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INSULIN RESISTANCE IN CHRONIC HEPATITIS C NONĐIABETIC PATIENTS

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Abstract:

The study is a case control study conducted in Tropical Medicine and Gastroenterology Department AL-Azhar University Hospital. 60 patients and 30 healthy controls were included in the study. The patients were classified into two groups:

Liver function tests : Alanine transaminase **(ALT)**, Aspartate transaminase **(AST)**, total and direct bilirubin, total protein, serum albumin. Prothrombin time **(PT)** & international normalization ratio**(INR).**

Renal function tests: Blood urea nitrogen (BUN), Na, K. Complete blood count. Alpha feto protein**(αFP).**

Results: It was 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.

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Introduction

HepatitisCvirusinfection(HCV)affecte daround170millionindividualsglobally (1). In western world, Chronic Hepatitis C virus infection(CHC) is the primary cause for development of liver fibrosis, cirrhosis, hepato cellular carcinoma (HCC) that eventually lead to liver transplantation (1). One of the pathological features in CHC patients is insulin resistance (IR) (1). IR condition characterized by hyper-insulinaemia that occurs when the requirement of the insulin amount to obtain a quantitative glucose response normally is greater than normal means the body's ability to respond to insulin become impairment(2).

As a result, IR plays an important role in the development of CHC-related problems.IR defined as the pre-diabetic state where it plays a vital role inType 2 Diabetes Mellitus (T2DM) development (3).Hui et al (4) stated that T2DM is more frequent among CHC patients comparing to thosewith other liver illnesses and general population (4). It is now well-established from a variety of studies that CHC and T2DM are associated,wherehavingCHC increasetheriskofT2DM(5).Furthermore,IRmaycontribute tofibroticprogression(4). Synthesis of fatty acids in liver is regulated by insulin, which is an anabolic hormone that promotes hepatic lipogenesis and inhibits lipolysis. As IR manifestation, the insulin secretion increase (hyper-insulinaemia) to compensate for hepatic glucose production increases in both the fasting and postprandial stages, resulting in the conversion of hepatic glucose to fatty acids, culminating in lipid buildup in hepatocytes (6). Blood glucose levels rise because of this, as well as decreased glucose removal from the circulation (7).After10-20yearspost-HCVinfection,20%-50% of CHC patients progress to cirrhosis (8). There are two main stages of liver cirrhosis; compensated and decompensated. Ascites, upper gastrointestinal hemorrhage due to varices or portal hypertensive gastropathy, hepatorenal syndrome, and hepatic encephalopathy are all symptoms of decompensated cirrhosis (9). Following the onset of cirrhosis, the rate of HCC development ranges from 1% to 4% each year (9). Compensated cirrhosis is a type of cirrhosis that has no symptoms. Regardless of when HCV infection occurred, after the age of 60 years, thecirrhosis and its complications were most common. In 2030, of CHC with cirrhosis projected to reach45 %(10).

Numerous studies have been conducted in recent years on the association between CHC and IR. In this study, we anticipated that IR occurred more frequently in CHC patients with cirrhosis than in other individuals. Furthermore, we hypothesized that decompensated liver cirrhosis patients are more likely to develop IR than compensated liver cirrhosis patients.

Subjectsand Methods

This was case-control research with 90 participants: patients (n = 60) and healthy controls (n = 30) from the AL-Azhar University Hospital's Tropical

Medicine and Gastroenterology Department. The participants were divided into three categories:

Group A: 30 adult CHC patients of both sexes, 19 (63.3%) males and 11 (36.7%) females, ranging in age from 22 to 54 years, with a mean age of 39.59.5 years. Patients in the CHC were chosen based on the following criteria: positive HCV RNA in serum for at least 6 months; evidence of chronic hepatitis corroborated by liver biopsy in some patients; and patients who were not on antiviral medication at the time of sampling.

