INSULIN RESISTANCE AS A PREDICTOR OF EARLY VIROLOGIC RESPONSE TO HCV THERAPY AMONG CHRONIC HCV EGYPTIAN PATIENTS

Ashraf Mikheal [1,3] , Hanan Zakaria Shatat[1], Fathallah Sidkey[2], Ekram Wassim Abd El- Wahab[1]

[1] Tropical Health Department, High Institute of Public Health, Alexandria University, Egypt
[2] Department of Internal Medicine, Faculty of Medicine, Alexandria University, Egypt
[3] Damanhour Fever Hospital, Ministry of Health, Egypt

ABSTRACT

Prior assessment of insulin resistance by HOMA-IR is emerging as an important milestone in the treatment of patients with chronic hepatitis C. This cost-effective tool is recommended to individualize treatment duration, or to exclude those with low insulin sensitivity from being treated until ameliorating their state of insulin resistance (IR). The present work aimed to elucidate further the effect IR state on early viral kinetic response to HCV therapy and the impact of HCV treatment and viral eradication on insulin sensitivity. Insulin sensitivity was assessed using the HOMA-IR method. All enrolled patients were treated with a dual therapy (pegylated interferon-alpha plus ribavirin) for 48 weeks and evaluated using qRT-PCR for early virologic response as well as the impact of treatment on insulin sensitivity throughout the early period of therapy. Of a total 392 chronic HCV cases, early virologic response was achieved by 318 (81.1%). IR was detected in 241 (61.5%) chronic HCV patient of which 73.4% responded to treatment. Early virologic response among patients with > 2.18 HOMA-IR value were significantly lower than those with HOMA-IR values ≤2.18 (P < 0.0001). IR was significantly associated with high baseline BMI. Steatosis and fibrosis correlated with IR but neither independently predicted early virologic response. Pretreatment IR < 2.18, low fasting blood glucose, low and intermediate HCV viral load, normal BMI, and non-smoking were independent factors associated with early virologic response. IR interferes with early virologic response to the antiviral care. Clinical application of pretreatment HOMA-IR assessment could help in predicting early treatment outcome and thus enable treatment regimens to be optimized and individually tailored.

J Med Virol. 2015 Mar;87(3):428-40.

INTRODUCTION

Chronic hepatitis C virus (HCV) infection affects approximately 200 million people worldwide, comprising 3% of global population and is currently the most frequent cause for liver transplantation in the United States and Europe. HCV infection is strongly associated with the development of insulin resistance (IR) and predispose to the onset of type-2 diabetes irrespective of liver disease severity through interactions with different components of the insulin signaling pathway or with factors involved in its regulation. Growing evidence from several studies supports the central role of IR in response failure to antiviral therapy among HCV patients. IR is strongly implicated in liver fibrosis and contributes to fibrotic liver progression, steatosis, development of complications, and response to HCV therapy. Treatment of chronic HCV infection with Pegylated-interferon alpha (PegIFN-a) and ribavirin combination therapy has favorable efficacy in genotypes 2 and 3 but a limited one among genotypes 1 and 4 infected patients. The treatment is costly and involves severe side effects. The prediction of non-response is thus of utmost interest for both patient wellbeing and health care economy. A number of host-related factors have been reported to interfere with HCV treatment response. These included old age, male gender, ethnicity, obesity, advanced liver fibrosis or cirrhosis, high transaminase levels, established state of diabetes, HLA class, and host genetic polymorphisms. Pretreatment assessment of IR has emerged as an important milestone in the treatment of patients. Elevated HOMA-IR was associated with a lower cure rate of patients with hepatitis C treated with Peg-IFN-a/ribavirin irrespective of the infecting genotype Pretreatment assessment of IR has emerged as an important milestone in the treatment of patients. Elevated HOMA-IR was associated with a lower cure rate of patients with hepatitis C treated with Peg-IFN-a/ribavirin irrespective of the infecting genotype. Early virologic response is a major determinant for identifying non-responder patients and has a great impact on subsequent rapid and sustained virologic response, thus constitutes the earliest treatment-stopping rule.

