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DOES VISCERAL ADIPOSITY INFLUENCE THE STANDARD OF CARE RESPONSE FOR HEPATITIS C PATIENTS?

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ABSTRACT

Background: A considerable amount of evidence showed how metabolic factors may influence the natural history of patients with chronic hepatitis C and affect the outcome of antiviral therapies. Aim: To evaluate the clinical significance of visceral adiposity index (VAI) as a new predictor of early and sustained virological response (SVR) in hepatitis C patients. Materials and Methods: A total of 50 hepatitis C virus infected patients under treatment with pegylated interferon and ribavirin and who had a baseline serum lipid profile were included in this prospective study. Results of lipoprotein profiles and clinical data, including body mass index and waist circumference, were compared between patients with a sustained virological response and non-SVR or a non-virological response (NVR) and virological responses other than NVR (non-NVR). In addition, significant predictive factors independently associated with virological response to peg-IFNα-2b plus RBV were determined by statistical analysis. Results: End of treatment complete response was seen in 56% (n=28) and whereas 26% (n=13) were breakthroughers. SVR was seen in 40% (n=20) patients giving 60% failure response. The basal VAI was low in SVR (mean $\pm$ SD = 1.27 $\pm$ 0.7) in comparison to the failure group (1.7 $\pm$ 0.8) and tend to be not markedly elevated at the 48 week when compared with the failure group (1.6 $\pm$ 56 and 2.22 $\pm$ 0.71, respectively).

Conclusion: Pre-treatment and on-treatment VAI can predict response to treatment and SVR that can help in individualizing treatment and patient selection and optimize treatment outcomes.

Keywords: Visceral adiposity index, Hepatitis C, Standard care response.

Contribution/ Originality

This study is one of very few studies which have investigated the value of the VAI as a new tool for response predictability pre-therapy and on-therapy. The paper's primary contribution is

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finding that how simple clinical and laboratory parameters (weight, WC, BMI, triglyceride, and HDL) can form a good predictor tool in selecting hepatitis C infected candidates for therapy who will benefit from it by predicting the responders. This study documents the reliability and predictability of VAI to response in hepatitis C patients.

1. INTRODUCTION

Hepatitis C virus (HCV) infection is a major health problem worldwide, affecting more than 170 million people [1]. HCV infection is a common cause of chronic liver disease, which may progress to hepatocellular carcinoma, and it is the most common indication of liver transplantation [2]. Current treatment is based on the association between pegylated interferon-α (PEG-IFN- α) and ribavirin (RBV). This treatment is effective in about 55% of patients [3, 4]. Treatment outcome has been shown to be influenced by viral factors such as the HCV RNA baseline or HCV genotype [5], as well as by host factors such as obesity, cirrhosis, ethnic background, or fibrosis [6].

The World Health Organization defines obesity as an abnormal or excessive fat accumulation in adipose tissue, to the extent that health is impaired [7]. Obesity is major public health issue with a rapidly increasing prevalence [8]. Obesity, genetic susceptibility, aging, and male sex were found to be associated with increased visceral fat accumulation [9]. Despite having lower average body mass index (BMI) than whites, Asian women have a higher degree of central adiposity for a given BMI [10], which confers an increased risk for metabolic syndrome, type 2 diabetes, and cardiovascular diseases [11], [12]. In particular, visceral adiposity has been reported to play a key role in these diseases compared with other measurements of regional or generalized obesity [13].

Visceral adipose tissue is believed to secrete a variety of substances that regulate the metabolism and participating in the pathogenesis of liver damage. Metabolic factors have been associated with liver damage in patients with HCV especially genotype 1. Amato, et al. [14] demonstrated that in genotype 1 HCV patients, higher visceral adiposity index (VAI) score is independently associated with both steatosis and necroinflammatory activity and has a direct correlation with viral load. The whole body magnetic resonance imaging (MRI) is the gold standard technique to accurately measure visceral adiposity [15]. Waist circumference (WC) as a measure of visceral adiposity may be less reliable in older persons [16]. BMI is considered a poor indicator of cardiovascular risk than WC across ethnicities, suggesting that BMI may not be a very good measure of visceral adiposity [17]. In the light of limitations and lack of exciting methods and the recognition that more reliable measure of visceral adiposity are needed. Amato, et al. [14] proposed the modification of Model Of Adipose Distribution (MOAD). To correct MOAD for fat function, triglyceride and High density lipoprotein (HDL) levels were introduced in the formula. This was defined as VAI:

$$Males: VAI = \left(\frac{WC}{39.68 + (1.88\ X\ BMI)}\right) X \left(\frac{TG}{1.03}\right) X \left(\frac{1.31}{HDL}\right)$$

$$Females: VAI = \left(\frac{WC}{36.58 + (1.89\ X\ BMI)}\right) X \left(\frac{TG}{0.81}\right) X \left(\frac{1.52}{HDL}\right)$$

2. MATERIALS AND METHODS

This observational prospective study was carried out at the internal medicine, faculty of medicine, Zagazig University and Alahrar Hospital, Zagazig from June 2012 till March 2014. This study protocol was conducted in accordance with the provisions of the Declaration of Helsinki and Good Clinical Practice guidelines and was approved by the Institutional Review Board of each participating facility. Informed consent was obtained from all patients. Eligible patients were previously untreated adults who had HCV RNA detectable in serum by PCR; who had undergone liver biopsy within one year before entry that was consistent with chronic hepatitis, and who had ALT values from normal (> 30 IU/L for men and 19 IU/L for women) to four times the normal, with the hematological and biochemical values within normal limits. Patients were excluded if they had decompensated cirrhosis; other causes of liver disease, seizure disorders, cardiovascular disease, hemoglobinopathies, thyroid disease, hemophilia, poorly controlled diabetes, autoimmune disease, previous organ transplant or if they were unable to use contraception.

