score	Class	Total	Normal		Impaired		≥200mg%	
			Number	%age	Number	%age	Number	%age
5-6	A	22	13	59.09	9	40.91	0	0.00
7-9	B	38	23	60.53	14	36.84	1	2.63
10-15	C	40	23	57.50	17	42.50	0	0.00
Total		100	59		40		1	
p-value		0.323288						

[Table/Fig-4]: Showing the assessment of GTT in relation to CTP score and class

USG abdomen	Total	Normal		Impaired		≥200mg%	
		Number	%age	Number	%age	Number	%age
Hepatomegaly	1	1	100.00	0	0.00	0	0.00
Fatty liver	5	4	80.00	0	0.00	1	20.00
HSM	7	2	28.57	5	71.43	0	0.00
Cirrhosis	80	51	63.75	29	36.25	0	0.00
SOL liver	7	1	14.29	6	85.71	0	0.00
p-value	0.000528						

[Table/Fig-5]: showing the assessment of GTT in relation to severity of liver disease based on ultrasonography

The pathogenesis of DM in patients with HCV infection is still not well understood, although various mechanisms like insulin resistance, β cell autoimmunity, direct injury causing impaired secretion have been studied [16-19]. Other mechanisms involving Tumour Necrosis Factor-a (TNF-a), development of hepatic steatosis and iron overload causing insulin resistance, lack of phosphatidylinositol (PI)-3 kinase activation have also been reported [20-22]. However, our study did not look into the aspect of pathogenesis causing IGT/DM in our patients.

After the first reported association of chronic hepatitis C with DM by Allison et al., [10], a number of studies have been conducted to find correlation between Hepatitis C infection and glucose intolerance. In 2000, Mehta et al., reported an important survey addressing a link between DM and HCV status in a representative sample of the general population of the USA through Third National Health and Nutrition Examination Survey (NHANES III) [23]. Another large community based study done by Wang et al., also found that anti HCV positivity was strongly associated with Type 2 Diabetes in those aged 35-49 y. Data from this study suggests that HCV infection is moderately associated with Type two Diabetes; the association was strongest for subjects aged 35-49 y and increased with severity of the liver condition [24]. The prevalence of advanced histological disease in genetically predisposed HCV patients was associated with a higher prevalence of DM/ Impaired Fasting Glucose (IFG) as studied by Zein et al., [25]. In concordance with previous studies, the present study also showed the total prevalence of patients with impaired GTT to be 40% and frank DM to be 1%.

A multivariate analysis by Mason et al., revealed that HCV infection and age were independent predictors of diabetes [13]. In our study it was found that, age plays an important role in the development of DM alone or in association with any other causative factor. As the age of the patient increases, the risk for development of DM also increases. It was found that the maximum number of patients with impaired glucose tolerance were in the age group 60-69 y (13 patients). Mason et al., [13] and Wang et al., [24,26] also studied correlation of gender with IGT/DM and found that gender did not have significant influence on the development of diabetes. However, our study revealed that females did have a significantly higher prevalence of impaired glucose tolerance (14 out of 22 females v/s 26 out of 78 males). The lone diabetic patient was also a female.

It has also been found that there is a definitive association of the BMI with the prevalence of IGT and development of frank diabetes. This has been highlighted in various studies conducted previously and also in our study. Mehta et al, in their study did conclude that amongst patients with HCV related liver disease, the incidence of DM was higher in those who were older and those who had a high BMI [23]. A study conducted in Taiwan by Wang et al., showed that the risk ratio for diabetes in anti-HCV positive patients increased when BMI levels increased [26]. Our study also revealed that increase in the BMI increases the prevalence of impaired glucose tolerance. This correlation was more statistitically significant in males but not in females. This shows that, though BMI does affect the development of DM in patients with HCV related liver disease, but other factors also influence the prevalence.

Various studies have been conducted in the past to relate the incidence of diabetes mellitus with the stage of liver disease. Though chronic hepatitis C(CHC) is associated with increased risk of development of Type 2 Diabetes [27], still prevalence is found to be higher in cirrhotics as compared to patients with CHC [28,29]. Even within the patients with cirrhosis, the prevalence of diabetes varies with CTP score as evident from a study conducted by Caronia et al., (OR 3.83; 95% CI 2.38-6.17; p-0.0001) [11]. In our study, however it was found that though increase in the class does increase the incidence of impaired glucose tolerance but there was no statistically significant difference as the p-value was >0.05. Petit et al., demonstrated that insulin resistance in non diabetic HCV infected patients is correlated with the staging of liver fibrosis [30]. Zein et al., also proved that the prevalence of DM and IFG was higher among HCV infected patients with advanced verses those with early histological disease (p-value 0.0004) [25]. Our study also supported that severity of the liver disease does affect the development of diabetes mellitus as maximum number of patients with impaired glucose tolerance in our study belonged to the group having cirrhosis, the findings being statistically significant (p-value 0.000528). However, our study showed that the lone diabetic in our study had fatty liver on USG. The patients was a female with BMI>25kg/m^2. This clearly shows that other factors like gender and BMI also play an important role along with the stage of the disease and insulin resistance may begin even in presence of fatty liver if other factors like obesity, increased BMI favour the occurrence of diabetes.

CONCLUSION

This study was the first study conducted in Indian scenario assessing the correlation between HCV and IGT. Studies have been conducted to study occurrence of DM in patients with CLD taking all aetiologies into concern. This present study specifically assessed the prevalence of IGT in patients with HCV related liver disease. It was found that there was higher prevalence of IGT in these patients (40% had IGT and one percent DM). When assessed according to various parameters, it was found that HCV infection, increasing age, high BMI, and higher severity of liver injury, all played important role in increasing the prevalence either independently or in association with each other. However, the sample size was small and this correlation between the two leading diseases needs to be assessed on a larger scale.

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