OBJECTIVES

At present, no individualized treatment schedule is tailored on the basis of any baseline predictor of response. The present work aimed to validate directly measured IR state as a pre-treatment clinical parameter interfering with early viral kinetics in response to HCV therapy and whether early treatment outcome could also be predicted at baseline virologic and host characteristics. The impact of HCV treatment and viral eradication on insulin sensitivity was also addressed.

METHODS

Study Design and Patients

A prospective cross sectional study was conducted between October 2012 and February 2013 at the Liver Center of El-Qabbary Hospital. The study patients comprised 384 chronic HCV positive patients eligible for receiving pegyinterferon/ribavirin combination therapy.

Data collection

All enrolled patients were interviewed using structured predesigned questionnaire to collect sociodemographic data and subjected to complete medical examination (general and abdominal) including estimation of the BMI.

Baseline laboratory investigations, abdominal US, ECG, and liver biobsy for proper selection of eligible cases for treatment were done.

HOMA-IR was assessed using the given mathematical equation;

HOMA-IR= fasting insulin (mU/ml) fasting plasma glucose (mmol/l)/22.5.

A HOMA value of 2.18, signifies IR (AUC=0.630.03, 95% CI=0.56–0.69; P=0.001, sensitivity=60%, specificity=55%).

Regimen of Combination Therapy

All enrolled patients received Peg-IFN-a-2a or Peg-IFN-a-2, which was given in weekly doses adjusted to body weight according to the manufacturer's instructions at 1.5mg/kg/week, plus ribavirin, in two divided daily oral doses adjusted to body weight (800mg for weights <50 kg, 1,000mg for weights 50–65 kg, 1,200mg for weight 65–80 kg, and 1,400mg for weights >80 kg).

METHODS

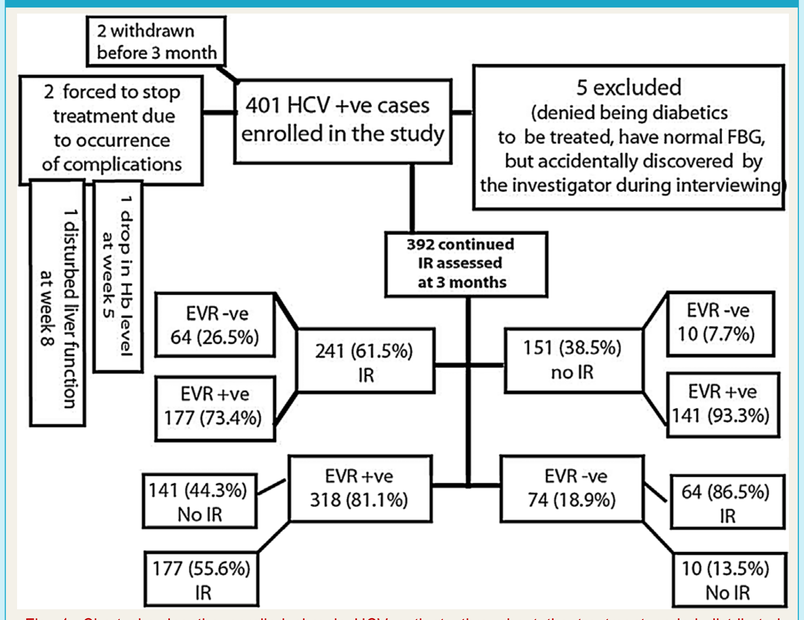

Fig. 1. Chart showing the enrolled chronic HCV patients throughout the treatment period distributed according to early virologic response and insulin resistance state (IR)

Patient Follow-up

Laboratory investigations, including complete blood count and liver function tests were repeated at 4 and 12 weeks during treatment.

