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Internal Medicine

Prognostic Value of Serum Retinoic Acid Receptor Responder Protein 2 (RARRES2) on Chronic Hepatitis C Patients

Heba Mahmoud Ibrahim Mahmoud Mohammed [1,*] M.B.B.Ch., Karima Youssef Ahmed [1] MD. Asmaa Sobhy Hassan [1] MD. and Eman Mostafa Nasef [1] MD.

** Corresponding Author:*
Heba Mahmoud Ibrahim Mahmoud
hebasleem77@gmail.com

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[1]Internal Medicine Department, Faculty of Medicine, Al-Azhar University (for girls) , Cairo, Egypt.

ABSTRACT

Background: A major worldwide health issue impacting 1% of the global population is infection with chronic hepatitis C virus (HCV). Egypt has the greatest prevalence of HCV worldwide, representing 14.7% of the population, yet deaths from hepatocellular carcinoma (HCC) and cirrhosis remain a major problem in Egypt.

Aim of the work: To measure the concentration of serum retinoic acid receptor responder 2 (RARRES2) as well as whether patients with CHC may benefit from using it as a further non-invasive indicator of predictive importance.

Patients and Methods: This investigation involved 40 participants. The included participants will be classified into two groups: Group I: included (25) participants with normal weight and chronic hepatitis C virus disease. Group II: included (15) healthy normal-weight subjects as a control group. Inclusion criteria: Female aged middle age 25 -45 years old, Positive anti-HCV antibody test and HCV RNA, Normal body weigh 18.5-24.9.

Result: The average level of RARRES2 was 1767.53± 2326.75 ng/ml in the HCV group and 451.51± 144.42 ng/ml in the control group. The level of RARRES2 in the HCV group was significantly greater in comparison with the control group (p=0.010).

Conclusion: The findings of the present investigation show that levels of serum chemerin rose in patients suffering from CHC and that these levels increased concurrently with the deterioration of liver functional reserves. It is possible to conclude that chemerin could be employed as an additional technique for assessing CHC prognosis and monitoring metabolic abnormalities caused by a virus.

Keywords: *Serum Retinoic Acid Receptor Responder Protein 2; Chronic Hepatitis C; chemerin.*

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INTRODUCTION

A major worldwide health issue impacting 1% of the global population is infection with chronic hepatitis C virus (HCV).[2]

Egypt has the greatest prevalence of HCV worldwide, representing 14.7% of the population, yet deaths from hepatocellular carcinoma (HCC) and cirrhosis remain a major problem in Egypt. HCV infection causes chronic hepatitis in around 60–80% of cases, and cirrhosis develops in 10–20% of those cases in 20–30 years. Patients with cirrhotic livers can develop HCC in 1% to 5% of cases.[4] HCV infection increases pro-inflammatory cytokine secretion, oxidative stress and tissue damage, all of which lead to progressive fibrosis, cirrhosis, liver failure and cancer.[9] CHC includes a variety of characteristics that distinguish it not just as a viral illness but also as a metabolic liver illness that includes liver steatosis, insulin resistance (IR), lipid metabolism disturbances, and T2DM or glucose intolerance.[6] Further research revealed chemerin to be a retinoid-responsive gene, leading to its designation as RARRES2. Chemerin's retinoic acid responsiveness has been subsequently validated in many cells and tissues.[5]

Inflammatory chemokine chemerin has initially been identified as a new retinoic acid-responsive gene in psoriasis cutaneous lesions, suggesting a role of immunomodulation.[11]

It was discovered that it was expressed in a range of tissues, including the pancreas, liver, and lungs, and also in adipose tissue. One of the primary organs that secretes chemerin is the liver.[7]

It was demonstrated to be connected to insulin resistance, blood pressure, plasma triglycerides (TG), and body mass index (BMI).

