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Research Article

Insulin Resistance in Chronic Hepatitis C Non Diabetic Patients

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Abstract

Background: 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. We aimed to evaluate insulin resistance in non-diabetic patients with chronic hepatitis C virus infection.

Subjects and Methods: The study was a case-control study conducted in Tropical Medicine and Gastroenterology Department King Abdullah University Hospital. 60 patients and 30 healthy controls were included in the study. The patients were classified into three groups:

1. **Group A**: 30 patients with chronic hepatitis C infection were selected with positive HCV RNA in serum for at least 6 months; Patients were not receiving anti-viral therapy at the time of sampling. They showed no evidence of cirrhosis.
2. **Group B**: 30 patients with HCV related liver cirrhosis. They were divided according to Child Pugh score; twenty patients with HCV related compensated liver cirrhosis (Child A). Ten patients with HCV related decompensated liver cirrhosis (Child B and C).
3. **Group C:** The control group: Included 30 healthy individuals. All patients and controls were subjected to the following:
    a. **Liver function tests**: Alanine transaminase (ALT), Aspartate transaminase (AST), total and direct bilirubin, total protein, serum albumin. Prothrombin time (PT) and international normalization ratio (INR).
    b. **Renal function tests**: Blood urea nitrogen (BUN), Na, K. Complete blood count. Alpha fetoprotein (αFP).

Diagnosis of chronic hepatitis C infection was based on positive HCV by PCR, persistent elevation of liver enzymes more than 6 months and liver biopsy for some of the patients. Anti-hepatitis C virus antibody (HCV Ab) using third generation enzyme linked immune sorbent assay (ELISA) test, Hepatitis B virus (HBV): HBVsAg. Overnight fasting and two hours postprandial blood glucose level. Fasting serum insulin of everyone. Insulin resistance was determined via the Homeostasis Model assessment (HOMA-IR) by the following equation:

$$\text{Insulin resistance: } \frac{\text{Fasting insulin (μu/ml) x Fasting glucose (mmol/L)}}{22.5}$$

An index value of > 2.5 was defined as IR. This cutoff value was chosen because studies suggested that a HOMA-IR of 2.4 - 3.0 is probably suitable to define IR in CHC patients. Blood samples were collected after 12 hours of overnight fasting.

Results: We found that out of 30 CHC and 30 LC (20 compensated LC, 10 de compensated LC) 8 (26.7%); 8 (40%) patients and 5 (50%) respectively had HOMA-IR levels greater than 2.5, which is consistent with IR diagnosis. Decompensated cirrhotic patients showed higher frequency of IR compared to CHC and compensated cirrhotic patients.

Conclusion: In chronic hepatitis C patients, HOMA-IR, fasting serum insulin and fasting blood glucose were significantly higher than healthy controls ($p < 0.0001$).

Keywords: *Insulin Resistance; Chronic Hepatitis C; HOMA-IR; INR; HBV*

Introduction

Hepatitis C virus infection (HCV) has affected about 160 million person around the world [1]. In Europe, Chronic Hepatitis C virus infection (CHC) is the main cause of cirrhosis, liver fibrosis, hepatocellular carcinoma (HCC) that in the end ought of transplantation of liver [1]. One of the pathological character in CHC diseases is insulin resistance (IR) [1]. IR condition identify by high level of insulin in blood that appears when the demand of the insulin level to acquire a quantitative glucose act ordinary is more than normal manner the body's potential to act to insulin suit defect [2].

Properly, IR has a core role in the growth of CHC-related defects. IR explained as the pre-diabetic condition where it has a precise act in Type 2 Diabetes Mellitus (T2DM) expansions [3]. Hui., *et al*. [4] expressed that T2DM is more recurrent through CHC patients contrasting to those with other liver diseases and public population [4]. It is now well established from a different of studies that both CHC and T2DM are correlated, where having CHC is high the risk of T2DM [5]. Furthermore, IR may come up with fibrotic progression [4]. production of fatty acids in liver is controlled by insulin hormone, which is an anabolic hormone that assists hepatic lipogenesis and reduces lipolysis. As IR demonstration, the insulin production rise (hyper-insulinaemia) to reimburse for hepatic glucose manufacture expands in both the fasting and postprandial stages, leading to the moving of hepatic glucose to fatty acids, coming up in lipid buildup in hepatocytes [6]. Levels of blood glucose increase due to of this, as well as lessen glucose shifting from the blood stream [7]. during 9 - 19 years post- HCV infection, 20% - 50% of CHC people progress to cirrhosis [8]. There have been two main major of liver cirrhosis; compensated and decompensated. Ascites, upper gastrointestinal hemorrhage owing to varices or portal hypertensive gastropathy, hepatorenal syndrome, and hepatic encephalopathy are all sign of degenerated cirrhosis [9]. Following the onset of cirrhosis, the rate of HCC progress scope from 1% to 4% every year [9]. remunerated cirrhosis is a kind of cirrhosis that has no signs. nevertheless, when HCV disease appeared, after the age of 60 years, the cirrhosis and its issues were most regular. In 2030, of CHC with cirrhosis thought to reach about 45% [10].