At week 12 of treatment, all enrolled patients were subjected to qRT-PCR for viral load to detect early virologic response and re-assessment of HOMA-IR to evaluate the impact of treatment on insulin sensitivity.

Statistical Analysis: All statistical analysis was done using two-tailed tests and alpha error of 0.05 P-value. The means with standard deviation and percent were used to describe the scale and categorical data, respectively. Numeric data were analyzed using one-sample Kolmogorov–Smirnov test and Mann–Whitney test. For categorical data, Pearson's Chi square test, Fisher's exact test, Mont Carlo exact test, and Kruskal–Wallis test for several independent groups. Multiple logistic regression analysis with the backward stepwise variable selection was used to identify the independent predictors of treatment outcome.

RESULTS

Table 1: Factors associated with insulin resistance

	HOMA0 categories				OR (95% CI)	P value
	≤2.18 (no IR)		> 2.18 (IR)			
	No	%	No	%		
Age						
19-	26	44.8	32	55.2	1	
30-	46	45.5	55	54.5	0.97 (0.51-1.9)	
40-	52	40.0	78	60.0	1.2 (0.65-2.3)	0.021
50-59	27	26.2	76	73.8	2.3 (1.2-4.5)*	
Gender						
Male	88	40.6	129	59.4	1	
Female	63	36.0	112	64	1.2 (0.80-1.8)	0.35
Residence						
Urban	123	38.6	196	61.4	1	0.97
Rural	28	38.4	45	61.6	1.0 (0.60-1.7)	
Education						
Illiterate	22	30.6	50	69.4	1.1 (0.35-3.7)	
Read & Write	27	34.6	51	65.4	0.94 (0.29-3.1)	
Primary Education	16	38.1	26	61.9	0.81 (0.24-2.8)	0.38
Preparatory Education	19	39.6	29	60.4	0.76 (0.23-2.6)	
Secondary Education	62	45.3	75	54.7	0.61 (0.19-1.9)	
University Education	5	33.3	10	66.7	1	
Smoking	31	33.3	62	66.7	1.3 (0.82-2.2)	0.24
BMI1_cat						
<18-	0	0.0	1	100.0	1	
18-	120	90.2	13	9.8	0.11 (0.01-1.8)	
25-	26	14.4	154	85.6	5.9 (0.36-97.7)	0.0001
30+	5	6.4	73	93.6	14.6 (0.79-87.6)	
Viral load						
Very low < 10,000	13	50	13	50	1	
Low 10000-100000	37	40.2	55	59.8	1.5 (0.62-3.5)	
Intermediate 100000-1000000	73	38.6	116	61.4	1.6 (0.69-3.6)	
High > 1000000	28	32.9	57	67.1	2.0 (0.83-4.9)	0.44
Hemoglobin level						
Below normal (10-12.9 g/dl)	133	38.4	213	61.6	1.0 (0.55-1.9)	0.93
Normal (13-17.9 g/dl)	18	39.1	28	60.9	1	
White Blood Cells						
Below normal (3.2-3.9 k/mm²)	12	32.4	25	67.6	1.4 (0.66-2.8)	
Normal (4-11 k/mm²)	137	39.5	210	60.5	1	0.54
Above normal (>11-13.5 k/mm²)	2	25	6	75	1.9 (0.34-9.8)	
Platelet count						
Below normal (24000-)	32	40.5	47	59.5	0.90 (0.54-1.5)	0.68
Normal (150-404000 k/mm²)	119	38	194	62	1	
Prothrobin activity						
Below normal (62-74%)	3	15.8	16	84.2	3.5 (1.1-12.2)*	0.037
Normal (75-100%)	148	39.7	225	60.3	1	
Total serum Bilirubin						
< 2	121	42.5	164	57.5	1	
> 2	30	28	77	72	1.9 (1.2-3.1)*	0.009
Alpha Feto Protein						
Normal (up to 10 ng/ml)	142	40.7	207	59.3	1	
Elevated (>10 ng/ml)	9	20.9	34	79.1	2.6 (1.3-5.6)*	0.013
Fasting Blood Glucose						
Below normal (50-69 mg/dl)	3	75	1	25	1	
Normal (70 -110 mg/dl)	148	40.9	214	59.1	4.3 (0.45-42.1)	
Prediabetics (111-130mg/dl)	0	0	26	100	77.0 (4.2-125.7)*	0.0001
Insulin						
Below normal <5 ul unit/ml	15	100	0	0	1	
Normal 5-9 ulUnit/ml	136	61.8	84	38.2	19.2 (1.1-158.3)*	0.0001
Above normal > 10 ul unit/ml	0	0	157	100	524.3 (187.1-1257.3)*	
Peri-portal fibrosis	61	39.1	95	60.9	0.96 (0.63-1.5)	0.84
Steatosis	24	27.3	64	72.7	1.9 (1.2-3.2)*	0.014
Ishake score						
stage 1	31	50.8	30	49.2	1	
stage 2	111	41.1	159	58.9	1.5 (0.85-2.5)	
stage 3	9	15.8	48	84.2	5.5 (2.3-13.2)*	0.0001
stage 4	0	0	4	100	3. (4.5-82.6)*	