Group B: Thirty adults with CHC-related liver cirrhosis (CHC-LC) were separated into two groups based on their Child Pugh scores. The first included 20 patients with compensated liver cirrhosis caused by HCV (Child A), 14 (70%) of whom were men and 6 (30%) of whom were girls, with ages ranging from 30-64 years and a mean of 50.309.81 years. The other group included 10 patients with HCV-related decompensated liver cirrhosis (Child B and C), 8 (80%) of whom were men and 2 (20%) of whom were females, ranging in age from 48 to 75 years, with a mean age of 58.38.315.81 years.

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 mean 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 haemo-chromatosis, Wilson's disease, autoimmune hepatitis, primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), and 1 antitrypsin deficiency (1 ATD) were excluded from this study. Patients getting antiviral therapy, receiving medications, or having diseases that may cause fatty liver (steroids, tomoxifen, gastric bypass surgery, recent extreme weight loss) were excluded from this study.

Patients who refused to participate in the trial or who had a confirmed diagnosis of diabetes, as well as pregnant or breastfeeding women, were all excluded. The AL-Azhar University Hospital's Human Ethics Committee authorized the study plan, and all subjects signed written informed permission.

Methodology:

ClinicalandLaboratoryAssessment

Age, gender, and the occurrence of symptoms such as bleeding tendency, weariness, abdominal distention, and lower limb swelling were all gathered. The BMI was computed by dividing body weight in kilograms by height in square meters (kg/m2). Physical indications of liver cell failure such as jaundice, ascites, lower limb edema, palmar erythema, and spider naevi are examined clinically.

All patients had an abdominal ultrasonography with a 3.5-5 MHz convex transducer. After a 12-hour fast, venous blood was collected to evaluate glucose levels as well as serum levels of albumin, bilirubin,

alanine amino transferase (ALT), and aspartate amino transferase (AST). CHC was established by PCR positive HCV results, persistent liver enzyme increases for more than 6 months, and liver biopsy in some of the patients.

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

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

IR was defined as an index value greater than 2.5. Because studies have shown that a HOMA-IR of 2.4-3.0 is likely acceptable for defining IR in CHC patients, this cutoff value was used.

Results

The participants in this study were 60 CHC patients in various 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 utilized. We discovered 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 compatible with IR diagnosis. In comparison to CHC and compensated LC patients, decompensated LC patients had a greater rate of IR. HOMA-IR, fasting serum insulin, and fasting blood glucose levels were considerably higher in CHC patients than in healthy controls ($p<0.0001$).

Table (1): Comparison between CHC and healthy controls regarding HOMA-IR, fasting insulin andbloodglucoseand themean valuesofBMI

Variable	Control groupN=30	CHCN=30	Pvalue
MeanBMI	23.44	21.63	0.179
Fasting glucose	4.687	7.756	0.0001
Fastinginsulin	4.20	7.37	0.0001
HOMA-IR	1.055	1.84	0.0001

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 identical in compensated and decompensated cirrhotic individuals, according to Table (2).

Table(2):Comparison offasting glucose, fasting insulinandHOMA-IRamongthe studied groups

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* compensatedLC versus CHC						

There was a statistically significant difference for cut off values of HOMA-IR between compensated and decompensated LC groups with more frequency of high value for HOMA-IR occurred in decompensated LC group ($\chi 2$=4.48, P=0.034) Table(3).

Table(3):Comparison between compensated LC and decompensated LC regarding HOMA - IR values

HOMAvalues	Compensated LC	DecompensatedLC	Total
<2	12(60%)	3(30%)	15
2-4	6(30%)	4(40%)	12
>4	2(10%)	3(30%)	3
Chi-squaretest	**χ^2=4.48,P=0.034**		

When compared 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 had a greater rate of IR (50.0 percent versus 40 percent; 2=0.30, P= 0.582). BMI, Prothrombin time, AFP, and fasting insulin had significant positive correlations; serum albumin, bilirubin, AST, ALT, platelets, AST/ALT ratio, HCV level by PCR, and fasting blood glucose levels had non-significant correlations (4).

