Resistin Hormone A Possible Marker of Insulin resistance in chronic HCV and Type 2 Diabetic patients

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Abstract: Background: Insulin resistance is a state in which a given concentration of insulin produces a less than expected biological effect**.** Chronic (HCV) infection triggers a multistep vicious cycle of insulin resistance (IR) and hyperinsulinaemia that gradually progress to frank type 2 diabetes mellitus (DM)**.** HCV induces several complex mechanisms that lead to inflammation, insulin resistance, steatosis, fibrosis, apoptosis, altered gene expression, and hepatocellular carcinoma (HCC). Up to one third of patients with chronic (HCV) develop type 2 DM. This prevalence is much higher than that observed in the general population and in patients with other chronic liver diseases such as hepatitis B virus, alcoholic liver disease and primary liver cirrhosis. Resistin, an adipose-derived polypeptide hormone, offers a novel application potential as a clinical biomarker in the assessment of liver cirrhosis. Elevated resistin may contribute to insulin resistance in advanced liver dysfunction. **Objective:** To assess the level of resistin hormone in patients with chronic HCV and in Type 2 diabetic patients and its possible relation to insulin resistance and severity of liver disease in HCV patients. **Study design:** This study was conducted on sixty patients recruited from the Hepatology Clinic and Internal Medicine out-patients clinic of Ain Shams University Hospitals. Patients were divided into 4 groups, Group (1): This group included 15 patients with type 2 DM and compensated chronic HCV infection (child A), Group (2) This group included 15 patients with type 2 DM and decompensated chronic HCV infection (child C), Group (3) This group included 15 patients with type 2 DM and normal liver function tests (clinical, biochemical and by ultra sound). Group (4) this group included 15 normal subjects as a control group without any metabolic or liver diseases. **Results:** serum Resistin was significantly higher among group (2) Diabetic patients with decompensated liver disease (19.20±3.19 ng/ml) than group (1) (15.68±3.42 ng/ml) group (3) (15.29±3.04) and group (4) (5.09±2.00) (P<0.01). Group 2 had significant higher FBG, Fasting insulin, HOMA-IR, AST, ALT, PT, Bilirubin and significant lower serum albumin when compared to other groups.Correlation studies showed a significant direct correlation between Resistin and FBG (r = 0.780), fasting insulin(r = 0.839) and HOMA-IR (r = 0.685) in group 1,and a significant direct correlation between resistin and FBG (r = 0.847), and HOMA-IR (r = 0.812) in group 2, in group 3 there was a significant direct correlation between resistin and fasting insulin (r = 0.937), HOMA-IR (r = 0.784) and a direct significant correlation between resistin and Fasting insulin (r = 0.910), HOMA-IR (r = 0.905) and a significant indirect correlation between Resistin and serum albumin (r = - 0.519) in group 4.**Conclusion**: Resistin is increased in IR cases like type 2 DM and HCV patients and is related to the severity of liver disease**.**

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1. Introduction:

Type 2 DM is the predominant form of diabetes worldwide accounting for 90-95% of cases globally. The prevalence of type 2 DM is expected to rise more rapidly in the future because of increasing obesity and reduced activity levels ***(1).*** *In* Egypt, DM is a major emerging clinical and public health problem. Some studies estimated that in Egypt 10.4% of the adult population (aged 10-79 years) have diabetes ***(2).*** Type 2 diabetes is characterized by increased hepatic glucose output, increased peripheral resistance to insulin action (due to receptor and post-receptor defects), and impaired insulin secretion ***(3).*** Insulin resistance is a cardinal feature of type 2 DM. It is present in individuals predisposed to type 2 DM before the onset of hyperglycemia. It is caused by acquired factors such as obesity; sedentary life style, pregnancy, and hormone excess ***(4).*** Insulin resistance is associated with hypertension, atherogenic dyslipidemia, impaired fibrinolysis and obesity (metabolic syndrome). Metabolic syndrome is associated with three folds increase in risk of coronary heart disease, myocardial infarction and stroke and three to five folds increase in risk of cardiovascular death ***(5)*** The World Health Organization (WHO) estimates 170 million individuals worldwide to be infected with hepatitis C virus (HCV). However, the prevalence of HCV infection varies throughout the world. Egypt has the highest number of reported infections, largely attributed to the use of contaminated parenteral anti-schistosomal therapy (***6)***. Liver plays a key-role in carbohydrate metabolism. Glucose intolerance, overt diabetes mellitus and insulin