All the patients fulfilling the inclusion criteria were treated according to the treatment protocol based on response-guided therapy [18]. Patients were treated with standard PEG-IFN- α and RBV therapy according to the American Association for the Study of the Liver Diseases (AASLD) guidelines [6]. Briefly, patients with chronic HCV infection received subcutaneous peg-IFNα-2b at a dose of 1.5 μg/kg once weekly, and oral RBV at a dose of 600–1000 mg twice daily, adjusted according to body weight (600 mg for weight of 60 kg or less, 800 mg for weight of 60–80 kg or less, and 1000 mg for weight above 80 kg) or peg-IFNα-2a at a dose of 180 μg/kg once weekly, and oral RBV at a dose of 1000–1200 mg twice daily, adjusted according to body weight (1000 mg for weight of 70 kg or less, 1200 mg for weight above 70 kg). The standard treatment duration lasted 48 weeks. Patients who discontinued treatment within 24 weeks of treatment for reasons other than virological failure were excluded. During treatment, patients were assessed as outpatients at weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and at 48, and then at 24 weeks after the end of the therapy. Liver biopsy specimens were reviewed using the METAVIR scoring system for staging of fibrosis and grading of necroinflammation activity [19]. The serum HCV RNA was assessed using a quantitative PCR assay (COBAS TaqMan HCV test, Roche Diagnostics). PCR was done at weeks 0, 12, 24 and 48. At each visit, blood cell counts and ALT were measured and recorded. VAI was assessed at basal time (before beginning of treatment), at weeks 24 and 48. Side effects were also recorded at each visit.

2.1. Classification of Response

Early virological response (EVR), defined as an undetectable PCR (complete EVR [cEVR]) or ≥2 log reduction of HCV-RNA at week 12 of treatment to the baseline viral level (but still PCR positive; partial EVR). An end of treatment complete response (EOTCR) was defined as undetectable HCV RNA by qualitative PCR at 48 weeks of the treatment. A sustained virological response (SVR) was defined as undetectable HCV RNA by a qualitative PCR test 6 months after stopping treatment in patients who had achieved EOTCR. Non-response (NR) was defined as a positive qualitative PCR at any time before or at 24 weeks of the treatment. Breakthrough was defined as a positive PCR between 24-48 weeks in those who had a negative PCR at 24 weeks of

the treatment. Relapse was defined as a positive PCR 6 months after stopping treatment in those who had a negative PCR at 48 weeks [6].

2.2. Anthropometric and Body Fat Assessment

The following anthropometric measurements were obtained: Weight was assessed by a balance-beam scale while the participant was wearing lightweight clothing. Standing height was assessed by a stadiometer. BMI was calculated by the Quetelet index: weight in kilograms/height in meters squared (kg/m^2) [20]. WC was measured by use of a metal tape measure at the maximum WC between the lower rib and the iliac crest. Participants were asked to stand with their weight equally distributed on both feet, with arms hanging at their sides and head facing straight ahead, relaxing their abdomen and breathing normally. The measurement was made at the end of a normal expiration to the nearest 0.1 cm. The measurement was taken twice and the final WC value used was the mean of the 2 or 4 recorded values.

2.3. Biochemical Tests

Blood chemistry analyses were performed in Alahrar laboratories of the National Health Service in Zagazig. After fasting for 12 h, venous blood was taken for estimation of blood sugars, complete liver function, and complete blood picture. Tests for triglyceride were performed on Hitachi Chemistry analyzers with Roche chemistry reagents; settings were as specified by the manufacturer. HDL cholesterol was determined by precipitation with phosphotungstic acid, Sigma Chemical Reagent for in vitro diagnosis. Glomerular Filtration Rate (GFR) was estimated from serum creatinine using the MDRD formula and was expressed as ml/min/1.73 m^2 [21]. VAI score was calculated as described [14, 22] using the following sex-specific equations, where TG is Triglycerides levels expressed in mmol/l and HDL is HDL-Cholesterol levels expressed in mmol/l:

$$Males{:}VAI = \left(\frac{WC}{39.68 + (1.88\,X\,BMI)}\right) \times \left(\frac{TG}{1.03}\right) \times \left(\frac{1.31}{HDL}\right)$$

$$Females{:}VAI = \left(\frac{WC}{36.58 + (1.89\,X\,BMI)}\right) \times \left(\frac{TG}{0.81}\right) \times \left(\frac{1.52}{HDL}\right)$$

2.4. Statistical Analysis

Statistical analysis was performed using SPSS version 15.0 (SPSS Inc, Chicago, IL). Data are expressed as mean $\pm$ SD, or geometric mean and 95% confidence interval (CI) for variables requiring logarithmic transformation. Statistical significance was defined as $P \leq 0.05$.