In recent years, many studies have been found the connection between CHC and IR. In this search, there is an expected that IR appeared more commonly in CHC patients with cirrhosis than in other people. Furthermore, we surmised that decompensated liver cirrhosis people are more probably to evolve IR than compensated liver cirrhosis diseases.

Subjects and Methods

This study was case-control conduct with 90 participants: patients (n = 60) and healthy controls (n = 30) from the King Abdullah University Hospital's Tropical Medicine and Gastroenterology Department. The participants were separated into three groups:

1. **Group A:** Both gender of 30 adult CHC patients, 19 (63.3%) men and 11 (36.7%) women, mean age from 22 to 54 years, with a mean age of 39.59 years. CHC Patients were selected according to the specific standard: patient with HCV RNA in serum for at least 6 months; proof of chronic hepatitis confirmed by biopsy in some patients; and patients who were not taken antiviral medication at the time of having sampling.

2. **Group B:** Thirty adults with CHC-related liver cirrhosis (CHC-LC) were divided into two categories depend on their Child Pugh scores. The first group with 20 patients having recompense liver cirrhosis due to HCV (Child A), 14 (70%) of whom were male and 6 (30%) of whom were female, with years scope from 30-64 years and a mean of 50.309.81 years. The another group included ten patients with HCV-related decompensated liver cirrhosis (Child B and C), 8 (80%) of whom were male and two (20%) of whom were female, middle in age from 48 to 75 years, with a mean age of 58.38.315.81 years.

3. **Group C:** 30 healthy adults with no clinical or laboratory indications of liver disease (control group), 18 (60%) of whom were males and 12 (40%) of whom were females, with a middle age of 35.124.220 years. In terms of age and gender, the healthy control group matched the CHC group.

Patients with HCC or other liver diseases such as alcoholic liver disease, drug-induced hepatitis, other viral hepatitis, hereditary haemochromatosis, Wilson's disease, autoimmune hepatitis, primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC) and 1 anti-

trypsin deficiency (1 ATD) were expel from this research. Patients taking antiviral drugs, having medications, or being diseases that might be cause fatty liver (steroids, tamoxifen, gastric bypass surgery, recent extreme weight loss) were withdraw from this conduct.

Patients who declined to participate in the trial or who were positive diagnosis of diabetes, as well as pregnant or breastfeeding women, were all eliminated. The King Abdullah University Hospital's Human Ethics Committee approved the research proposal, and all document written were signed informed permission.

Methodology

Clinical and laboratory assessment

Age, gender, and the development of symptoms such as weariness, bleeding tendency, abdominal distention, and lower limb swelling were all collected. The BMI was calculated by dividing body weight in kilograms by height in square meters (kg/m^2). Clinical examination of liver cell failure such as lower limb edema jaundice, ascites, palmar erythema, and spider naevi are investigated clinically.

All patients with an abdominal ultrasonography with a 3.5 - 5 MHz convex transducer. After a 12-hour fast, venous blood was drawn to measure glucose in blood as well as level of albumin, bilirubin, alanine amino transferase (ALT), and aspartate amino transferase (AST) in serum. CHC was confirmed by PCR positive HCV tests, persistent liver enzyme are higher for about six months, and liver biopsy in half of the patients.

A chemiluminescent microparticle immunoassay was ran to evaluate fasting serum insulin (ARCHITECT plus 1 1000, 8K4 ARCHITECT insulin kit; Diagnostic Products Abbott Park, IL 60064 USA). The next equation was used to measure IR utilize the Homeostasis Model Assessment (HOMA-IR) method:

Fasting insulin (u/ml) x Fasting glucose (mmol/L) / 22.5 = HOMA-IR.