Table 2: Stepwise logistic regression model for factors associated with insulin resistance

	B	S.E.	Sig.	Exp(B)	95.0% C.I. for EXP(B)	
					Lower	Upper
Ishak_Score	.729	.214	.001	2.1	1.4	3.2
Total serum Bilrubin	.873	.405	.031	2.4	1.1	5.3
Fasting Blood Glucose	.076	.013	.000	1.1	1.2	2.1
Constant	-8.619	1.279	.000	.000		

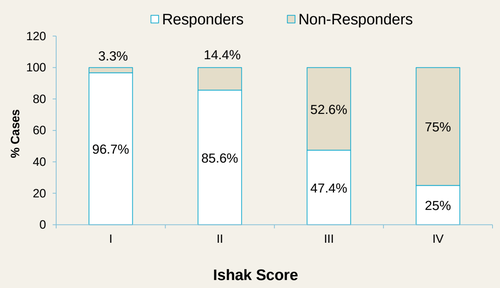

Figure 2: Impact of Ishak stage on EVR of chronic HCV patients

RESULTS

Table 3: Impact of some host characteristics on EVR in chronic HCV patients undergoing therapy

Variable	Total No. (%)	EVR (n=392)				OR (95%CI)	P
		Responders (n=318)		Non-Responders (n=74)			
		No.	%	No.	%		
Age (years)							
19-	58 (14.8)	48	82.8	10	17.2		
30-	101 (25.8)	82	81.2	19	18.8	0.9 (0.38-2.1)	0.377
40-	130 (33.2)	110	84.6	20	15.4	1.1 (0.5-2.6)	
50-59	103 (26.3)	78	75.7	25	24.3	0.65 (0.3-1.5)	
Mean±SD		41.2±10.2		42.5±9.8		t = 0.97	0.334
Gender							
Male	217 (55.4)	177	81.6	40	18.4	0.9 (0.56 -1.5)	0.802
Female	175 (44.6)	141	80.6	34	19.4		
Residence							
Urban	319 (81.4)	258	80.9	61	19.1	0.9 (0.5-1.8)	0.796
Rural	73 (18.6)	60	82.2	13	17.8		
Marital Status							
Single	56 (14.3)	47	83.9	9	16.1		
Married	316 (80.6)	256	81	60	19	1.28	0.703^
Divorced	4 (1.0)	3	75	1	25		
Widowed	16 (4.1)	12	75	4	25		
Education							
Illiterate	72 (18.4)	58	80.6	14	19.4	0.7 (0.4-1.9)	
Read & write	78 (19.9)	61	78.2	17	21.8	1 (0.4-2.7)	
Primary education	42 (10.7)	34	81	8	19	1.4 (0.5-3.8)	0.956^
Preparatory education	48 (12.2)	41	85.4	7	14.6	1.1 (0.5-2.2)	
Secondary Education	137 (34.9)	112	81.8	25	25.9	1 (0.2-3.9)	
University education	15 (3.8)	12	80	3	20	1	
Occupation							
Health care worker	2 (0.5)	2	100	0	0		
Employee	13 (3.3)	10	76.9	3	23.1		
Manual worker	24 (6.1)	20	83.3	4	16.7		
Farmer	67 (17.1)	56	83.6	11	16.4	1.801	0.996^
Housewife	165 (42.1)	132	80	33	20		