3. RESULTS

Response rates to standard PEG-IFN- α plus RBV therapy was studied over a 2 years period. A total of 50 patients were evaluated for the influence of potentially important factors on SVR. The mean age of patients was 32.3 $\pm$ 8.8 years, mean weight was 76.6 $\pm$ 8.84 kg, mean BMI was 52.82 $\pm$ 3.2 m^2/kg, and mean WC was 87.48 $\pm$ 9.3 cm. The histology at liver biopsy showed stage 1 fibrosis in 20% of patients, stage 2 fibrosis in 58% of patients, and stage 3 fibrosis in 22% of

patients. In the total of 50 patients, EOTCR was seen in 56% (n=28 patients (m/f=24/4)), whereas 18% (n=9 patients (m/f=6/3)) were NR, and whereas 26% (n=13 patients (m/f=11/2)) were breakthroughers (BT). SVR was seen in 40% (n=20 (m/f=16/4)) patients, 16% (n=8 male patients) were relapsers giving a relapse/non-response/break-through rate of 60%. The Baseline demographic and clinical characteristics of our studied patients are present in table 1. The effect of demographic and clinical characteristics on achieving EVR is given in Table 2.

Table-1. Baseline demographic and clinical characteristics of 50 treatment-naïve patients who underwent treatment for chronic hepatitis C and were included in the study.

	Mean ± SD (Number)	Range (Percentage)
Age (in years)	32.3 ± 8.8	20 – 57
Gender (M/F), n	(total 50) 41/9	82% – 18%
Height (m)	1.727 ± 0.075	1.55 – 1.84
Weight (Kg)	76.6 ± 8.84	62 – 99
BMI (m^2/Kg)	25.82 ± 3.2	19.2 – 34.13
WC (cm)	87.48 ± 9.3	70 – 106
TG (mmol/l)	1.144 ± 0.4681	0.462 – 2.22
HDL (mmol/l)	1.0782 ± 0.3296	0.4204 – 2.202
VAI	1.5712 ± 0.788	0.519 – 3.264
Hb	13.24 ± 0.64	12 – 14.4
ALT	43.24 ± 2.454	40 – 48
AST	43.6 ± 2.286	40 – 48
Albumin	4.22 + 0.216	4 – 4.6
Serum creatinine	1.22 + 0.19	0.8 – 2
Viral Load	1001080 ± 2380951.54	752.0 -- 15209850
Fibrosis (F1;F2;F3)	10/29/11	20% / 58% / 22%

Table-2. Comparison of demographic and clinical characteristics of subjects with EVR and NR to HCV therapy.

Variables	EVR	NR	P-value
	Mean ± SD (Number)	Mean ± SD (Number)	
Number of patients	41 (82%)	9 (18%)	
Age (in years)	32.2 ± 8.26 (20—50)	32.8 ± 11.6 (20—57)	0.878
Gender (M/F)	35/6	6/3	X^2=0.52
Height (m)	1.74 ± 0.071 (1.55—1.84)	1.68 ± 0.08 (1.55—1.82)	0.015
Weight (Kg) 0 weeks	77.15 ± 8.4 (62—97)	74.3 ± 10.9 (64—99)	0.581
BMI (m^2/Kg) 0 weeks	25.73 ± 3.3 (19.62—34.13)	26.3 ± 3 (22.1—30.12)	0.318
WC (cm) 0 weeks	87.7 ± 9.3 (70—105)	86.6 ± 9.84 (72—106)	0.906
TG (mmol/l) 0 weeks	1.09 ± 0.43 (0.46—2.19)	1.40 ± 0.581 (0.59—2.22)	0.275
HDL (mmol/l) 0 weeks	1.07 ± 0.33 (0.42—2.2)	1.098 ± 0.33 (0.73—1.63)	0.639
VAI 0 weeks	1.497 ± 0.76 (0.52—3.27)	1.91 ± 0.88 (0.89—3.127)	0.102
Fibrosis (F1;F2;F3)	(10; 22; 9)	(0; 7; 2)	0.594
Viral load	981975.3 ± 2605649 (725—15209850)	1088113.3 ± 874510 (50143—2345142)	0.009

Table-3. Comparison of demographic and clinical characteristics of subjects with virologic response to HCV therapy.

Variables	EVR	EOTCR	SVR	P-value
	Mean ± SD (Number)	Mean ± SD (Number)	Mean ± SD (Number)	
Age (in years)	32.2 ± 8.26 (20—50)	32.4 ± 7.181 (21—45)	32.3 ± 7.4 (22—45)	0.843
Gender (M/F)	35/6	24/4	16/4	
Height (m)	1.74 + 0.071 (1.55—1.84)	1.74 ± 0.07 (1.58—1.82)	1.73 + 0.07 (1.58—1.82)	0.520
Weight (Kg):0 weeks	77.15 ± 8.4 (62—97)	77.86 + 7.7 (65—95)	77.45 ± 8.31 (65—94)	0.872
				Continue

