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Assessment of serum Resistin in detecting Insulin Resistance and their impact on response to direct acting antiviral in chronic viral hepatitis C patients

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Abstract

Background: Chronic hepatitis C (CHC) virus is associated with insulin resistance and diabetes which have been linked to progressive liver fibrosis and sustained virologic response (SVR) to antiviral treatment. Resistin is a polypeptide hormone belonging to adipokines that may contribute to the development of obesity, insulin resistance, and metabolic syndrome. Also, the link between resistin and insulin resistance in patients with chronic hepatitis C and the effect of new direct acting antivirals on them seems unclear at present. The aim of this study is to evaluate the role of Resistin in detecting Insulin Resistance and their impact on response to direct acting antiviral in chronic hepatitis C patients.

Results: The Study was prospective Cohort clinical study, in Hepatology outpatient clinic at Ain Shams University Hospitals .This study was performed on 40 Egyptian patients who have Chronic viral hepatitis C, divided into 3 groups: GROUP I includes: 20 patients with Chronic viral hepatitis C on Sofosbovir- Daclatasvir before start of treatment and Sustained viral response after 12 weeks [SVR 12]. GROUP II includes: 20 patients with Chronic viral hepatitis C and non-responders before start of 2nd line of treatment and SVR 12. GROUP III includes: 10 subjects not infected with HCV as control group. The following investigations were done: body mass index calculation, Laboratory investigations including CBC, complete hepatic function tests, FIB-4 calculation, fasting serum insulin, HOMA-IR and serum Resistin level at baseline and re-assessed 12 weeks post end of treatment. Fasting serum Insulin, HOMA-IR and Resistin level were statistically significant higher in both naïve & relapser chronic HCV infected patients than in control group (p value <0.001). SVR 12 weeks post treatment was achieved in all 40 patients received new direct acting antivirals with a Significant reduction in Fasting serum Insulin, HOMA-IR and Resistin level at SVR 12 week (p value 0,001, <0.001, <0.001) respectively. Significant positive correlation was found between Resistin level and HOMA-IR in both naïve and relapse chronic HCV patients. Calculation of FIB-4 among patients showed significant higher FIB-4 in naïve patients than relapser (p value 0,002). Serum Resistin at a cut off value >1800 ng/ml had 38.89 % sensitivity, 86.36 % specificity, 70 % PPV, 63.3 % NPV (with an overall accuracy of 57.1 %) in predicting absence of liver cirrhosis based on FIB-4. And at a cutoff value ≥2400 ng/ml had 93.55% sensitivity, 33.3% specificity, 82.9% positive predictive value, and 60% negative predictive value with an overall accuracy of 62.4% in prediction of significant insulin resistance among chronic HCV patients.

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Conclusion: Serum Resistin level was significantly up regulated in patients with chronic HCV, with significant reduction in its level after achievement of SVR. Resistin has the potential to be a biomarker for screening of insulin resistance among chronic HCV patients.

Keywords: Resistin, Chronic hepatitis C, Insulin resistance, Direct acting antiviral

Background

Hepatitis C virus infection a leading cause of liver cirrhosis that has a significant global impact, where it infects about 71 million in 2015 with highest prevalence in the Eastern Mediterranean and European regions, According to WHO. In Egypt it is 10% prevalent before the National Campaign done in 2018-2019 [1].

The direct-acting antivirals (DAAs) have become the new gold standard of HCV treatment. DAAs are safe and highly effective and achieve a sustained virologic response (SVR) in 90-98% of cases [2].

Experimental and clinical evidences demonstrated that HCV core protein plays a pathogenic role in the development of insulin resistance. Epidemiological studies show that the prevalence of insulin resistance and type 2 diabetes in HCV-infected patients is significantly higher than that observed in hepatitis B virus infection and in the general population. It has been reported that the risk of developing type 2 diabetes mellitus is 11 times higher in patients with HCV infection, in which there is a direct correlation between viremia and insulin resistance levels and the development of type 2 diabetes [3].

Furthermore, insulin resistance in HCV patients is strictly correlated with metabolic syndrome, and it is a determinant for increased vessel wall stiffness. Thus, clearance of HCV could improve insulin resistance related cardiovascular events [4].