IR was interpreted as an index value greater than 2.5. Due to studies have appeared that a HOMA-IR of 2.4 - 3.0 is mostly acceptable for explained IR in CHC patients, this cutoff value was utilized.

Results

The participants in this research were 60 CHC patients in many phases of chronic HCV infection. A control group of 30 healthy people was also included in the study. For HOMA-IR, a cut-off value of more than 2.5 was employed. We found that 8 (26.7%), 8 (40%), and 5 (50%) of the 30 CHC and 30 CHC-LC patients (20 compensated LC, 10 decompensated LC) had HOMA-IR levels greater than 2.5, which is reconcile with IR diagnosis. comparing to CHC and compensated LC patients, decompensated LC patients had a higher rate of IR. HOMA-IR, fasting serum insulin, and fasting blood glucose measure were greatly higher in CHC patients than in healthy controls ($p < 0.0001$).

Variable	Control group N = 30	CHC N = 30	P value
Mean BMI	23.44	21.63	0.179
Fasting glucose	4.687	7.756	0.0001
Fasting insulin	4.20	7.37	0.0001
HOMA-IR	1.055	1.84	0.0001

Table 1: *Comparison between CHC and healthy controls regarding HOMA-IR, fasting insulin and blood glucose and the mean values of BMI.*

Fasting insulin, HOMA-IR score, and fasting blood glucose were all considerably higher in cirrhotic patients than in CHC patients. Fasting insulin and HOMA-IR mean values were nearly uniform in compensated and decompensated cirrhotic individuals, according to table 2.

Variables	CHC (N = 30)	Compensated LC (N = 20)	Decompensated LC (N = 10)	P1	P2	P3
	Mean ± SD	Mean ± SD	Mean ± SD			
Fasting blood glucose (mmol/L)	5.76 ± 0.65	5.47 ± 0.77	6.10 ± 1.08	0.125	0.022	0.154
Fasting insulin (**µU**/mL)	7.37 ± 4.61	10.56 ± 4.05	11.54 ± 5.93	0.002	0.509	0.016
HOMA-IR	1.84 ± 1.06	2.58 ± 1.14	3.19 ± 1.84	0.001	0.177	0.027
P1 Decompensated LC versus CHC, P2 decompensated LC versus compensated LC, P3 compensated LC versus CHC						

Table 2: *Comparison of fasting glucose, fasting insulin and HOMA-IR among the studied groups.*

Statistically, there was a clear difference for cut off values of HOMA-IR from compensated to decompensated LC groups with high frequency of high value for HOMA-IR appeared in decompensated LC group (χ^2 = 4.48, P = 0.034) (Table 3).

HOMA values	Compensated LC	Decompensated LC	Total
< 2	12 (60%)	3 (30%)	15
2 - 4	6 (30%)	4 (40%)	12
> 4	2 (10%)	3 (30%)	3
Chi-square test	χ^2 = 4.48, P = 0.034		

Table 3: *Comparison between compensated LC and decompensated LC regarding HOMA-IR values.*

When contrast to compensated LC patients (50.0 percent vs 40 percent; 2 = 0.30, P = 0.582) or CHC (50.0 percent versus 26.7 percent; 2 =3.14, p = 0.076), decompensated LC patients were a higher rate of IR (50.0 percent versus 40 percent; 2 = 0.30, P = 0.582). BMI, Prothrombin time, AFP, and fasting insulin were clearly positive correlations; serum albumin, bilirubin, AST, ALT, platelets, AST/ALT ratio, HCV level by PCR, and fasting blood glucose amount were non-clearly correlations (Table 4).

Variable	HOMA-IR	
	Correlation coefficient	P value
BMI (Kg/ m^2)	0.518	0.003
Age (year)	0.248	0.187
AST (U/L)	0.045	0.815
ALT (U/L)	0.009	0.962
AST/ALT ratio	0.047	0.807
Albumin (g/dL)	-0.142	0.454
Bilirubin (mg/dL)	0.066	0.729
AFP (ng/mL)	0.371	0.043
Prothrombin time (seconds)	0.421	0.020
PCR (IU/L)	-0.066	0.728
Platelets (K/ µL)	-0.121	0.524
Hemoglobin (g/dL)	-0.174	0.284
WBCs (K/ µL)	-0.077	0.635
Fasting glucose (mmol/L)	-0.079	0.679
Fasting insulin (**µU**/mL)	0.946	0.000

Table 4: *Correlation between HOMA-IR and demographic and laboratory data in the CHC patients.*

The mean values of HOMA-IR is more higher considerably among CHC, compensated LC patients, and decompensated LC patients, and were connected with disease progression (F = 4.518; P = 0.014), as seen in table 5.

