ORIGINAL ARTICLE

A Descriptive Case Series Study to Evaluate the Association of Hepatitis C Virus Infection with Insulin Resistance

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ABSTRACT

Context: Hepatitis C virus (HCV) infection is a common problem worldwide, affecting millions of people across all populations. In some previous studies, HCV infection was associated with an increased risk of diabetes mellitus or insulin resistance (IR).Insulin Resistance is calculated by Homeostasis Model Assessment (HOMA).
Aim: The objective of our study was to evaluate the association between HCV and Insulin Resistance (IR)
Setting and Design: A single center, Descriptive case series study which was conducted at Division of Gastroenterology and Hepatology, Medical Unit I, Lahore General Hospital/Post graduate Medical Institute, Lahore.
Material and Methods: Total duration of study was about one year conducted from June 2012 to July 2013.HOMAR IR was calculated in all eligible candidates who had detectable HCV RNA PCR level. The cut off value for HOMA IR was taken as 3.8.
Statistical Analysis: Was performed using SPSS-release 17, standard version.
Results: 300 patients were enrolled and analyzed.154 (51.3%) were female and 146(48.7%) were male and M: F was 1:1.05.Mean BMI was 25.08 kg/m^2 .The Mean HOMA IR was 2.62 with S.D 1.76 and S.E. 0.1018. 253(84.33%) patients had HOMA IR <3.7 and 47(15.66%) had HOMA IR 3.8 ≥. No significant Correlation was observed between HOMA IR and BMI.
Conclusion: There is significant risk of development of Insulin Resistance in Chronic Hepatitis C infected patients. HCV infection should be taken as systemic disease and Blood glucose level should be regularly monitored in Chronic Hepatitis C patients.

Key Word: Hepatitis C Virus (HCV), Homeostasis Model Assessment (HOMA).Insulin Resistance (IR)

INTRODUCTION

Hepatitis C virus (HCV) infection is a common problem worldwide, affecting millions of people across all populations. Most acutely infected patients develop chronic hepatitis and become a potential source of virus transmission, and as many as 1 in 5 will develop cirrhosis and its complications [1].

In some previous studies, HCV infection was associated with an increased risk of diabetes mellitus [2-8] or insulin resistance (IR) [9-14]. IR is the main feature of the metabolic syndrome, a common metabolic disorder that is a result of the increasing prevalence of obesity worldwide [15-17]. IR and glucose metabolism impairment are also associated with cirrhosis, regardless of etiology [18]

IR is a complex pathophysiological condition where higher than normal concentrations of insulin are needed to maintain a normal glycemia and adequate glucose utilization in insulin target tissues [19]. IR is of global importance since it is closely linked to the epidemic of obesity and it precedes and predicts the development of type 2 diabetes mellitus (T2DM) and increases the risk of life-threatening complications such as cardiovascular diseases, renal failure and infections. The development of intrahepatic complications, including HCC, is known to be associated with IR [20].

In patients with extra hepatic manifestations of HCV, fasting insulin levels and homeostasis model assessment (HOMA) for IR are significantly higher than for the patients without extrahepatic manifestations [21]. Among various extrahepatic manifestations, IR is associated with oral lichen planus [22], oral squamous cell carcinoma and multiple primary cancers including gastric cancer

[23]. Although reasons for this association remain unclear, a high prevalence of precancerous lesions and cancers are seen in patients with T2 DM [24, 25], suggesting that IR or hyperinsulinemia may enhance carcinogenic activities.