Resistin is an adipocyte derived hormone with 12.5 kDa that forms multimeric complexes characterized by the presence of cysteine residues. It is involved in the regulation of glucose homeostasis, inflammation, and adipogenesis and thus influences the development of insulin resistance, obesity, and type 2 diabetes [5].

The resistin expression in the human liver is increased in various liver diseases and the positive correlation between resistin and inflammation and hepatic fibrosis, which suggests the involvement of this adipokine in the pathophysiology of liver fibrosis, has been demonstrated in alcoholic hepatitis and NAFLD [5].

Given the postulate of direct involvement of resistin expression on insulin resistance and their relation to HCV infection, the main aim of this study is to evaluate the role of resistin in detecting Insulin Resistance and their impact on response to Direct acting antiviral in chronic hepatitis C patients.

Methods

This study was conducted on 40 Egyptian > 18 years old, chronic HCV infected patients eligible for antiviral treatment with DAAs, agreeable to regular follow up, recruited from National Committee for Control of Viral Hepatitis (NCCVH) regional center in Ain Shams university hospital during the period from February 2019 to February 2020, and 10 healthy volunteers (non diabetic, non obese) as a control group after approval of the Ain Shams University ethics committee was granted, and informed consents were taken from all patients.

They were divided into three groups, GROUP I (Case group) twenty chronic HCV patients as evident by positive HCV Ab (at least six months duration) and detectable quantitative HCV RNA were subjected to treatment by Sofosbovir 400mg+ Daclatasvir 60mg & GROUP II includes: twenty patients with Chronic HCV and non-responders before start of 2nd line of treatment by Sofosbovir 400mg+ Daclactasvir 60mg+ Ribavirin 1000-1200mg or Sofosbovir 400mg+ Ombitasvir, Paritaprevir & Ritonavir + Ribavirin 1000-1200mg as per the Egyptian NCCVH protocol and accordingly administered an appropriate, personally tailored, DAA regimen for 3 months during the course of this study [6] & GROUP III including 10 subjects not infected with HCV as control group.

All female patients were neither pregnant nor lactating throughout the course of this study. Patients with concomitant HBV or HIV infection, hepatocellular carcinoma, patients with other causes of chronic liver diseases such as autoimmune hepatitis and hemochromatosis, History of alcohol abuse, Diabetes mellitus, intake of certain Medications such as biguanides and thiazolidinediones, renal impairment, and those who refused to be entitled in the study were excluded from the study.

All patients were subjected to the following:

1. Full history taking and clinical examination.
2. Laboratory investigations including:

- Complete blood count
- Liver function tests including serum alanine aminotransferase & aspartate aminotransferase, total & direct bilirubin, serum albumin, Prothrombin time and INR.
- HBsAg – HCVAb - HIVAb.

- Hepatitis C virus RNA levels evaluated by real-time polymerase chain reaction (PCR)
- Serum Alpha fetoprotein.
- Serum creatinine.
- Fasting blood glucose
- HbA1C (BioSystems S.A. Costa Brava, 30.08030 Barcelona (Spain), colorimetric method)
- Fasting Insulin hormone level: Normal values: 0.7-9 μU/ml. (Or mU/L),
- Calculating HOMA-IR.

HOMA was used to evaluate IR and β-cell function by the following formulas: HOMA-IR = ([glycemia (mg/dL) × insulinemia (μU/mL)]/405). ***Normal values:*** (0.5–1.4(, Above 1.9 indicates early insulin resistance. Above 2.9 indicates significant insulin resistance [7].

- Serum Resistin: (measured by ELISA kits, Bioassay Technology Laboratory) normal range of 0.02-6 ng/ml (20-6000 ng/L) was assessed for all patients included in the study, For group I and II, resistin was assessed before starting antiviral treatment (baseline) and three months after end of treatment (SVR)
- FIB-4 index: the fibrosis-4 score at a cut off value of 1.45 (FIB-4 <1.45 had a negative predictive value of 90%of advanced fibrosis. The **FIB-4** index is calculated using the **formula**: **FIB-4** = Age (years)×AST (U/L)/[PLT(10^9/L)×$ALT^{1/2}$ (U/L)] [8].
- Radiological examination: Abdominal ultrasonography

Statistical analysis

The collected data were coded, tabulated, and statistically analyzed using IBM SPSS statistics (Statistical Package for Social Sciences) software version 20. Quantitative data were expressed as mean ±SD (standard deviation) for normally distributed data.