	Normal	CHC	Compensated LC	Decompensated LC
Mean ± SD (Range)	1.055 ± 1.08 (0.15 - 2.135)	1.84 ± 1.06 (0.26 - 3.96)	2.58 ± 1.14 (1.15 - 5.26)	3.79 ± 5.50 (1.43 - 9.33)
Anova test		F = 4.518; P value = 0.014		

Table 5: *Comparison of the mean values of HOMA-IR in the studied groups.*

Discussion

There is a big doubt on IR reference amount among HCV carriers, or even among healthy individuals. employing the euglycemic/hyperinsulinemic clamping approach, the HOMA-IR index has been used as an indirect means to measure IR, and it correlates well with insulin sensitivity [11]. Another Brazilian conduct investigated 1,203 people who have not had diabetes or HCV infection. For IR diagnosis, they selected a HOMA-IR cut-off point of 2.7, which is same the evaluate employed in this conduct [12]. In addition, cut-off points for IR range from 1.5 to 3 in different inspections [13,14].

In this examination, a HOMA-IR cut-off value of more than 2.5 was occupied, and 8 (26.7 percent), 8 (40 percent), and 5 (50 percent) of the 30 CHC, 20 Compensated LC, and 10 Decompensated LC patients had serum HOMA-IR values higher than 2.5, which was well suited with IR examine. There were notable unmatch in mean HOMA-IR, fasting insulin, and fasting blood glucose between CHC and healthy controls in this inquiry, with CHC having greater mean values. The findings of this research went back up those of Elbedewy., *et al*. [15] who disclosed that CHC were greater serum insulin and HOMA-IR than healthy individuals.

The HOMA-IR value was examined in many clinical phases of CHC infection in this research. Decompensated LC patients were a higher IR frequency (50%) than CHC (26.7%), whereas compensated LC patients were a lower IR frequency (27.7%) than (40 percent). This is as same as the findings of Mohamed., *et al*. [16] who found that patients with LC were higher rate of HOMA-IR (61.8%) than those with CHC (39.5%) and severe fibrosis (48.8 percent). Irshad., *et al*. [17] noted that IR in 28.57 percent of CHC patients and 33.33 percent of LC patients [16,17]. According to different research, 30 to 70 percent of CHC patients who had manifestation of IR. The finding of their conducts suggested that the appearing of IR early during CHC infection irrespective of the severity of liver disease [18].

LC patients had clearly greater mean fasting insulin and HOMA-IR index amount than healthy normal and CHC patients in this conduct. Patients with LC showed clearly greater insulin measure and HOMA-IR than those infected with chronic hepatitis, based on many studies [19-22]. Furthermore, no significant difference had been found in the mean values of fasting insulin and HOMA-IR between the Compensated and Decompensated Cirrhotic groups in this research.

Mohamed., *et al*. [16] on the other hand, noted that there were no clearly differences in HOMA-IR values and insulin levels between CHC and Cirrhotic Egyptian patients when they measured the influence of HCV genotype-4 on the generality of IR in CHC and Cirrhotic Egyptian patients. We found that among CHC compensated and decompensated LC patients, the mean amount of HOMA-IR was higher over time. IR is a usual symptom of all liver disease stages, and the connection between IR and chronic liver illnesses may lead as the disease develops to be cirrhosis [23].

Prothrombin time was clearly prolonged in Cirrhotic patients with IR in this conduct. Based on another study, the HOMA-IR index may have a connection with the deterioration of hepatic function [23]. The HOMA-IR score was a significant positive connection with BMI,

prothrombin time, AFP, and fasting insulin in the CHC group, but not with age element, serum albumin, bilirubin, AST, ALT, or fasting blood glucose levels. Elbedewy., *et al*. [15] stated that substantial positive link between HOMA-IR and both fasting insulin and AFP, but no link with age element, serum albumin, bilirubin, AST, ALT, or fasting blood glucose levels.

Conclusion

HOMA-IR, fasting serum insulin, and fasting blood glucose had noticeably greater in chronic hepatitis C disease than in healthy controls ($p < 0.0001$).

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