According to the World Health Organization (WHO), IR is defined as below the 25th percentile on the euglycaemic hyperinsulinaemic clamp or above the 75th percentile on the HOMA-IR index for the population studied, i.e. these are the cut-off values discriminating healthy individuals from those at risk of diabetes [26].There is ongoing debate on setting a cut-off value for IR. HOMA approaching the value of 1 is considered to be related to insulin sensitivity, and the presence of IR has been defined as a HOMA value >4.65, or a value of 3.60 in individuals with a BMI >27.5 kg/m^2 [27]. However, this cut-off value may vary from one population to another according to obesity and ethnicity distribution [28]. These factors, at least in part, account for the heterogeneity in HOMA-IR cut-off values (ranging from 1.5 to >4) used to define IR in patients with chronic hepatitis C [29-40].Recently, Lam et al. showed that HOMA-IR >4 was the optimal value defining IR when compared with steady-state plasma glucose, in the hepatitis C setting [41]. Byb.Qu H-Q et al showed that the best cut-off HOMA-IR for identifying those with insulin resistance is 3.80 [42].In a study published in International Journal of Endocrinology, Volume 2012 (2012), Using the cut-off value of HOMA-IR >2.0, there was sensitivity at 84.0%, specificity at 61.0%, positive predictive value at 35.0%, negative predictive value at 93.8%, and accuracy at 65.6% [43]

Although the interference with the insulin effects shows some HCV genotype-specificity, IR has been reported to occur in all HCV genotypes, but to a different extent [44]. HCV genotype 3a, in addition, may alter the intrahepatic insulin signaling through a down regulation of peroxisome proliferators-activated receptor [45]. In HCV genotype 1b infections, substitutions of amino acids 70 and/or 91 in HCV-1b core were found to be significant determinants of severe IR, in patients without cirrhosis and diabetes mellitus, which suggests a real connection between HCV-1b infection and IR at early stages of liver disease [46]

IR is extremely common in patients with chronic HCV infection and has been associated with increased disease severity, extra hepatic manifestations and decreased response to antiviral therapy [47]. Understanding the basis of such associations is of paramount importance to inform treatment strategies for patients with HCV. The objective of our study was to evaluate the association between HCV and Insulin Resistance (IR).

MATERIAL & METHODS

It was a single center, Descriptive case series study which was conducted at Division of gastroenterology and Hepatology, Medical Unit I, Lahore General Hospital/Post Graduate Medical Institute, Lahore. Total duration of study was about one year conducted from June 2012 to July 2013.Study approval was taken from Ethical Review Board of Post Graduate Medical Institute/Lahore General Hospital, Lahore. The Objective of the study was to assess the association of Hepatitis C infection and Insulin Resistance.Insuline Resistance (IR) was determined by HOMA-IR: (Homeostasis Model of Assessment - Insulin Resistance) which was calculated using the following formula‘s;

Fasting Glucose (mg/dl) x fasting Insulin (uU/mL) / 405

Insulin Resistance was defined as a Homeostasis Model Of Assessment (HOMA) score of ≥3.8. Total 300 subjects presenting at Out Patients Department of Division of Gastroenterology and Hepatology, Medical Unit I, were enrolled in the study. Main inclusion criteria of the study were subjects of both genders who were treatment naïve for Chronic Hepatitis Virus infection (HCV) and aged 20 to 60 year.

Subjects with following criteria were excluded from the study.

- Known diabetics
- Confection with Hepatitis B & HIV
- Extremes of ages
- Solid organ transplant
- Any malignant disease
- End Stage Renal disease

Written informed consent was taken from every subject before enrollment in the study. Demographic History was obtained. Patient’s weight (in Kg) and height (in meter) was measured and BMI calculated using the standard formula weight *Kg*/height m^2

Laboratory Assays

Blood sample was taken in a vial each for Fasting blood glucose level, Fasting insulin level, HCV

RNA PCR Qualitative analysis, and Complete Blood Count and Liver Function test. All laboratory assays were performed at the locally approved laboratory. HCV RNA PCR Qualitative analysis was performed using Real Time Amplification & Detection Kit and Fasting Serum Insulin was measured in uU/ml with reference range of 3-28 uU/ml and Fasting Glucose level was measured in mg/dl. Laboratory Results were collected at appropriate time and were entered in predesigned Performa.

Statistical Analysis

Descriptive analysis was done for baseline characteristics of the patients. Mean, Minimum, Maximum and S.D was calculated for age, BMI, Fasting blood Glucose, Fasting insulin level, Hemoglobin, platelets count and blirubin. Frequencies and percentage were calculated for Gender. HOMA IR and BMI were calculated using the HOMA IR and BMI calculators on internet. Pearson correlation was determined between BMI and IR.Statistical analysis was performed using Statistical Package for Social Sciences {SPSS-release 17, standard version}.