In quantitative data, Independent t-test was used to compare two independent groups with normally distributed data and paired t-test in cases of two dependent groups with normally distributed data. Analysis of variance (ANOVA) was used to compare more than two independent groups with normally distributed data, followed by post hoc test to compare between each two groups. Tukey's test was used as a single-step multiple comparison procedure and statistical test to find means that are significantly different from each other. In qualitative data, inferential analyses for independent variables were done using Chi Square (X^2) test for differences between proportions.

Correlations were done using Pearson correlation coefficient test. The receiver operating characteristic (ROC) curve was constructed to obtain the most sensitive and specific cutoff values for different parameters, *P* value less than 0.05 was sufficient enough to show the statistical significance.

Results

Group I included 20 naive chronic HCV patients, comprising 9 (45%) males and 11 (55%) females, with a mean age of 45.15 ± 14.68 years, Group II included 20 relapser chronic HCV patients, comprising 13 (65%) males and 7 (35%) females, with a mean age of 40.15 ± 14 years, whereas group III included 10 healthy participants who served as a control group, comprising eight (80%) males and two (20%) females, with a mean age of 38.9 ± 13.78 years. The statistical differences between groups regarding age and sex were insignificant (*P*>0.05).

Concerning laboratory findings, naïve chronic HCV patients had statistically significant lower level of hemoglobin and platelets than relapser chronic HCV patients (P<0.001), while INR level was significantly higher among naïve chronic HCV patients (*P*=0.008). (The statistical differences between both studied groups regarding liver function tests were shown in the Table 1

Pretreatment fasting insulin level & HOMA-IR was statistically significantly higher in naive chronic HCV patients than in Relapser HCV patients (*P*<0.001) Table 2.

Regarding pretreatment serum resistin level, it was dramatically higher among both naïve and relapser chronic HCV patients in comparison to control group (*P*<0.001) Table 2.

On applying FIB-4 scoring among naïve chronic HCV patients, 7 (35%) patients had FIB-4 < 1.45 indicating absence of cirrhosis, while 13 (65%) patients had FIB-4 of 1.45-3.25 so they were deemed inconclusive, while among relapser chronic HCV patients, 15 (75%) patients had FIB-4< 1.45 indicating absence of cirrhosis, and 5 (25%) patients had FIB-4 of 1.45-3.25 so they were deemed inconclusive.

All patients among naive and relapser chronic HCV received new direct-acting antiviral drugs for 12 weeks and were reassessed 12 weeks after the end of treatment, where they all achieved undetectable serum HCV RNA concentrations (SVR 12 weeks).The statistical differences between pretreatment and 12 weeks after the end of treatment regarding CBC, liver function tests and FIB-4 are insignificant statistically Table 3.

After achieving SVR, a statistically significant improvement in fasting insulin and HOMA-IR was noticed among both naïve and relapser chronic HCV patients (*P*<0.001). Notably, there was also a statistically significant reduction in serum resistin level (1715 ± 514.80 versus 835.5 ± 668.07) for naïve patients and (1735 ± 707.86 versus 929.5 ± 619.98) for relapser group (*P*<0.001) Table 4.

Table 1 Comparison between the 3 groups regarding demographic and laboratory findings