24 weeks	72.56 ± 8.49 (58—91)	72.97 ± 7.87 (58—86)	72.05 ± 8.19 (58—86)	0.828
48 weeks		72.4 ± 8.29 (60—87)	72.4 + 8.19 (60—87)	1
p-value: *P1	< 0.001	< 0.001	< 0.001	
*P2		< 0.001	< 0.001	
*P3		0.557	0.634	
BMI (m^2/Kg):				
0 weeks	25.73 ± 3.3 (19.62—34.1)	25.9 ± 3.04 (19.62—30)	25.97 + 3.15 (19.62—30)	0.651
24 weeks	23.98 ± 3.04 (17.5—31.2)	24.15 ± 2.85 (17.5—28)	24.13 ± 2.92 (17.9—27.94)	0.638
48 weeks		24.211 ± 2.924 (18.42—28.67)	24.19 ± 2.94 (19.62—28.67)	0.527
p-value: P1	< 0.001	< 0.001	< 0.001	
P2		< 0.001	< 0.001	
P3		0.782	0.765	
WC (cm): 0 weeks	87.7 ± 9.3 (70—105)	87.93 ± 7.97 (74—105)	87 ± 8.59 (74—105)	0.542
24 weeks	83.39 ± 9.2 (68—102)	83.5 ± 8.4 (70—102)	82 ± 8.33 (70—99)	0.555
48 weeks		84.61 ± 7.95 (72—100)	83.4 ± 8.08 (72—100)	0.441
p-value: P1	< 0.001	< 0.001	< 0.001	
P2		< 0.001	< 0.001	
P3		0.118	0.105	
TG (mmol/l):0 weeks	1.09 ± 0.43 (0.46—2.19)	1.11 ± 0.41 (0.46—2.1)	0.99 ± 0.37 (0.46—1.83)	0.124
24 weeks	1.38 ± 0.37 (0.57 – 2.27)	1.41 ± 0.3 (0.81—2.1)	1.33 ± 0.28 (0.8—1.88)	0.382
48 weeks		1.7 ± 0.37 (1.2—2.62)	1.6 ± 0.284 (1.22—2.08)	0.112
p-value: P1	< 0.001	< 0.001	< 0.001	
P2		< 0.001	< 0.001	
P3		< 0.001	0.001	
HDL (mmol/l):				
0 weeks	1.07 ± 0.33 (0.42—2.2)	1.1 ± 0.32 (0.5—2.2)	1.37 + 0.33 (0.67—2.2)	0.761
24 weeks	1.12 ± 0.29 (0.52—1.82)	1.15 ± 0.26 (0.75—1.81)	1.12 ± 0.23 (0.88—1.71)	0.576
48 weeks		1.38 ± 0.27 (0.86—1.97)	1.45 ± 0.25 (101—1.97)	0.202
p-value: P1	0.531	0.551	0.894	
P2		0.001	0.004	
P3		0.001	< 0.001	
VAI: 0 weeks	1.497 ± 0.76 (0.52—3.27)	1.46 ± 0.68 (0.67—3.26)	1.27 ± 0.66 (0.67—3.27)	0.212
24 weeks	1.78 ± 0.69 (0.49—3.45)	1.73 ± 0.59 (0.82—2.99)	1.671 ± 0.6 (0.82—2.99)	0.147
48 weeks		1.77 ± 0.7 (1.1—4.11)	1.6 ± 0.56 (1.04—3.521)	0.016
p-value: P1	0.008	0.046	0.014	
P2		0.035	0.022	
P3		0.757	0.628	
Fibrosis (F1;F2;F3)	(10; 22; 9)	(9; 15; 4)	(8 ; 10 ; 2)	
Viral load	981975.3 ± 2605649 (725—15209850)	708995.9 ± 2848877.9 (725—15209850)	917233.5 ± 3371588.6 (725—15209850)	

* P1= 0 week versus 24 week; P2= 0 week versus 48 week; and P3 = 24 week versus 48 week.

During the course of treatment and follow up of our patients, we found that there were high significant differences in the EVR group between the basal reading and 24 week reading for weight, BMI, WC, triglyceride, and VAI ($P < 0.05$); but no significant difference for HDL ($P > 0.05$). About the EOTCR, there were also high significant differences between the basal reading and 24 week reading for weight, BMI, WC, and triglyceride ($P \leq 0.001$, for all) and significant difference for VAI ($P < 0.05$), but no significant difference for HDL ($P > 0.05$). Also, About the SVR, there were also high significant differences between the basal reading and 24 week reading for weight, BMI, WC, and triglyceride ($P \leq 0.001$, for all) and significant difference for VAI ($P < 0.05$), but no significant difference for HDL ($P > 0.05$). By comparing the results between the three groups (EVR, EOTCR, and SVR), we found that there were no significant differences for all variables except there was significant difference between the EOTCR and SVR groups for VAI at 48 week ($P = 0.016$). The VAI was less in the SVR group in comparison to the EOTCR at 48 week (mean ± SD = 1.77 ± 0.7 and 1.6 ± 0.56, respectively).

Table-4. Comparison of demographic and clinical characteristics of subjects without virologic response to HCV therapy