Trader	29 (7.4)	24	82.8	5	17.2		
Butcher	2 (0.5)	2	100	0	0		
Others	28 (7.1)	22	84.6	6	15.4		
Not working	62 (15.8)	50	80.6	12	19.4		
Smoking							
No	299 (76.3)	260	87	39	13	4 (2.3-6.9)	< 0.001*
Yes	93 (23.7)	58	62.4	35	37.6		
BMI							
<18 Under weight	1 (0.3)	0	0	1	100	0.4 (0.03-7.4)	
18- Normal weight	133 (33.9)	121	91	12	9	4.4 (2.1-9.5)	< 0.001*^
25- Over weight	180 (45.9)	143	79.4	37	20.6	1.7 (1.1-3.4)	
30+ Obese	78 (19.9)	54	69.2	24	30.8		

Table 4: Impact of pretreatment FBG, fasting blood insulin and HOMA-IR on EVR of chronic HCV patients

Variable	Total No. (%)	EVR (n=392)				95% CI	P
		Responders (n=318)		Non-Responders (n=74)			
		No.	%	No.	%		
Pretreatment Fasting Blood Glucose							
Below normal (50 - <70 mg/dl)	4 (1.0)	4	100	0	0	(0.1-7.7) 0.84	0.034*^
Normal (70-110 mg/dl)	362 (92.3)	298	82.3	64	17.7	2.5 (0.2-25.7)	
Prediabetics (111-130 mg/dl)	26 (6.6)	16	61.5	10	38.5		
Mean±SD !		90.3±11.3		98.2±13.4			
Median (Range)!		88 (53-130)		95.5 (72-130)		z= -5.151	< 0.001*
Q1; Q3		83; 96		90; 103.5			
Pretreatment Fasting blood Insulin							
Below normal (<5 ulUnit/ml)	15 (3.8)	14	93.3	1	6.7		0.316^
Normal (5-9 ulUnit/ml)	203 (51.8)	167	82.3	36	17.7	1.2 (0.1-10)	
Above normal (≥10 ulUnit/ml)	174 (44.4)	137	78.7	37	21.3	0.2 (0.03-1.7)	
Mean±SD !		15.3±27		11.5±8.2			
Median (Range)!		9.1 (3-270)		9.2 (4.8-58)		z= -2.168	0.030*
Q1, Q3		7, 12		7.8, 13.9			
Pretreatment HOMA-IR							
No ≤2.18	151 (38.5)	141	93.4	10	6.6	4.6 (2.3-9.5)*	< 0.001*
Yes >2.18	241 (61.5)	177	73.4	64	26.6		
Mean±SD !		3.46±5.9		3.1±2.3			
Median (Range)!		2.1 (0.57-51.7)		2.42 (1-19.2)		z= -3.71	< 0.001*
Q1, Q3		1.56, 2.8		2.1, 3.33			

Table 5: The effect of treatment of chronic HCV by a combination of pegylated interferon plus ribavirin on glucose metabolism and Insulin resistance