RESULTS

Total 300 patients were enrolled in the study. All subjects were positive for Hepatitis C Virus (HCV) detected by HCV RNA PCR Qualitative analysis. Baseline demographic characteristics of the patients were analyzed. The minimum age of the patients was 18yr and maximum age was 60yr and mean age was 34.4yrs.Minimum BMI was 14.5 kg/m^2 and maximum was 53.0 kg/m^2 and mean was 25.082 kg/m^2.Mean hemoglobin was 9.0 mg/dl and maximum Hemoglobin was 17.8 mg/dl and mean was 13.02 mg/dl,Minimum platelets count were 103 x 10^3 per mm3 and maximum 579 x 10^3 per mm3 and mean 232.69 × 10^3 per mm3, minimum Bilirubin was 0.3 mg/dl and maximum 1.6 mg/dl and mean 0.66 mg/dl ,whereas minimum Fasting Blood glucose level was 52mg/dl and maximum 261mg/dl and mean was 91.5mg/dl,Minimum fasting Insulin level was 0.1 u U/ml and maximum 10.4 u U/ml and mean was 2.62 u U/ml (Table.1).

Table 1: Base Line Characteristics of Patients (n=300)

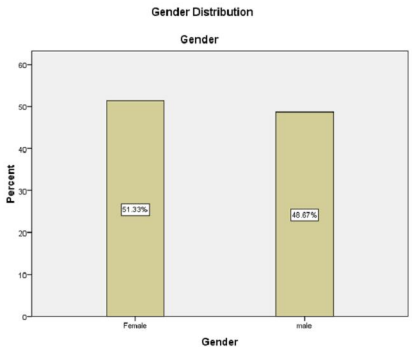
	N	Minimum	Maximum	Mean	Std. Error	Std. Deviation
Age	300	18	60	34.5	0.547	9.468
BMI	300	14.5	53.0	25.082	0.3552	6.1530
Hemoglobin	300	9.0	17.8	13.02	0.1038	1.7979
Platelets	300	10300	579000	232681.69	5498.320	95233.696
Bilirubin	300	0.3	1.6	0.66	0.011	.1904
Fasting Blood Glucose	300	52	261	91.5	1.271	22.012
Fasting Insulin Level	300	0.3	60.0	11.91	0.4443	7.6949

Out of 300 patients, 154(51.3%) were Female and 146(48.7%) were male and Male to Female Ratio was 1: 1.05. (Table 2 & Graph 1.1)

Table 2.Gender Distribution (n=300)

	Frequency	Percent	Valid Percent	Cumulative percent	M:F Ratio
Valid Female	154	51.3	51.3	51.3	
Male	146	48.7	48.7	100.0	1 : 1.05
Total	300	100.0	100.0		

Graph 1.1: showing Gender Distribution



HOMA IR was calculated in all patients. Minimum HOMA IR was 0.1 and maximum 10.4 with a mean of 2.62, Standard Error .1018 and Standard Deviation of 1.76. (Table.3)

The Cut-Off value for HOMA IR was taken as 3.8.Any subject with HOMA IR ≥ 3.8 was considered as Insulin Resistant. Out of 300 patients, 253 (84.33 %) patients had HOMA IR < 3.7 and 47 (15.66%) patients had HOMA IR ≥ 3.8, which showed that the subjects who are infected with chronic Hepatitis C virus have significant risk (15.66%) of developing Insulin Resistance .(Table 3.1 & Graph 1.2)

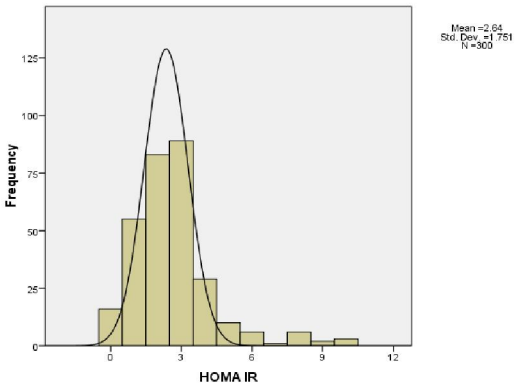
Table 3: Statistical analysis of HOMA IR (n=300)