It is a chemoattractant protein that is involved in glucose homeostasis, adipogenesis, and angiogenesis. Chemerin could be involved in liver physiology and pathology because of the expression of its receptors in the liver.[1]

Because it is both pro-and anti-inflammatory, it has a chimeric nature.The activation and recruitment of macrophages and natural killer (NK) cells into the inflamed tissue produces the pro-inflammatory effect.[10] Nevertheless, the anti-inflammatory activity happens via inhibition of pro-inflammatory mediators' production and promoting the expression of adiponectin.[13]

Chemerin expression has been verified in the livers of CHC patients

PATIENTS AND METHODS

Type of study: A case control study.

Patients: This study was carried out on conducted on (40) subjects. The included subjects will be classified into 2 groups Group I: included (25) subjects with normal- weight chronic hepatitis C virus disease Group II: included (15) healthy normal weight subjects as a control group.

The selection of participants in this research has been based on the following: Inclusion criteria: Female aged middle age 25 -45 years old, Positive anti-HCV antibody test and HCV RNA, Normal body weigh 18.5-24.9. Patients with the following criteria were excluded from the study: Obesity, Diabetes mellitus, Coinfection with HBV, HIV, Hepatocellular carcinoma, Heart or renal failure, Pregnancy or lactation.

Methods: All enrolled people will be exposed to the following: Full medical history, paying particular attention to the duration of hepatitis C infection, manifestation of liver cell failure (jaundice, ascites, hematemesis melena, hepatic comma), Clinical examination for each studied patients including measurement of body mass index and general and abdominal examination, Laboratory investigations will include the following:- Complete blood picture to assess: ● RBCs, HB%, platelets counts ● Differential of WBCS (neutrophil, lymphocyte) ● Neutrophil to lymphocyte ratio (NLR) b) Kidney function tests (serum creatinine and blood urea, eGFR), Liver function tests (serum albumin, total &direct bilirubin, SGOT, SGPT), Coagulation profiles (PT, PC, INR), lipid profiles, which include cholesterol and triglyceride, LDL, HDL, and hepatitis markers, are used to rule out co-infection with other viruses in the patients' group and to confirm that the controls are HBV and HCV seronegative. The diagnosis of CHC has been validated by using RT-PCR to detect serum HCV-RNA, serum alpha-fetoprotein to rule out hepatocellular carcinoma, fasting insulin and ELISA (enzyme-linked immunosorbent assay) kits to measure RARRES2, and abdominal ultrasonography to document the presence of cirrhosis and rule out co-existing hepatic focal lesion.

Samples collection & Preparation: The first sample, 8 ml of peripheral venous blood, was collected under complete aseptic conditions using a plastic disposable syringe from all subjects after fasting for 9 hours.

Statistical analysis: Microsoft Excel 2016 and the SPSS software (Statistical Package for Social Sciences) version 26.0 will be used to tabulate and statistically analyze the obtained data. Descriptive statistics have been computed for numerical parametric data using the mean±SD (standard deviation), minimum, and maximum of the range; for numerical non-parametric data using the median and first and third interquartile ranges; and for categorical data using percentage and number. When two independent patients had parametric data, independent t-tests were used for inferential analyses; when two independent patients had non-parametric data, Mann-Whitney U tests have been used. Inferential analysis of qualitative data has been conducted utilizing the Chi-square test for independent patients. The linear correlation coefficient [r] was used to detect any connection between two quantitative variables in a single group. The ROC curve is a valuable tool for assessing the specificity and sensitivity of quantitative diagnostic tests that classify patients into one of two groups. The significance level has been set at a P value of less than 0.05, which indicates that the data is significant; otherwise, it is not.

RESULTS

		Group I (HCV group)	Group II (Control group)	Test value	P-value
		n = 25	n = 15		
AFP	Mean	1.04	0.36	T=9.18	<0.001*
	± SD	0.32	0.15		
	Median	1.00	0.36		
	IQR	.86-1.20	.27-.49		
	Min.	0.51	0.14		
	Max.	1.62	0.63		

Table 1: Comparison between the study groups as per AFP.