Baseline parameter	Naive group (*n*=20)	Relapser group (*n*=20)	Control group (*n*=10)		
	Mean ± SD	Mean ± SD	Mean ± SD	F	*p*-value
Age (years)	50.150 ± 14.684	43.150 ± 14.050	41.900 ± 13.788	1.649	0.203
BMI(kg/m^2)	28.895 ± 4.75	25.695±5.18	23.590±4.12	2.216	0.12
AST (IU/L)	39.750 ± 17.302	34.150 ± 19.288	29 .100 ± 10.785	0.768	0.469
ALT (IU/L)	39.200 ± 18.574	40.500 ± 40.565	38.000 ± 14.142	0.026	0.974
Albumin (g/dl)	3.605 ± 0.373	3.775 ± 0.236	3.730 ± 0.306	1.559	0.221
Total bilirubin (mg/dl)	0.925 ± 0.510	0.840 ± 0.357	0.910 ± 0.341	0.221	0.802
INR	1.173 ± 0.208	1.015 ± 0.158	1.002 ± 0.097	5.418	0.008*
Hemoglobin(g/dL)	10.450 ± 0.774	13.110 ± 1.922	12.320 ± 1.062	18.722	<0.001*
TLC(×10^3/μL)	7.005 ± 2.173	6.470 ± 2.682	8.590 ± 2.456	2.538	0.090
Platelets(×10^3/μL)	139.800 ± 57.430	216.600 ± 65.303	289.500 ± 63.400	20.654	<0.001*
HbA1C	6.1 ± 0.3	6 ± 0.5	5.9 ± 0.4	2.443	0.091
Total Cholesterol (mg/dL)	186 ± 20	178 ± 25	159 ± 22	1.54	0.22
LDL (mg/dL)	90 ± 19	84 ± 21	79 ± 27	8.441	0.061
Triglycerides (mg/dL)	132 ± 30	147 ± 24	121 ± 29	10.45	0.07

This table shows no statistical significant difference between the three groups as regards the demographic and laboratory findings of the patients except Hemoglobin and platelets with *p* value <0.001* and INR with *p* value <0.008

For naïve chronic HCV patients' group, there was a positive correlation between baseline *HOMA-IR* and serum resistin level (*P*<0.001), also among relapse group a positive correlation between baseline HOMA-IR and serum resistin level (*P*<0.001) was noticed Table 5.

Notably among naïve chronic HCV patients baseline serum *resistin* level was positively correlated with baseline fasting blood sugar, fasting insulin, HOMA-IR (*P*<0.001, *P*<0.001, *P*<0.027 respectively), while among relapsers it was positively correlated with fasting insulin and HOMA-IR (*P*<0.001, *P*<0.02 respectively) Table 6.

The receiver operating characteristic curve analysis of serum resistin for prediction of absence of liver cirrhosis based on FIB-4 scoring showed the following: fasting serum resistin level at a cutoff value greater than 1800 ng/ml had 38.89% sensitivity, 86.36% specificity, 70% positive predictive value, and 63.3% negative predictive value with an overall accuracy of 57.1% (as shown in figures file, Fig. 1).

The receiver operating characteristic curve analysis of serum resistin for prediction of significant insulin resistance among chronic HCV patients showed the following: fasting serum resistin level at a cutoff value greater than 2400 ng/ml had 93.55% sensitivity, 33.3% specificity, 82.9% positive predictive value, and 60% negative predictive value with an overall accuracy of 62.4% (as shown in figures file, Fig. 2).

Discussion

Chronic HCV infection is the leading cause of hepatocellular carcinoma and the leading indication for liver transplantation in developed countries [9]. Newer combination of DAAs offers cure rates exceeding 90%. However, achieving SVR does not immediately reverse HCV related liver fibrosis or cirrhosis [10].

Table 2 Comparison between the three groups regarding *baseline* Fasting blood sugar, fasting insulin, HOMA-IR and resistin

		Groups			ANOVA		TUKEY'S		Test
		Naïve	Relapser	Control	F	*P*-value	N&R	N&C	R&C
FBS Pre (mg/dl)	Mean ±SD	85 ± 13	83 ± 16	87 ± 13.5	0.16	0.851			
Fasting Insulin Pre (μU/ml)	Mean ±SD	29 ± 7.4	17 ± 5.0	5.9 ± 1.8	59.9	< 0.001	< 0.001	< 0.001	< 0.001
HOMA Pre	Mean ±SD	6.33 ± 2.2	3.5 ± 1.1	1.25 ± 0.4	36.2	< 0.001	< 0.001	< 0.001	0.001
Resistin Pre (ng/L)	Mean ±SD	1715.000 ± 514.807	1735.000 ± 707.869	353.000 ± 85.512	24.209	<0.001	0.99	<0.001	<0.001