HOMA IR	N	Minimum	Maximum	Mean	Std.Error	Std.Deviation
	300	0.1	10.4	2.62	.1018	1.7626

Table 3.1: HOMA IR (n=300)

HOMA IR	N	Percent
0.1 – 3.7	253	84.33 %
3.8 – 10.4	47	15.66 %

Graph 1.2: showing Frequency distribution of HOMA IR (n=3)



We calculated the correlation between HOMA IR and BMI and we observed that there was no significant correlation between HOMA IR and BMI (Table 4 & Table 4.1)

Table 4.Correlation between BMI and HOMA IR (n=300)

Descriptive Statistics			
	Mean	**Std. Deviation**	**N**
HOMA IR	2.63	1.760	300
BMI	25.082	6.1530	300

Table 4.1; Correlation between BMI and HOMA IR (n=300)

Correlations			
		HOMA IR	**BMI**
HOMA IR	Pearson Correlation	1	.254**
	Sig. (2-tailed)		.000
	N	300	300
BMI	Pearson Correlation	.254**	1
	Sig. (2-tailed)	.000	
	N	300	300
**. Correlation is significant at the 0.01 level (2-tailed).			

DISCUSSION

This study was designed to evaluate the relationship between Hepatitis C Virus Infection (HCV) and Insulin Resistance (IR) and we observed a significant association between HCV and IR. We have also analyzed the correlation between IR and BMI and we observed no significant correlation between HOMA IR and BMI.

IR is one of the pathological features in patients with HCV infection and it plays a crucial role in the development of various complications and events associated with HCV infection. HCV-associated IR may cause hepatic steatosis, hepatic fibrosis, resistance to anti-viral treatment, hepatocarcinogenesis and proliferation of hepatocellular carcinoma; and extrahepatic manifestations.

IR arises from the impairment of the insulin-signaling pathway at multiple steps. Various studies have reported that the core protein of HCV induces IR mainly by modulating the insulin-signaling pathway at the level of IRS. Since the exact mechanisms of the molecular pathways of HCV-induced IR have not yet been understood, further research is required to determine how virus-induced IR can be managed.

It was reported that the incidence of diabetes mellitus in adults with Chronic HCV and Chronic HBC was 25% and 22.5% respectively and is four times higher than that in the general population [48]. Hui et al. [49] reported that HCV patients without history of diabetes mellitus had significantly higher levels of all markers of IR including fasting glucose, fasting insulin and HOMA IR. In our results, the mean serum Fasting blood glucose, Mean fasting Insulin level and Mean HOMA IR was 91.5mg/dl, 11.91 u U/ml and respectively 2.62.

Patients with chronic hepatitis have impaired glucose metabolism with hyperinsulinemia and insulin resistance. This hyperinsulinemia has been shown to be due to decreased insulin catabolism rather than increased pancreatic insulin secretion. Marked insulin resistance is common in patients with liver disease and represents a causative factor for the impaired glucose metabolism seen in these patients [12]. In our study the mean fasting Insulin level was 11.9 u U/ml.

HCV-associated IR is a therapeutic target at any stage of HCV infection. However, therapeutic guidelines for preventing the distinctive complications of HCV-associated Insulin Resistance have not yet been established. Insulin-sensitizing agents are reported to improve Sustained Virologic Response (SVR) rates, but further validation for safety is required. Little is known regarding the effect of anti-diabetic agents on HCV infection, and a possible association between use of exogenous insulin or a sulfonylurea agent and the development of HCC has recently been reported.

RECOMMENDATIONS

- Chronic Hepatitis C infection (HCV) should be evaluated as a systemic disease and not only as a liver disease.
- Monitoring and follow-up of serum glucose level in the fasting and postprandial states is of important issue in euglycemic Chronic Hepatitis C (HCV) patients.

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