		Group I (HCV group)	Group II (Control group)	Test value	P-value
		n = 25	n = 15		
Glucose (mg/dl)	Mean ± SD	96.64 11.81	84.87 6.0	T=4.17	<0.001*
	Median	94.0	84.0		
	IQR	88.0-104.0	79.0-88.0		
	Min.	81.0	78.0		
	Max.	125.0	99.0		
Fasting insulin	Mean ± SD	39.99 5.28	14.81 3.95	T=5.28	<0.001*
	Median	20.10	13.65		
	IQR	15.20-24.50	12.60-16.40		
	Min.	11.20	10.53		
	Max.	29.10	26.30		

Table 2: Comparison between the study groups as per glucose and fasting insulin.

			Group I (HCV group)	Group II (Control group)	Test value	P-value
			n = 25	n = 15		
US	Chronic parenchymatous liver disease	n	4	0	X^2 = 12.5	0.002§
		%	16.0%	0.0%		
	Fatty liver	n	6	0		
		%	24.0%	0.0%		
	Normal	n	15	15		
		%	60.0%	100.0%		

Table 3: US findings among the studied groups.

		HCV group (n=25)	Control group (n=15)	Test	P-value
RARRES2 (ng/ml)	Mean± SD	1767.53± 2326.75	451.51± 144.42	Z MWU = 2.58	0.010
	Median (IQR)	596.80 (452.1-1531.5)	445.40 (371.10 – 487.10)		
	Range	245.10 – 7093.60	262.0 – 882.30		

Table 4: Comparison between the study groups regarding RARRES2.

Parameters	RARRES2			
	HCV group (n=25)		Control group (n=15)	
	r	P-value	r	P-value
Age	.083	.527	.022	.909
Weight	.170	.195	.002	.987
BMI	.251	.225	-.177-	.527
alpha fetoprotein	.866	<0.001	.465	.081
PT	.778	<0.001	.592	.020
PC	-.820-	<0.001	-.592-	.020
INR	.675	<0.001	.592	.020
Potassium	-.310-	.131	-.363-	.184
Sodium	-.490-	.013	.097	.730
Phosphorus	-.055-	.794	-.109-	.698
Calcium	-.376-	.064	-.114-	.686
TAG	.284	.169	-.329-	.230
Cholesterol	.426	.034	.075	.789
Albumin	.625	<0.001	-.294-	.288
AST	.776	<0.001	.213	.446
ALT	.832	<0.001	.148	.598

Direct bilirubin	.778	**<0.001**	.246	**.376**
Total bilirubin	.629	**0.001**	.538	**.039**
APRI score	.630	**0.001**	0.637	**0.248**
AlBl score	0.397	**0.049**	-	-
uric acid	.286	.165	.519	**.047**
Urea	.435	**.033**	.252	**.364**
Creatinine	.244	.240	.052	**.853**
Glucose	.716	**.000**	.288	**.297**
Fasting insulin	.809	**<0.001**	.564	**.028**
WBCs	.150	.473	-.027-	**.924**
platelets	-.580-	**.002**	.007	**.980**
NLR	-.670-	**<0.001**	0.118	**0.676**
MCH	-.405-	**.045**	-.182-	**.515**
MCV	-.425-	**.034**	-.410-	**.129**
Hb	**-.552-**	**.004**	**-.323-**	**.241**

Table 5: Correlation between RARRES2 and other parameters among the study groups.

parameters	**RARRES2**
Cutoff value	**>487.1 ng/ml**
AUC (95% CI)	**0.747 (0.584 - 0.871)**
Sensitivity	**72.0%**
Specificity	**80.0%**
PPV	**78.3%**
NPV	**74.0%**
Accuracy	**94.0%**
P value	**0.001**

Table 6: Validity of RARRES2 in prediction of HCV patients

DISCUSSION

Infection with the HCV is a prevalent reason for chronic hepatitis around the world as well as a significant factor in cirrhosis of the liver and hepatocellular carcinoma (HCC).[3]

HCV induces hepatic insulin resistance, immune mediated extra hepatic diabetogenic effect and steatosis, HCV geno-type 1 induces insulin resistance as it interferes with insulin signaling on hepatocytes. It also contributes to steatosis, fibrosis progression and resistance to interferon and ribavirin treatment.