This table shows no statistically significant difference between the studied groups before treatment as regard fasting blood sugar. Yet as regard Pre-treatment fasting insulin, HOMA IR & resistin, they were found to be statistically significantly higher in naïve and relapse groups in comparison to control group with *P*-value <0.001, and fasting insulin, HOMA IR were higher in naïve group in comparison to Relapsers with *P*-value <0.001

Table 3 Comparison between baseline and post-treatment different laboratory parameters and FIB-4 in both naive and relapse group of patients

		Naive			Relapser		
		Before ttt	After ttt	*P*-value	Before ttt	After ttt	*P*-value
TLC(×10^3/μL)	**Mean ±SD**	7.005±2.173	6.512±1.99	0.45	6.470±2.682	5.7±2.44	0.48
HB(g/dL)	**Mean ±SD**	10.450±0.774	10.1± 0.764	0.85	13.110±1.922	11.5±1.877	0.56
PLT(×10^3/μL)	**Mean ±SD**	139.8±57.430	126±55.41	0.51	216.60±65.303	203.5±63.32	0.54
ALT(IU/L)	**Mean ±SD**	39.200±18.574	40.5± 19.44	0.89	40.50±40.565	41.4± 41.57	0.87
AST(IU/L)	**Mean ±SD**	39.750± 17.302	40.74 ±17.23	0.92	34.150± 19.288	32.132± 20.22	0.78
Albumin(g/dL)	**Mean ±SD**	3.605± 0.373	3.51± 0.31	0.83	3.775 ±0.236	3.665± 0.231	0.89
T bilirubin (mg/dL)	**Mean ±SD**	0.925± 0.510	0.956 ±0.523	0.88	0.840 ±0.357	0.81± 0.345	0.9
INR	**Mean ±SD**	1.173± 0.208	1.21± 0.213	0.56	1.015 ±0.158	1.055± 0.167	0.7
Fib4	**<1.45**	7	8	0.41	15	16	0.52
	>1.45	13	12		5	4	

This table shows no statistical significant difference between baseline and post-treatment different laboratory parameters and FIB-4 in both naive and relapse group of patients

In addition to causing liver disease, CHC infection is associated with wide metabolic disarrangements. HCV interacts with lipid metabolism leading to steatosis, causing wide adipocytokine changes and impairs glucose metabolism leading to increased prevalence of insulin resistance and type 2 diabetes [11]. This association is important because the presence of insulin resistance is associated with increased rates of fibrosis [12] and lower rates of rapid and sustained response to antiviral therapy [13].

The mechanism of how metabolic factors influence disease progression is not clearly understood. Adipose tissue secretes bioactive proteins known as adipokines, including leptin, adiponectin, and resistin. These proteins exert different effects on insulin resistance and inflammation [14].

The behavior of circulating resistin during liver disease owing to viral hepatitis is still under investigation. The current study aimed at determining the value of assessment of serum resistin in prediction of insulin resistance among chronic HCV infected patients and their potential prognostic value in CHC patients under new direct-acting antiviral therapy.

On applying a non-invasive scoring to identify liver cirrhosis among the studied patients, pretreatment FIB -4 was statistically significantly higher in naïve group than in relapse group which could be attributed to decline in steatosis index among relapse group as a result

Table 4 Comparison between baseline & post-treatment fasting blood sugar, fasting insulin, HOMA-IR & resistin in *naive* and *relapser* group of patients

			Time		Differences		Paired Test	
			Pre	Post	Mean	SD	t	*P*-value
Naive	**FBS (mg/dL)**	**Mean ±SD**	85.350 ± 13.758	76.400 ± 15.551	8.950	6.970	5.743	<0.001*
	Fast Insulin (μU/ml)	**Mean ±SD**	29.850 ± 7.499	19.150 ± 8.145	10.700	7.263	6.589	<0.001*
	HOMA	**Mean ±SD**	6.334 ± 2.214	3.645 ± 1.925	2.689	1.477	8.144	<0.001*
	Resistin (ng/L)	**Mean ±SD**	1715.000 ± 514.807	835.500 ± 668.072	879.500	566.424	6.944	<0.001*
Relapser	**FBS (mg/dL)**	**Mean ±SD**	83.800 ± 16.376	74.750 ± 12.422	9.050	8.281	4.887	<0.001*
	Fast Insulin (μU/ml)	**Mean ±SD**	17.650 ± 5.050	11.250 ± 4.800	6.400	6.992	4.094	<0.001*
	HOMA	**Mean ±SD**	3.596 ± 1.156	2.012 ± 0.774	1.584	1.495	4.739	<0.001*
	Resistin (ng/L)	**Mean ±SD**	1735.000 ± 707.869	929.500 ± 619.987	805.500	693.393	5.195	<0.001*