resistance are characteristic features of patients with cirrhosis. Central hyper-insulinemia and peripheral insulin-resistance are the main explanations for the high prevalence of diabetes in patients with cirrhosis. On the other hand, type 2 diabetes is associated with a wide spectrum of liver diseases ranging from non-alcoholic fatty liver to cirrhosis and hepatocellular carcinoma. Carbohydrate metabolism abnormalities are major aggravating risk factors in cirrhosis ***(7)***. Increase in the fasting insulin and a decrease in insulin sensitivity have been observed in HCV- infected subjects with a moderate or severe degree of hepatic fibrosis. However, HCV- infected patients without fibrosis (fibrosis stage 0) also present higher insulin resistance than patients with primary biliary cirrhosis with different degrees of hepatic fibrosis (stages 1-3) and healthy individuals. These data suggest that HCV is capable of producing an increase in insulin resistance, even before a minimal degree of hepatic fibrosis is present ***(8)***. Resistin, predominantly expressed in adipocytes mediates insulin resistance in rodents. In contrast, Resistin is mainly expressed in mononuclear cells, including macrophages in humans. Although genetic and pharmacologic studies strongly supports links between Resistin, obesity and insulin resistance in mice,the role of human resistin as a modulator of metabolism in reports suggest that circulating levels of resistin inflammatory states is not well understood **(9)**. Given the convergence of adipocyte and macrophage function, resistin may provide unique insight into links between obesity, inflammation, and atherosclerosis in humans.

2. Subjects and methods:

This study was conducted on sixty patients recruited from the Hepatology Clinic and Internal Medicine out-patients clinic of Ain Shams University Hospital. Patients were divided into 4 groups:

Group (1): This group included 15 patients with proved type 2 diabetes mellitus and compensated chronic HCV infection (child A).

Group (2): This group included 15 patients with proved type 2 diabetes mellitus and decompensated chronic HCV infection (child C).

Group (3): This group included 15 patients with proved type 2 diabetes mellitus and normal liver (clinical, biochemical and by ultra sound).

Group (4): This group included 15 normal subjects as a normal control group matched same age and sex.

Exclusion criteria:

Obese and overweight patients [BMI and waist circumference in Group 3 (decompensated liver disease complicated by ascites) were the highest but were not considered a marker of obesity], pregnant females, patients with hepatocellular carcinoma, patients taking drugs that may affect insulin resistance at least 6 months prior to the study such as steroids, insulin sensitizers or thiazide diuretics and patients with HBV infection.

A written consent was obtained from all the participants, and the procedure of the research explained to them. They had the right to refuse to participate and the right to quit at any stage.

Methods:

1. All studied individuals were subjected to:
2. Careful history taking focusing on manifestations of liver cell failure if present, history of DM and drug therapy.
3. Full clinical examination focusing on measuring blood pressure, level of consciousness and detecting signs of liver cell failure and its complications.
4. Anthropometric measures including body weight, height, Body mass index (BMI).
5. Blood samples for AST, ALT, serum Albumin, bilirubin, FBG, PT, Fasting insulin, (calculation of HOMA-IR), HBV surface antigen, HCV antibody, serum Resistin.
6. Abdominal ultrasound.

Statistical analysis:

Data were statistically described in terms of mean ± standard deviation (± SD), frequencies (number of cases), and percentage when appropriate comparison of quantitative variables between the study groups was done using student t test for independent samples. t-test is any statistical, hypothesis test in which the test statistic follows a student's t distribution, if the null hypothesis is supported. It is most commonly applied when the test statistic would follow a normal distribution if the value of a scaling term in the test statistic were known. When the scaling term is unknown and is replaced by an estimate based on the data, the test statistic (under certain conditions) follows a student's distribution. For comparing categorical data, Chi square (X2) test was performed. Exact test was used instead when the expected frequency is less than 5.

P value <0.05 Significant(S)
P value >0.05 nonsignificant (NS)
P value <0.01 highly significant (HS).