Variable	Treatment Phase				95% CI	P
	Pretreatment		12 week			
	No.	%	No.	%		
Fasting blood glucose						
Below normal (50 - <70 mg/dl)	4	1	16	4	0.6 (0.3-1.4)	< 0.0001*^
Normal (70-110 mg/dl)	362	92.37	369	94.23		
Prediabetics (111-130 mg/dl)	26	6.63	7	1.77		
Mean±SD !	91.8±12.1		83±10.1			
Median (Range)	89 (53-130)		81 (60-126)		z= -12.416	< 0.0001*
Q1, Q3	84, 97		75.2, 90			
Fasting blood Insulin						
Below normal (<5 ulUnit/ml)	15	3.83	4	1	8.4 (4.1-17.1)	< 0.0001*^
Normal (5-9 ulUnit/ml)	220	56.12	302	57.9		
Above normal (>=10 ulUnit/ml)	157	40.05	86	21.94		
Mean±SD !	14.8±24.5		10.5±13.8			
Median (Range)	9.2 (3-270)		7.4 (4.5130)		z= -10.27	< 0.0001*
Q1; Q3	7.1; 12.2		5.9; 9.6			
HOMA-IR						
No ≤2.18	151	38.5	341	87	0.02 (0.01-0.04)	< 0.0001*
Yes > 2.18	241	61.5	51	13		
Mean±SD !	3.38±5.4		2.18±3			
Median (Range)	2.15 (0.57-51.7)		1.58 (0.86-27.1)		z= -13.45	< 0.0001*
Q1, Q3	1.62, 2.91		1.25, 1.85			

* P value based on Mont Carlo exact test
* P < 0.05 (significant)
Z: Mann Whitney test for two independent groups

Table 6: Stepwise multiple logistic regression analyses for factors affecting response to chronic HCV therapy

Predictors	B	S.E.	Sig.	Exp(B)	95.0% C.I. for EXP(B)	
					Lower	Upper
HOMA-IR<2	1.629	0.358	0.000	5.098	2.663	10.290
FBG (pre-treatment)	-0.041	0.012	0.000	0.960	0.938	0.982
Viral load			0.024			
Low	1.298	0.438	0.003	3.662	1.552	8.640
Intermediate	0.673	0.331	0.042	1.960	1.023	3.752
Non smoker	1.401	0.309	0.000	4.060	2.217	7.436
BMI			0.028			
Normal	1.393	0.462	0.003	4.027	1.629	9.954
Overweight	0.590	0.354	0.096	1.804	0.901	3.612
Constant	4.340	10216.368	1.000	76.675		
P value for the model	0.000					
Classification accuracy	80.6%					

CONCLUSION & RECOMMENDATIONS

- Both host-related variables including BMI, smoking, and metabolic state of IR and viral factors in terms of high viral load are involved in the early treatment failure.
- Chronic HCV patient with no IR responded more rapidly and more efficiently by achieving apparent early virologic responses than those having low insulin sensitivity state.
- Further studies using randomized controlled trial for assessing early virologic response in patients with/without insulin resistance treated for 16–18 versus 48 weeks are needed.
- Treatment regimen of 48 weeks for early responders could be shortened to only 16–18 weeks without compromising the outcome, thus avoiding side effects of unnecessary drug and saving unaffordable costs.
- Strategies to reverse or improve insulin resistance state before treatment initiation may have a positive effect on early and sustained viral kinetics in response to HCV therapy.
- Pre-treatment assessment of insulin using HOMA-IR is a cost effective tool, does not need a laborious methods to estimate, and is a potentially modifiable factor that could be improve thus it may be used as a determinant for regimen optimization and individualization in CHC patients.

LIMITATIONS OF THE STUDY

- Basing all findings on dual anti-HCV therapy, since access to novel treatments is limited in low resource countries including Egypt.
- Lack of determination of the infecting HCV genotype and the IL28B polymorphism, two important factors that could affect the treatment outcome.