	NR	Breakthrough	Relapse	P-value
	Mean ± SD (Number)	Mean ± SD (Number)	Mean ± SD (Number)	
Age(in years)	32.8 ± 11.6 (20—57)	31.9 ± 10.54 (20—50)	32.4 ± 7.13 (21—42)	0.869
Gender(M/F)	6/3	11/2	8/0	
Height (m)	1.68 ± 0.08 (1.55—1.8)	1.73 ± 0.09 (1.55—1.8)	1.77 ± 0.041 (1.7—1.82)	0.227
Weight (Kg)				
0 weeks	74.3 ± 10.9 (64—99)	75.6 ± 9.9 (62—97)	78.88 ± 6.22 (67—87)	0.375
24 weeks		71.7 ± 9.98 (58—91)	75.25 ± 6.9 (60—82)	0.762
48 weeks		68.92 ± 8.98 (56—86)	75.9 ± 7.3 (61—85)	0.469
p-value: *P1		0.048	0.019	
*P2		0.022	0.098	
*P3		0.317	0.747	
BMI (m^2/Kg)				
0 weeks	26.25 ± 3 (22.1—30.12)	25.4 ± 3.83 (20.68—34.13)	25.7 ± 2.94 (20.23—28.72)	0.636
24 weeks		23.6 ± 3.5 (20.1—31.2)	24.2 ± 2.9 (18.11—22)	0.718
48 weeks		23.2 ± 3.7 (19.2—31.2)	24.3 ± 3.08 (18.4—27.4)	0.996
p-value: P1		< 0.001	0.04	
P2		0.017	0.126	
P3		0.595	0.903	
WC (cm)				
0 weeks	86.6 ± 9.84 (72—106)	87.2 ± 12.03 (70—105)	90.25 ± 6.02 (80—100)	0.796
24 weeks		83.16 ± 11.1 (68—98)	87.25 ± 7.9 (75—102)	0.965
48 weeks		82.9 ± 12.43 (67.5—100)	87.6 ± 7.19 (76—98)	0.874
p-value P1		< 0.001	0.009	
P2		0.150	0.046	
P3		0.921	0.778	
TG (mmol/l)	1.4 ± 0.581 (0.59—2.2)	1.04 ± 0.48 (0.54—2.2)	1.41 ± 0.36 (0.93—2.07)	0.503
0 weeks				
24 weeks		1.32 ± 0.51 (0.57—2.3)	1.61 ± 0.25 (1.232—2.1)	0.805
48 weeks		2.16 ± 0.7 (1.15—3.38)	1.94 ± 0.46 (1.19—2.62)	0.293
p-value: P1		0.005	0.03	
P2		< 0.001	0.01	
P3		0.002	0.032	
HDL(mmol/l)	1.1 ± 0.33 (0.73—1.6)	1.04 ± 0.38 (0.4—1.49)	0.98 ± 0.27 (0.5—1.29)	0.193
0 weeks				
24 weeks		1.05 ± 0.34 (0.52—1.56)	1.2 ± 0.34 (0.75—1.8)	0.710
48 weeks		1.32 ± 0.36 (0.86—1.87)	1.21 ± 0.237 (0.86—1.55)	0.170
p-value: P1		0.864	0.193	
P2		0.057	0.107	
P3		0.059	0.938	
VAI	1.911 ± 0.88 (0.891—3.127)	1.58 ± 0.933 (0.519—3.174)	1.94 ± 0.46 (1.5—2.908)	
0 weeks				0.434
24 weeks		1.88 ± 0.9 (0.49—3.45)	1.86 ± 0.572 (1.04—2.77)	0.649
48 weeks		2.25 ± 0.64 (1.23—3.8)	2.19 ± 0.86 (1.416—4.105)	0.644
p-value: P1		0.079	0.725	
P2		0.021	0.520	
P3		0.137	0.181	
Fibrosis (F1;F2;F3)	(0; 7; 2)	(1;7;5)	(1 ; 5 ; 2)	0.446
Viral load	1088113 ± 874511 (50143—2345142)	1569930.7 ± 1954929 (4414—5972007)	188402 ± 128090.2 (30985—355502)	0.29

* P1= 0 week versus 24 week; P2= 0 week versus 48 week; and P3 = 24 week versus 48 week.

Also, we found that there were significant differences in the Breakthrough group between the basal reading and 24 week reading for weight, BMI, WC, and triglyceride ($P < 0.05$); but no significant difference for HDL and VAI ($P > 0.05$). By comparing the results of basal reading and 48 week for weight, BMI, triglyceride, and VAI; we found that there were significant differences between these variables ($P < 0.05$); but no significant difference for WC and HDL ($P > 0.05$). By comparing the results of 24 week reading and 48 week for weight, BMI, WC, HDL, and VAI; we found that there were no significant differences between these variables ($P > 0.05$); but there was significant difference for triglyceride ($P < 0.05$). About the Relapse group, there were also significant differences between the basal reading and 24 week reading for weight, BMI, WC, and triglyceride ($P < 0.05$) and no significant difference for HDL and VAI ($P > 0.05$). By comparing

the results of basal reading and 48 week for weight, BMI, HDL, and VAI; we found that there were no significant differences between these variables (P > 0.05); but there were significant difference for WC and triglyceride (P < 0.05). By comparing the results of 24 week reading and 48 week for weight, BMI, WC, HDL, and VAI; we found that there were no significant differences between these variables (P > 0.05); but there was significant difference for triglyceride (P < 0.05). By comparing the results between the three groups (NR, Breakthrough, and Relapse), we found that there were no significant differences.

Table-5. Comparison of demographic and clinical characteristics of subjects with SVR and with failure of virologic response to HCV therapy.