3. Results:

There was no statistical significant difference between the 4 groups as regards age, sex or height. Group 2 had significant higher weight (77.27±3.80) vs Group 1 (72.40±5.26),Group 3 (71.07±7.87) and group 4 (71.20±8.14), significant higher BMI (24.43±0.36) vs Group 1 (23.57±0.64),Group 3 (23.47±0.76) and Group 4 (23.35±0.64), FBG was found to be significantly higher among group (2) (249.5 ± 90 mg/dl) than group (1) (205.3±59.4 mg/dl), group (3) (183.3±65.6 mg/dl)

and control group (4) (86.07±9.5). Fasting insulin level was found to be significantly higher among group (2) (23.25±4.7mg/dl) than group (1) (14.2±5.2mg/dl) group (3) (15.96±6.2 mg/dl) and control group (4) (4.5±2.2). HOMA-IR was significantly higher among group (2) (14.7±6.6 mg/dl) than group (1) (8.9±6 mg/dl) group (3) (7.8 ± 5.4mg/dl) and control group (4) (0.96±0.52), We also found serum Resistin to be significantly higher among group (2) mean ±SD (19.2±3.1 ng/ml) than group (1) (15.6±3.4 ng/ml), group (3) (15.2±3) and group (4) (5.9±2) (P<0.01). Our study also found serum ALT to be significantly higher among group (2) (55.2±17 U/L) than group (1) (22.8±7.2 U/L), group (3) (24.8±8.3 U/L) and control group (4) (18.7±5.8), Also AST was significantly higher among group (2) (79.8±17.2 U/L) than group (1) (26.6±6.8 U/L), group (3) (24.8±7.5 U/L) and control group(4) (18.6±5.6). Serum total bilirubin was significantly higher in group (2) (4.05±0.8 U/L) than group (1) (1.2±0.2 U/L), group (3) (0.8±0.2 U/L) and control group (4) (0.7±0.2), furthermore, Prothrombin time was significantly higher in Group 2 (28.40+2.47) vs Group 1 (14.20+2.04), group 3 (11.67+0.97) and group 4 (11.47+1.06). Serum albumin was significantly lower among group (2) (2.3±0.2 U/L) than group (1) (4 ±0.2 U/L), group (3) (4.4±0.4 U/L) and control group (4) (4.7±0.4) (P<0.01). Correlation studies showed a significant direct correlation between Resistin and FBG (r = 0.780), fasting insulin(r = 0.839) and HOMA-IR (r = 0.685) in group 1, and a significant direct correlation between resistin and FBG (r = 0.847), and HOMA-IR (r = 0.812) in group 2, in group 3 there was a significant direct correlation between resistin and fasting insulin (r = 0.937), HOMA-IR (r = 0.784) and a direct significant correlation between resistin and Fasting insulin (r = 0.910), HOMA-IR (r = 0.905) and a significant indirect correlation between Resistin and serum albumin (r = - 0.519) in group 4.

Table (1): Comparative study between patients groups as regard FBG and fasting Insulin using One Way ANOVA test:

		N	Mean	±SD	F	*P* value	Sig.
FBG	Group (1)	15	205.33	59.434	17.837	0.000	HS
	Group (2)	15	249.53	90.033			
	Group (3)	15	183.33	65.669			
	Group (4)	15	86.07	9.513			
Fasting Insulin	Group (1)	15	14.247	5.2755	37.568	0.000	HS
	Group (2)	15	23.253	4.7939			
	Group (3)	15	15.967	6.2590			
	Group (4)	15	4.507	2.2689			

Table (2): Comparative study between patients groups as regard Liver functions using One Way ANOVA test:

		N	Mean	±SD	F	*P* value	Sig.
AST	Group (1)	15	26.67	6.821	111.506	0.000	HS
	Group (2)	15	79.80	17.288			
	Group (3)	15	24.80	7.589			
	Group (4)	15	18.60	5.654			
ALT	Group (1)	15	22.87	7.259	37.387	0.000	HS
	Group (2)	15	55.20	17.085			
	Group (3)	15	24.80	8.368			
	Group (4)	15	18.73	5.861			
Albumin	Group (1)	15	4.073	0.2738	129.451	0.000	HS
	Group (2)	15	2.307	0.2344			
	Group (3)	15	4.493	0.4803			
	Group (4)	15	4.720	0.4411			
Prothrombin time	Group (1)	15	14.20	2.042	316.420	0.000	HS
	Group (2)	15	28.40	2.473			
	Group (3)	15	11.67	0.976			
	Group (4)	15	11.47	1.060			
Total bilirubin	Group (1)	15	1.220	0.2274	186.624	0.000	HS
	Group (2)	15	4.053	0.8096			
	Group (3)	15	0.820	0.2007			
	Group (4)	15	0.760	0.2197			
Direct bilirubin	Group (1)	15	0.273	0.1033	99.036	0.000	HS
	Group (2)	15	1.413	0.4454			
	Group (3)	15	0.141	0.0905			
	Group (4)	15	0.148	0.1121			