Table(4):CorrelationbetweenHOMA-IR anddemographic andlaboratorydataintheCHCpatients

Variable	HOMA-IR	
	Correlationcoefficient	P value
BMI(Kg/m2)	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/ALTratio	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
Prothrombintime(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
Fastingglucose(mmol/L)	-0.079	0.679
Fastinginsulin (µU/mL)	0.946	0.000

The mean values of HOMA-IR increased considerably among CHC, compensated LC patients, and decompensated LC patients, and were linked with disease progression (F=4.518; P=0.014), as shown in Table (5).

Table(5):ComparisonofthemeanvaluesofHOMA-IRin thestudied groups

	Normal	CHC	Compensated LC	DecompensatedLC
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**			

Discussion

There is no agreement on IR reference levels among HCV carriers, or even among healthy people. Using the euglycemic/hyperinsulinemic clamping approach, the HOMA-IR index has been utilized as an indirect means to quantify IR, and it correlates well with insulin sensitivity (11). A Brazilian study looked at 1,203 people who didn't have diabetes or HCV infection. For IR diagnosis, they chose a HOMA-IR cut-off point of 2.7, which is like the level employed in this study (12). In addition, cut-off points for IR range from 1.5 to 3 in different investigations (13, 14).

In this investigation, a HOMA-IR cut-off value of more than 2.5 was employed, 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 greater than 2.5, which was consistent with IR diagnosis. There were significant differences in mean HOMA-IR, fasting insulin, and fasting blood glucose between CHC and healthy controls in this investigation, with CHC having higher mean values. The findings of this study backed up those of Elbedewy et al (15), who revealed that CHC had greater serum insulin and HOMA-IR than healthy participants.

The HOMA-IR value was evaluated in different clinical stages of CHC infection in this study. Decompensated LC patients had a greater IR frequency (50%) than CHC (26.7%), whereas compensated LC patients had a lower IR frequency (27.7%) than (40 percent). This is consistent with the findings of Mohamed et al (16), who discovered that patients with LC had a greater rate of HOMA-IR (61.8%) than those with CHC (39.5%) and severe fibrosis (48.8 percent). Irshad et al (17) discovered IR in 28.57 percent of CHC patients and 33.33 percent of LC patients (16, 17). According to another study, 30 to 70 percent of CHC patients have some indication of IR.Theresultsoftheirstudieshavesuggested the occurrence of IR early during CHC infection irrespective of the severity of liver disease (18).

LC patients had significantly higher mean fasting insulin and HOMA-IR index values than healthy normal and CHC patients in this study. Patients with LC exhibited significantly higher insulin levels and HOMA-IR than those with chronic hepatitis, according to several studies (19-22).In addition, there was no significant difference in the mean values of fasting insulin and HOMA-IR between the Compensated and Decompensated Cirrhotic groups in this study.

Mohamed et al (16), on the other hand, observed no significant differences in HOMA-IR values and insulin levels between CHC and Cirrhotic Egyptian patients when they evaluated the impact of HCV genotype-4 on the prevalence of IR in CHC and Cirrhotic Egyptian patients. We discovered that among CHC compensated and decompensated LC patients, the mean values of HOMA-IR increase over time. IR is a common symptom of all phases of liver disease,

and the relationship between IR and chronic liver illnesses is stronger as the disease progresses toward cirrhosis (23).

Prothrombin time was significantly prolonged in Cirrhotic patients with IR in this study. According to another study, the HOMA-IR index has a favorable relationship with the deterioration of hepatic function (23). The HOMA-IR score had a significant positive connection with BMI, prothrombin time, AFP, and fasting insulin in the CHC group, but not with age, serum albumin, bilirubin, AST, ALT, or fasting blood glucose levels. Elbedewy et al (15) showed substantial positive relationships between HOMA-IR and both fasting insulin and AFP, but no connections with age, serum albumin, bilirubin, AST, ALT, or fasting blood glucose levels.

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

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