This table shows statistically significant difference between baseline and post-treatment fasting blood sugar, fasting insulin, HOMA-IR, and resistin in naïve and Relapser group of patients being lower post-treatment with *p* value <0.001*

Table 5 Correlation between Pre-treatment HOMA -IR with demographic and laboratory data in *both* Groups of patients

Correlations				
	HOMA Pre			
	Naive		**Relapser**	
	r	***P*-value**	**r**	***P*-value**
Age(years)	-0.086	0.717	0.175	0.460
BMI(kg/m^2	-0.097	0.683	0.265	0.258
ALT (IU/L)	0.187	0.431	0.468	0.307
AST(IU/L)	0.004	0.987	-0.416	0.068
Alb(g/dL)	0.095	0.691	-0.227	0.335
Bil(mg/dL)	0.191	0.420	0.107	0.653
Hb(g/dL)	-0.091	0.702	0.130	0.585
TLC(×10^3/μL)	0.244	0.300	0.090	0.705
Plat(×10^3/μL)	-0.093	0.696	-0.013	0.957
INR	0.361	0.118	-0.270	0.251
FBS Pre(mg/dL)	**0.667**	0.001*	0.507	0.075
Fasting Insulin Pre(μU/ml)	**0.856**	<0.001*	**0.794**	<0.001*
Resistin Pre(ng/L)	**0.745**	<0.001*	**0.769**	<0.001*
PCR(IU/mL)	0.014	0.953	-0.061	0.800
AFP(ng/mL)	0.162	0.494	0.070	0.769
FIB4	-0.115	0.629	-0.134	0.573

This table shows a significant positive correlation between Pre-treatment HOMA-IR and Fasting Insulin & Resistin among Naïve & Relapser Patients and FBS among naïve patients with insignificant correlation with all other parameters

Table 6 Correlations between the Resistin Pre-treatment and all other parameters in the study in both groups of patients

Correlations				
	Resistin Pre			
	Naive		**Relapser**	
	r	***P*-value**	**r**	***P*-value**
Age(years)	0.224	0.343	-0.109	0.646
BMI(kg/m^2)	0.232	0.325	-0.186	0.432
ALT(IU/L)	-0.207	0.382	0.245	0.298
AST(IU/L)	-0.118	0.621	0.157	0.509
Alb(g/dL)	-0.054	0.822	-0.116	0.627
Bil(mg/dL)	0.232	0.325	-0.039	0.870
Hb(g/dL)	-0.087	0.717	-0.187	0.429
TLC(×10^3/μL)	-0.146	0.538	-0.259	0.271
Plat(×10^3/μL)	0.040	0.866	-0.033	0.889
INR	-0.234	0.321	0.445	0.050
FBS Pre(mg/dL)	**0.695**	<0.001*	0.054	0.822
Fast Insulin Pre(μU/ml)	**0.756**	<0.001*	**0.725**	<0.001*
HOMA	0.494	0.027*	0.510	0.021*
PCR(IU/mL)	-0.026	0.913	-0.047	0.843
AFP(ng/mL)	-0.099	0.677	0.030	0.900
FIB4	0.160	0.499	0.054	0.821

This table shows a significant positive correlation between Pre-treatment Resistin and 'Fasting Insulin and HOMA-IR' among Naïve & Relapser Patient and 'FBS in Naïve patients only' with insignificant correlation with all other parameters