In humans, high serum levels of RARRES2 were conveyed with impaired glucose tolerance and both types of diabetes (diabetes that are insulin-dependent and insulin-independent).[12]

Its receptors expressed in the liver suggest that RARRES2 could have an important effect on the liver physiology and the pathogenesis of CHC.

This research has been done to measure the level of serum RARRES2 and whether its level can be regarded as an additional non-invasive marker of prognostic importance in patients with CHC.

This investigation has been performed at the Gastroenterology and Hepatology Unit, Departments of Internal Medicine AlAzhar University.

Forty Egyptian patients were recruited and have been split into two groups as follow:

Group I: included (25) subjects with normal weight chronic hepatitis C virus disease.

Group II: included (15) healthy normal weight subjects as a control group.

In this work, only female subjects were investigated to study the impact of gender on adipokines levels in the CHC patients, as it was reported by some studies that gender may affect the serum RARRES2 levels. Many studies observed that the levels of serum RARRES2 (chemerin) were significantly higher in women in comparison with men with metabolic disturbances such as type 2 diabetes mellitus.

The ALBI score can be used to diagnose the stage of fibrosis, especially advanced liver fibrosis and cirrhosis.

For patients suffering from cirrhosis, either with or without HCC, the albumin-bilirubin (ALBI) grade has been examined for predicting prognosis. The ALBI grade is determined by calculating the ALBI score, which is determined using the serum total bilirubin and albumin levels, which indicate the liver's function in cirrhosis.

In our study: ALBI score was done to HCV patient for staging of fibrosis, and it was significantly low in HCV (p=0.001).

Another non-invasive marker for exclusion of fibrosis in HCV patient is Aspartate Aminotransferase-to-Platelet Ratio Index (APRI) which was done in our study for exclusion of fibrosis

and revealed that APRI scores in HCV groups was 0.53 ± 0.30 and ranged from 0.15 to 1.20.

In our study, CBC was done, and hemoglobin and MCV levels in the HCV group were significantly decreased in comparison with the control group (p=0.007 & 0.004 respectively).

In our study, there was a significant elevation in the HCV group for total bilirubin (p= 0.008), direct bilirubin (p=0.002), (ALT) (p=0.022) and (AST) (p<0.001) in comparison with the control group, while albumin level was significantly decreased in the HCV in comparison with the control group (p=0.001).

While PC in the HCV group was significantly lower than in the control group (p = 0.006), PT and INR were significantly greater in HCV patients in comparison with controls (p = 0.011 and 0.013, respectively).

In our study, fasting glucose and fasting insulin levels were significantly greater in the HCV group in comparison with the control group (p<0.001) and (p=0.002), respectively.

In our study, significant increases in the HCV group were recorded for AFP (p<0.001)

In our study, the HCV group's level of RARRES2 was significantly greater than that of the control group (p=0.010)

In this study correlation between RARRES2 and other parameters among the study groups.

The prothrombin time (INR) was significantly greater in the patients with CHC in comparison with the normal control, and there was a significant positive connection between serum RARRES2 and the prothrombin time (INR) (r=.778, p<0.001).

Albumin was significantly decreased in the patients with CHC versus the normal control, and there was a significant negative association between both serum RARRES2 (r = –0.720) and albumin. These findings reveal that significant increases in the serum levels of RARRES2 occur as the functions of the liver deteriorate, which was verified by the significant drop in albumin and elevation in INR.

In our study, ultrasonography revealed a statistically significant difference between the two groups regarding US findings (p= 0.002), as in the HCV group, 15 (60%) patients had normal US, 6 (24%) patients had fatty liver, and 4 (16%) patients had chronic parenchymatous liver disease.

The average chemerin levels in obese people with fatty liver were significantly greater in comparison with controls, with a significant positive connection between chemerin and BMI and its SDS.

CONCLUSION

The findings of the present investigation show that serum chemerin levels rose in patients suffering from CHC and that these levels increased concurrently with the deterioration of liver functional reserves. It is possible to conclude that chemerin could be employed as an additional technique for assessing CHC prognosis and monitoring metabolic abnormalities caused by a virus.

Conflict of interest : none

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