Table (3): Comparative study between patients groups as regard FBG, HOMA and Resistin level using One Way ANOVA test:

		N	Mean	±SD	F	P value	Sig.
FBG mmol\L	Group (1)	15	11.40	3.305	17.848	0.000	HS
	Group (2)	15	13.87	5.001			
	Group (3)	15	10.18	3.647			
	Group (4)	15	4.78	0.529			
HOMA equation	Group (1)	15	8.94	6.070	17.306	0.000	HS
	Group (2)	15	14.73	6.640			
	Group (3)	15	7.84	5.427			
	Group (4)	15	0.96	0.522			
Resistin level	Group (1)	15	15.680	3.4252	55.138	0.000	HS
	Group (2)	15	19.200	3.1940			
	Group (3)	15	15.293	3.0403			
	Group (4)	15	5.907	2.0052			

Table (4): Correlation study between baseline numeric data and Resistin level among group (1) using Pearson Correlation test:

	Resistin level	
	R	P-value
Age	0.011	0.969
Weight	-0.234	0.401
Height	-0.221	0.429
BMI	-0.115	0.684
FBG	.780(**)	0.001
Fasting Insulin	.839(**)	0.000
AST	-0.015	0.959
ALT	0.110	0.697
Albumin	0.133	0.635
Prothrombin time	-0.477	0.072
Total bilirubin	0.254	0.362
Direct bilirubin	0.101	0.719
HOMA equation	.685(**)	0.005

Table (5): Correlation study between baseline numeric data and Resistin level among group (2) using Pearson Correlation test:

	Resistin level	
	R	P-value
Age	-0.059	0.834
Weight	-0.321	0.244
Height	-0.294	0.287
BMI	-0.035	0.900
FBG	.847(**)	0.000
Fasting Insulin	0.427	0.113
AST	0.247	0.374
ALT	0.289	0.296
Albumin	0.469	0.078
Prothrombin time	-0.221	0.429
Total bilirubin	-0.300	0.277
Direct bilirubin	-0.364	0.182
HOMA equation	.812(**)	0.000

Table (6): Correlation study between baseline numeric data and Resistin level among group (3) using Pearson Correlation test:

	Resistin level	
	R	P-value
Age	0.018	0.948
Weight	-0.002	0.995
Height	0.026	0.925
BMI	-0.091	0.746
FBG	0.511	0.052
Fasting Insulin	.937(**)	0.000
AST	-0.224	0.423
ALT	-0.354	0.196
Albumin	0.065	0.819
Prothrombin time	-0.242	0.386
Total bilirubin	-0.172	0.540
Direct bilirubin	-0.287	0.299
HOMA equation	.784(**)	0.001

Table (7): Correlation study between baseline numeric data and Resistin level among group (4) using Pearson Correlation test:

	Resistin level	
	R	P-value
Age	0.079	0.779
Weight	0.115	0.683
Height	0.109	0.700
BMI	0.076	0.787
FBG	0.159	0.571
Fasting Insulin	0.910(**)	0.000
AST	-0.038	0.894
ALT	0.155	0.581
Albumin	-0.519(*)	0.048
Prothrombin time	-0.217	0.438
Total bilirubin	0.067	0.812
Direct bilirubin	0.302	0.273
HOMA equation	0.905(**)	0.000

4. Discussion:

In Egypt, HCV is the most common etiologic factor of chronic liver disease, where prevalence of antibodies to HCV (anti HCV) is >10-fold greater than in the United States and Europe with a large underlying reservoir of HCV liver disease ***(10).*** Patients with HCV are more likely to develop diabetes (21%) than patients with hepatitis B (10%), suggesting that HCV, rather than liver disease perse, predisposes patients to diabetes ***(11).*** Taken together, these observations suggest that HCV may play a pathogenic role in type 2 diabetes. Recent studies suggest that the core protein of HCV impairs insulin receptor substrate signalling, which plays an important role in the metabolic effects of insulin ***(12).*** Increased prevalence of type 2 diabetes in patients with hepatitis C associated liver cirrhosis compared with those with liver cirrhosis due to other causes, supporting the likelihood of a causal relations (***13)***. In evaluating resistin and its association with insulin sensitivity in humans, several studies have identified positive correlations between resistin levels and insulin resistance in vivo and in vitro ***(14)***. Additionally, serum resistin levels were increased by approx. 20% in T2DM subjects, such findings have been re-affirmed by ***(15)***. The aim of this work was to evaluate serum resistin levels in patients with various stages of chronic HCV liver diseases and type 2 diabetes and its relation to insulin resistance.