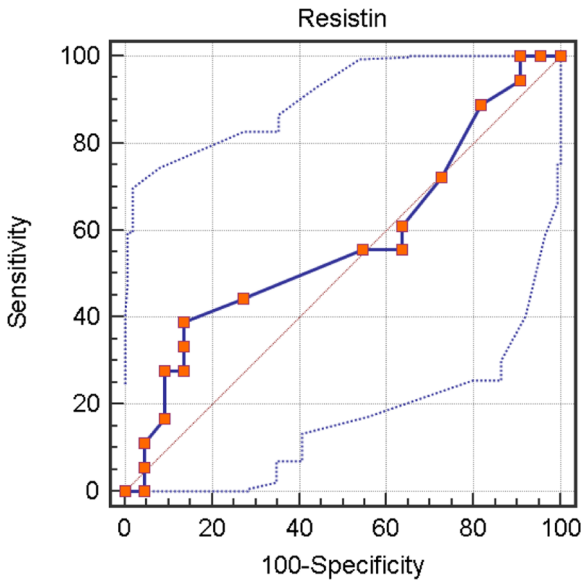

Fig. 1 ROC Curve of serum resistin level in prediction of liver cirrhosis based on FIB4 score in both studied groups of patients

of previous treatment regimen and this was in agreement with Tada et al who stated that viral eradication reduces both liver stiffness and steatosis [15].

In this study, we found that baseline fasting insulin level, HOMA-IR were statistically significantly higher in naïve and relapse chronic HCV patients in comparison to control with P-value <0.001 and these results were in agreement with El Sebaey et al who proved that there is strong link between hepatitis C virus infection and the insulin resistance panel & concluded that Insulin sensitivity improved markedly in patients who achieved SVR [16].

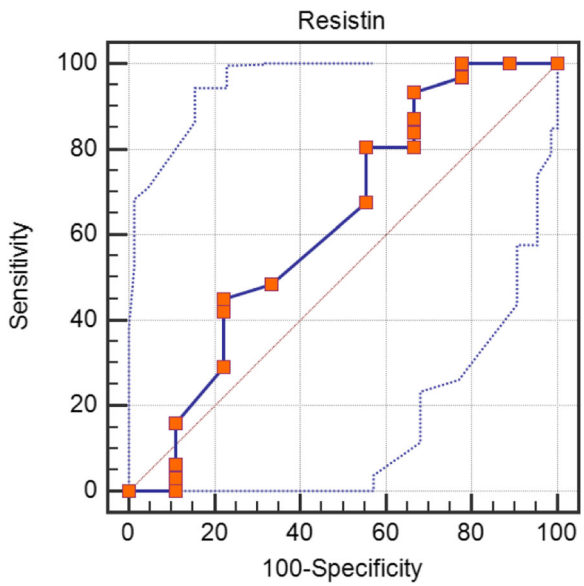

Fig. 2 ROC Curve of serum resistin level in prediction of significant insulin resistance in both studied groups of patients

Also in agreement with Adinolfi et al. who stated that the prevalence of insulin resistance & type 2 diabetes in HCV-infected patients is significantly higher than that observed in hepatitis B virus infection & the general population with a direct correlation between viremia and IR levels and the development of type 2 diabetes [3].

Insulin Resistance in HCV patients has been reported to be mediated by the HCV core protein, which interferes with glucose metabolism and insulin signaling by inhibiting the expression of insulin receptor substrate (IRS)1 and IRS2 [17]. HCV-induced IR in the tissue of HCV-infected patients and animal models has also been indicated to be mediated via several cytokines, including tumor necrosis factor-α [18].

The current study results also showed that there was a statistically significant decline in FBS, Fasting Insulin, HOMA-IR in Both naïve and relapse groups of patients after treatment with DAA in relation to their pre-treatment levels And This goes in agreement with previous data that showed that interferon-based treatment improves insulin resistance and blood glucose levels in patients who clear HCV [19].

Another meta-analysis evaluated data from 8 studies comparing the reduction in IR between SVR and non-SVR groups of HCV patients treated with IFN-based therapy indicated no significant difference in the reduction of IR between the SVR and non-SVR groups. However, patients who achieved SVR had a significantly higher mean reduction in HOMA-IR compared to patients in the non-SVR group [18].

The current study results also showed that pre-treatment serum resistin level was statistically significantly higher in naïve and relapse groups in comparison to control group with a statistically significant decline in its post-treatment level in both groups in relation to pre-treatment level.