	Failure group	SVR	P-value
Age (in years)	32.3 ± 9.8 (20—57)	32.3 ± 7.4 (22—45)	0.824
Gender (M/F)	30 (25/5)	20 (16/4)	X^2=0.09
Height (m)	1.73 ± 0.079 (1.55—1.84)	1.73 ± 0.07 (1.58—1.82)	0.566
Weight (Kg): 0 weeks	76.1 ± 9.3 (62—99)	77.45 ± 8.31 (65—94)	0.530
24 weeks	73.05 ± 8.94 (58—91)	72.05 ± 8.19 (58—86)	0.252
48 weeks	71.6 ± 8.88 (56—86)	72.4 ± 8.19 (60—87)	0.692
p-value: *P1	0.004	< 0.001	
*P2	0.006	< 0.001	
* P3	0.420	0.634	
BMI (m^2/Kg):0 weeks	25.7 ± 3.28 (20.23—34.13)	25.97 ± 3.15 (19.62—30)	0.793
24 weeks	23.83 ± 3.22 (18.11—31.22)	24.13 ± 2.92 (17.9—27.94)	0.892
48 weeks	23.6 ± 3.5 (18.42—31.22)	24.19 ± 2.94 (19.62—28.67)	0.492
p-value: P1	< 0.001	< 0.001	
P2	0.004	< 0.001	
P3	0.728	0.765	
WC (cm): 0 weeks	87.8 ± 9.9 (70—106)	87 ± 8.59 (74—105)	0.244
24 weeks	84.7 ± 9.98 (68—102)	82 ± 8.33 (70—99)	0.447
48 weeks	84.7 ± 10.8 (67.5—100)	83.4 ± 8.08 (72—100)	0.749
p-value: P1	< 0.001	< 0.001	
P2	0.05	< 0.001	
P3	0.989	0.105	
TG (mmol/l): 0 weeks	1.25 ± 0.504 (0.54—2.22)	0.991 ± 0.37 (0.462—1.83)	0.018
24 weeks	1.43 ± 0.44 (0.565—2.27)	1.33 ± 0.28 (0.8—1.88)	0.162
48 weeks	2.08 ± 0.62 (1.15—3.38)	1.603 ± 0.284 (1.22—2.08)	0.017
p-value: P1	< 0.001	< 0.001	
P2	< 0.001	< 0.001	
P3	< 0.001	0.001	
HDL (mmol/l)0 weeks	1.039 ± 0.329 (0.42—1.63)	1.37 ± 0.33 (0.67—2.2)	0.650
24 weeks	1.105 ± 0.34 (0.518—1.813)	1.123 ± 0.23 (0.88—1.71)	0.604
48 weeks	1.28 ± 0.313 (0.86—1.9)	1.45 ± 0.25 (101—1.97)	0.248
p-value: P1	0.212	0.894	
P2	0.011	0.004	
P3	0.085	< 0.001	
VAI: 0 weeks	1.72 ± 0.81 (0.519—3.174)	1.267 ± 0.663 (0.665—3.264)	0.043
24 weeks	1.87 ± 0.77 (0.489—3.452)	1.671 ± 0.6 (0.822—2.994)	0.191
48 weeks	2.22 ± 0.71 (1.23—4.105)	1.6 ± 0.56 (1.036—3.521)	0.045
p-value: P1	0.239	0.014	
P2	0.024	0.022	
P3	0.042	0.628	
Fibrosis (F1;F2;F3)	(2 ; 19 ; 9)	(8 ; 10 ; 2)	0.163
Viral load 0 weeks	1056977.8 + 1456953.1 (4414—5972007)	917233.5 + 3371588.6 (725—15209850)	0.830

* P1= 0 week versus 24 week; P2= 0 week versus 48 week; and P3 = 24 week versus 48 week.

We gathered the whole patients who did not achieve the target response of treatment (NR, Breakthrough, and relapsers) in a one group called failure group. By comparing the result of this group with SVR group, we found that there were no significant differences between the basal reading of the two groups for age, height, weight, BMI, WC, HDL, fibrosis stage, and viral load (P > 0.05); but there were significant difference for triglyceride and VAI (P < 0.05). By comparing the

results of 24 week reading of the two groups for weight, BMI, WC, triglyceride, HDL, and VAI; we found that there were no significant differences between these variables ($P > 0.05$). By comparing the results of 48 week reading of the two groups for weight, BMI, WC, and HDL; we found that there were no significant differences between these variables ($P > 0.05$); but there was significant difference for triglyceride and VAI ($P < 0.05$). About the failure group, there were high significant differences between the basal reading and 24 week reading for weight, BMI, WC, and triglyceride ($P < 0.05$) and no significant difference for HDL and VAI ($P > 0.05$). By comparing the results of basal reading and 48 week for weight, BMI, WC, triglyceride, HDL, and VAI; we found that there were significant differences between these variables ($P < 0.05$). By comparing the results of 24 week reading and 48 week for weight, BMI, WC, and HDL; we found that there were no significant differences between these variables ($P > 0.05$); but there was significant difference for triglyceride and VAI ($P < 0.05$). About the SVR group, there were high significant differences between the basal reading and 24 week reading for weight, BMI, WC, triglyceride, and VAI ($P < 0.05$) and no significant difference for HDL ($P > 0.05$). By comparing the results of basal reading and 48 week for weight, BMI, WC, triglyceride, HDL, and VAI; we found that there were high significant differences between these variables ($P < 0.05$). By comparing the results of 24 week reading and 48 week for weight, BMI, WC, and VAI; we found that there were no significant differences between these variables ($P > 0.05$); but there was high significant difference for triglyceride and HDL ($P < 0.05$).

4. DISCUSSION

Currently, the combination of PEG-IFN- α and RBV is the treatment of choice for patients with chronic hepatitis C. Unfortunately this treatment is very challenging. Antiviral treatment is very expensive, often has many side effects, and lasts too long up to 48 weeks for genotype 1 and 4 with a limited SVR rate (50-60%). Moreover, there is a group of HCV infected patients that are not good candidates for PEG-IFN-α and RBV due to systemic diseases. Although there are new therapies in development, it's likely that PEG-IFN-α/RBV will remain the mainstay of HCV treatment for the near future. Probably PEG-IFN-α and RBV will continue to be administered together with protease or polymerase inhibitors of HCV replication. Thus, due to an overall low response to standard HCV therapy, it would be important to predict during the pre-treatment evaluation period those patients who will respond treatment as well as those who will not. In addition, it would also be important to help decide for whom to start treatment and when to stop the therapy. Predicting SVR to HCV treatment before the beginning of therapy is possible by different well known host and virus related factors as BMI, pre-treatment HCV RNA level, and doses of interferon. Yet none of these have been able to accurately and consistently predict the patients who will respond to interferon [23]. So we studied the predictability of visceral adiposity as a pre-treatment and during treatment predictor for SVR in HCV.A low response to treatment is generally associated with male gender; females are considered to be better responders to interferon based treatments [24]. It was not observed in this study. The difference was not statistically significant between the failure group and the SVR group ($P>0.05$). Age is also considered to be a weak predictor of response [25]. Age below 40 years is associated with better response, again not seen in