In our study HOMA-IR was found to be significantly higher in group (2) (decompensated liver & DM) as compared to group (1) (compensated liver & DM) and the latter showed highly significant higher results compared to group (3) (diabetic with healthy liver) with a lower (normal) level in healthy control cases, this finding supports the presence of an insulin resistance state in HCV infected cases (whether with compensated or decompensated liver) as was reported by ***Yagmur et al.,);*** **Bahr *et al.*, who referred these results to the higher degree of insulin resistance** in chronic liver disease patients in comparison to healthy controls.**(16,17).** ***Elzayadi and Anis*** who concluded that, IR is one of the pathological features in patients with HCV infection and that IR plays a crucial role in the development of various complications and events associated with HCV infection like hepatic steatosis, hepatic fibrosis, resistance to anti-viral treatment, hepatocarcinogenesis and proliferation of hepatocellular carcinoma; and extrahepatic manifestations **(18).** Chronic hyperinsulinemia could be a cause of insulin resistance in cirrhosis through desensitization. Continuous exposure to high levels of insulin causes a reduction in both number of insulin receptors exposed on the cell surface and their affinity to insulin ***(19).*** Moreover, accumulation of free fatty acids in hepatic steatosis can down regulate insulin receptor signalling ***(20).*** Also ***Yagmur et al.*** and ***Bahr et al.*** founded significant decrease in insulin sensitivity in advanced stages in comparison to less advanced stages **(16,17)**. However ***Hui et al.,*** stated that hepatitis C virus induces insulin resistance irrespective of the severity of liver disease **(21).**

Furthermore in our work serum resistin level was found to be significantly higher in group (2) (decompensated liver & DM) as compared to group (1) (compensated liver & DM) and the latter showed highly significant higher results compared to group (3) (diabetic with healthy liver) with a significant lower (normal) level in healthy control cases (the same as HOMA). Moreover serum resistin level was recorded to be positively correlated with HOMA–IR in all studied groups, so a possible link between resistin hormone & insulin resistance in DM or HCV infected cases (with compensated or decompensated liver) can be suggested, a finding that agreed with studies which confirmed a direct correlation between Resistin levels and patients with type 2 diabetes mellitus ***(15). Rajala et al.*** also found positive correlations between Resistin levels and insulin resistance. Plasma resistin levels have been observed to be higher in diabetic individuals than in apparently healthy individuals **(22)**. In addition, ***Nagaev and Smith*** reported that increased resistin secretion was correlated to impaired glucose tolerance and insulin action in mice, while thiazolidinedione treatment greatly down regulated *resistin* gene expression, and neutralization of the resistin protein enhanced blood glucose uptake and insulin sensitivity. It has been suggested that resistin antagonizes insulin, modulating one or more steps in the insulin-signaling pathway and possibly playing a role in the pathogenesis of insulin resistance***(23).*** Also ***Bajaj et al.*** reported that the liver is the major target organ for Resistin, where Resistin induces insulin resistance and increase glucose production **(24).** The higher resistin level in advanced stages of chronic liver disease could be explained by either increased severity of the cirrhotic inflammatory process-the main source of resistin being the infiltrating inflammatory cells within the cirrhotic liver - or the increased insulin resistance in cirrhotic patients, or both ***(25).*** Also, ***Steppan et al.*** reported that resistin antagonizes the action of insulin **(26)** while ***Lin et al.2005;*** reported that elevated insulin induces adipose resistin expression in liver cirrhosis and therefore indicate that resistin is a target molecule by which hyperinsulinemia causes insulin resistance in liver cirrhosis ***(27).*** Unlike our results, ***Tsochatzis et al.*** didn't find a statistically significant relation between resistin and insulin resistance in chronic liver disease patients **(28)**, also ***Yagmur et al.*** did find a significant correlation between them **(16).** In contradictory, ***Pagano et al.*** found increased resistin in non- alcoholic fatty liver disease (NAFLD) to be related to liver

disease severity and not to insulin resistance **(29)**. In our work Group (3) cases despite having within normal level of serum ALT & AST, the level of their enzymes showed significant higher values compared to those of normal healthy control group (4), this finding agreed with ***Moseley,*** who recorded diabetes mellitus cases to have mild elevation of one or more of serum biochemical tests due to hepatic steatosis **(30).** In the present study, serum PT level was recorded to be significantly higher in group (2) (diabetic decompensated liver) compared to other groups, a result which is expected since PT is known as prognostic factor for liver function **(*31).***

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