Concerning the role of resistin in liver damage associated with viral hepatitis, Resistin expression in human liver was found to be increased in alcoholic liver disease, HCV-induced hepatitis or non-alcoholic steato-hepatitis (NASH). Its expression during liver damage positively correlated with infiltration of inflammatory cells, which represent the principal source of intrahepatic resistin [20].

Regarding this, our results matched with Tiftikci et al. who stated that patients with chronic HCV infection had elevated levels of adipocytokines, such as leptin and resistin, in their sera compared to healthy subjects, although low levels of resistin were associated with the presence of fibrosis in the patient group [21].

Although the possible relationship between resistin and anti-viral treatment has been scarcely studied, Our

results go in agreement with Durrazzo et al. who found a significant reduction in resistin levels after anti-viral treatment in a group of CHC patients [22]. On the contrary, the analysis by Lo Iacono et al. found no changes in resistin level in a cluster of chronic HCV patients before and after the anti-viral therapy [23].

Nevertheless, it is yet unclear whether the presence of logistic state stresses the action of resistin as a mediator of IR and moreover its real patho-physiological role is still debated in chronic hepatitis [24].

Resistin may play an important role in the regulation of glucose homeostasis and adipogenesis [25] thereby influencing the development of insulin resistance, type 2 diabetes, and endothelial dysfunction, thrombosis, and angiogenesis [5].

The present study showed that baseline resistin level was found to have significant positive correlation with baseline Fasting insulin in both Naïve and relapser group with r value equal 0.756 and 0.725 with *P*-value <0.001, and with baseline HOMA-IR with r-value 0.877 and 0.789 respectively and *P*-value <0.001. These results agreed with Makni et al who highlighted a significant correlation between resistin and HOMA-IR through Multiple regression models [26].

Possible explanation could be attributed to the important role of resistin in the inflammatory response associated with chronic liver inflammation, such as hepatitis C and NASH [27]. Resistin presents a directed pro-inflammatory activity or mediated by other cytokines such as interleukin (IL)1, IL6 and the TNFα, through nuclear factor-κB pathway. In the course of chronic liver disease, elevated serum levels have been associated with IR, disease progression, severity, clinical complications, and a more severe prognosis [28].

Finally, the present study revealed the best cutoff value of serum resistin in predicting absence of liver cirrhosis based on FIB-4 score among patients with CHC to be greater than 1800 ng/L. This value had 38.89% sensitivity, 86.36% specificity and an overall accuracy of 57.1%.

It also revealed that the best cutoff value of serum resistin in prediction of presence of significant insulin resistance among CHC patients to be greater than 2400ng/L. This value had 93.55% sensitivity, 33.33% specificity and an overall accuracy of 62.4%.

Conclusion

Serum resistin level was significantly upregulated in patients with chronic HCV, with significant reduction in its level after achievement of SVR. Resistin has the potential to be a biomarker for screening of insulin resistance among chronic HCV patients.

Limitation of the study:

- Small number of studied population

Abbreviations

ALT: Alanine Aminotransferase; AST: Aspartate aminotransferase; CHC: Chronic hepatitis C; DAA: Direct acting antiviral; FBS: Fasting Blood sugar; FIB4: Fibrosis 4; HCV: Hepatitis C virus; HOMA-IR: Homeostatic Model Assessment of Insulin Resistance; INR: International Normalized Ratio; IRS: Insulin receptor substrate; IL: interleukin; PCR: Polymerase Chain reaction; SVR: sustained virologic response; TLC: Total leucocytic count

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Authors' contributions

AIS, RSA, KHA had proposed the subject for research and had conducted final revision of gathered data. HSR, GSR had collected the relevant data. IBI, AIS had prepared the manuscript. HHK, RSA had outlined the study design and revised the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Declarations

Ethics approval and consent to participate

This study was performed according to the ethical standards for human experimentation and in accordance with the ethical principles of the 1975 Declaration of Helsinki. Patients included in this study signed an informed written consent to participate and all the procedures were in accordance with the standards of the Research Ethics Committee (REC) of the Faculty of Medicine, Ain Shams University. (FWA 000017585)

Consent for publication

Consent was taken from each author for publication.

Competing interests

The authors declare that they have no competing interests.

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