this study. SVR were between 22-45 years of age and the differences between them and the failure patients were not statistically significant (P>0.05). A low baseline body weight is predictor of a SVR and increased body weight has been shown to be associated with low SVR in genotypes 1, 2 and 3 [25]. This was found to be statistically not significant in this cohort of patients as SVR group when compared to failure group had nearby weights (P > 0.05) and also EVR group when compared to NR group had nearby weights (P > 0.05). The effect of weight is limited as a predictor of response because both responder and non-responder had a significant change of weight during treatment. There were weight reductions in both. Hany, et al. [26] found that spontaneous weight loss at 4 and 12 weeks of CHC therapy was associated with improved EVR and weight loss at 4 weeks was an independent predictor of EVR. However, weight loss at 4 and 12 weeks of therapy was not a predictor of SVR. SVR is constantly higher in patients with low HCV RNA levels regardless of genotype. Manns [4] in an original study that compared peg INF/RBV with INF/RBV showed that those with a viral load lower than 2×10^6 copies/ml had a SVR of 78% compared with a SVR of 42 in those with a viral load higher than 2×10^6 copies/ml. Nowadays there is a debate about the real definition of a low viral load and who will be candidates for a reduced duration of treatment based on the fourth week response. In our study, there was no significant difference in the viral load of SVR and the failure group as a whole (P>0.05). But early at 12 week response, there was significant difference between the EVR and NR (P < 0.05). Iacobellis, et al. [27] found that SVR in patients with advanced fibrosis (Metavir F3/F4) was achieved in 8% - 44%, depending on the treatment adopted and the intensity of liver dysfunction. The same study has shown that in patients with mild disease (Metavir F0/F1) the SVR could reach 74% even in genotype 1 patients. In our study, we did not studied patients with F0/F4. According to our patients there was no significant difference between the EVR and NR at 12 week (P= 0.594) (In EVR group, F1 / F2 / F3 comprise 20% / 44% / 18% and NR group, F1 / F2 / F3 comprise 0% / 14% / 4%; respectively). At 48 week, also there was no significant difference between the SVR and the failure group (P=0.163) (In SVR group, F1 / F2 / F3 comprise 4% / 38% / 18% and NR group, F1 / F2 / F3 comprise 16% / 20% / 4%; respectively). Numerous techniques have been developed to assess visceral fat. The most clinically expedient are those that can be performed quickly and bedside without extensive technical training. However, visceral adipose tissue (VAT) is only an indirect measure when using these approaches. Only CT and MRI can provide direct measures of cross-sectional areas or volumetric measures of VAT [28]. In our study we depend on these simple, quick, and bedside indirect methods of VAT measurement. Although the VAI was modelled on a Caucasian population, several studies confirm the validity of its use with other races. For example, in a large case-control study, a high VAI is associated with elevated risk of CHD in Chinese men and women [29]. Moreover, in a large cross-sectional study on 1,764 primary care patients, appropriate stratified-for-age cut-offs were identified that were able to identify a supposed adipose tissue dysfunction (ATD) [30] (Table 6). These cut-offs have been more or less confirmed in a recent study [31] in which ATD was directly investigated through a large panel of proinflammatory adipokines.

Table-6. Age-stratified cut-off points of VAI for identification of adipose tissue dysfunction (ATD).

	ATD absent	Mild ATD	Moderate ATD	Severe ATD
Age < 30 years	≤ 2.52	2.53—2.58	2.59—2.73	> 2.73
≥ 30 < 42 years	≤ 2.23	2.24—2.53	2.54—3.12	>3.12
≥ 42 < 52 years	≤ 1.92	1.93—2.16	2.17—2.77	>2.77
≥ 52 < 66 years	≤ 1.93	1.94—2.32	2.32—3.25	> 3.25
> 66 years	≤ 2	2.01—2.41	2.42—3.17	> 3.17

In the field of hepatology, the VAI has been investigated in several studies in patients with NAFLD, with the main objective of identifying a clinical marker predictive of evolution towards necroinflammatory injury and fibrosis [32-37]. In this respect, there are contrasting results between the various studies, since according to some authors the VAI accurately predicted progressive liver histology more accurately than other validated noninvasive scores and identified patients with NAFLD at increased CVD risk [32, 34, 37], while according to other authors [32, 33, 35, 36] the VAI is not more powerful than other anthropometric indices in discriminating steatosis from steatohepatitis. Another opinion, these discrepancies are attributable to differences between the patients enrolled, especially concerning the variables included in the VAI. This especially applies to the mean of triglyceride levels in the various populations [22]. Moreover, an interesting result was obtained from a study [38] on patients with chronic HCV due to genotype 1. In these patients only older age, high VAI, and fibrosis were independently associated with moderate-severe necroinflammatory activity by a logistic regression analysis; a higher VAI also has a direct correlation with viral load. Probably, ATD (indirectly expressed by the VAI) by way of free fatty acid and proinflammatory cytokine secretion could directly participate in both liver steatosis and induction of inflammation. In this complex interplay between the liver and adipose tissue, HCV could have an important role. It is possible not only that adipose tissue could provide fatty substrates and a proinflammatory status, favouring HCV replication, but also that HCV could interfere with adipocyte function indirectly by increasing the inflammatory status and directly by colonizing adipocytes or immune cells infiltrating adipose tissue [39, 40].

In our study, there was no significant difference in VAI between the EVR group and the NR group at the basal reading before the start of treatment (P= 0.102). By comparison of the result of VAI of the failure group and the SVR at various times of the study, we found that there was significant difference between the two groups at basal reading (P= 0.043) and at the end of the study (48 week) (P= 0.045). But there was no significant difference between the two groups at 24 weeks (P= 0.191). By comparison of the VAI of the failure group at various times of the study, we found that there was no significant difference between the basal reading and the 24 week reading (P= 0.239), but there was significant difference between the basal reading and the 48 week reading (P= 0.024) and the 24 week reading and the 48 week reading (P= 0.042). By comparison of the VAI of the SVR group at various times of the study, we found that there was significant difference between the basal reading and the 24 week reading (P= 0.014) and between the basal reading and the 48 week reading (P= 0.022), but there was no significant difference between the 24 week reading and the 48 week reading (P= 0.628).

By comparison of VAI of subjects with virologic response to HCV therapy during various stages of the study, we will notice that there was no significant difference between the three groups

(EVR, EOTCR, SVR) by comparing the basal readings (P= 0.212) and also by comparing the 24 week readings (P= 0.147) but there was significant difference by comparing the 48 week between the EOTCR and SVR (P = 0.016). Inside each group, there was high significant difference between the basal reading and 24 week reading in EVR (P = 0.008), the basal reading and 24 week in EOTCR (P = 0.046), the basal reading and 48 week reading in EOTCR (P = 0.035), the basal reading and 24 week reading in SVR (P = 0.014), and basal reading and 48 week reading in SVR (P = 0.022). There were no significant difference between the 24 week and 48 week readings in EOTCR (P = 0.757) and the 24 week and 48 week readings in SVR (P = 0.628). From the previous results, we will note that there were significant changes in VAI from the start of therapy to the 24 week in the responder patients which may result in continuation of response to the end of therapy.

By comparison of VAI of subjects with virologic without response to HCV therapy during various stages of the study, we will notice that there was no significant difference between the three groups (NR, breakthrough, Relapse) by comparing the basal readings (P= 0.434) and also by comparing the 24 week readings (P= 0.649) between the breakthrough and relapse groups and also by comparing the 48 week readings (P= 0.644) between the breakthrough and relapse groups. Inside each group, there was significant difference between the basal reading and 24 week reading in breakthrough (P = 0.079), the basal reading and 48 week reading in breakthrough (P = 0.021). There were no significant difference between the 24 week and 48 week readings in breakthrough (P = 0.137) and the basal reading and 24 week readings in relapse group (P = 0.725), the basal reading and 48 week readings in relapse group (P = 0.520), and the 24 week and 48 week readings in relapse group (P = 0.181). From the previous results, we will note that there were significant changes in VAI from the start of therapy to the 24 week in the breakthrough group but no in the relapse and the VAI reading in both breakthrough and relapse groups tend to be high at 48 week which may result in loss of response to the end of therapy. By analyzing the previous results, we will note that the VAI in SVR group has mild elevation during the first 24 weeks of the study course staring from low normal values and then nearly no change during the following weeks (1.27 $\pm$ 0.7; 1.67 $\pm$ 0.6; 1.6 $\pm$ 0.56). The same changes occur in the EVR and EOTCR. In the NR group the starting (basal) VAI was high in comparison to that of SVR (1.9 $\pm$ 0.9 and 1.27 $\pm$ 0.7, respectively). The same was noticed in the breakthrough and relapse group. Also in contrast to the SVR, there were marked and continued elevations of the VAI during the study course in the two groups (1.58 $\pm$ 0.9; 1.88 $\pm$ 0.9; 2.25 $\pm$ 0.6 and 1.94 $\pm$ 0.5; 1.86 $\pm$ 0.6; 2.19 $\pm$ 0.9, respectively). By doing ROC curve analysis, we can obtain the following table (Table 7) for various cutoff values of VAI during the different stages of treatment course which can predict the response to treatment and predict the SVR patients.

Table-7. Cut-off points of VAI for identification of the standard of care treatment response.

	Cutoff	Sensitivity	Specificity	+ve predictivity	-ve predictivity	Accuracy
At 0 week	0.735	97.4%	25%	80.43%	75%	80%
At 24 week	0.99	92.1%	100%	100%	50%	92.68%
At 48 week	1.73	87.5%	60%	46.67%	92.3%	67.86

5. CONCLUSION

In conclusion, this work presents a simple and reliable pre-therapy tool to identify unlikely and anticipated responders to treatment with Peg-IFN plus RBV in HCV-infected patients, including clinical and laboratory parameters. Three of these parameters were routinely used many years ago (weight, BMI, WC) and the other has been recently incorporated into clinical practice (triglyceride, HDL, VAI). This tool may be used to select HCV-infected candidates for immediate and, more importantly, deferred therapy against HCV and it is able to identify as anticipated or unlikely responders in respectable ratio of patients.

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