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High BMI Is an Important Predictive Factor for Non-Response in Chronic Hepatitis C Patients Treated with Peginterferon and Ribavirin

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Abstract

Introduction: It is known that overweight/obesity (BMI > 25 kg/m2) is as an independent factor for hepatic steatosis in patients with chronic hepatitis C (CHC) while steatosis accelerates the progression of hepatic fibrosis. It is of interest to assess among other host and viral factors, the impact of overweight/obesity as a modifiable factor at *baseline* on treatment response.

Patients and methods: The study enrolled 151 patients diagnosed with CHC in the Service of Gastrohepatology, UHC "Mother Tereza". All the patients were treated with peginterferon-alfa and ribavirin according the protocols. Each patient was assessed for host and viral factors at *baseline* like age, sex, HCVRNA, number of thrombocytes (PLT), weight, height and on-treatment factors (HCVRNA negative at week 4 or RVR). Success of treatment (SVR) was considered undetectable value of HCVRNA during treatment and 24 weeks after the end of it. To assess the impact of BMI on SVR and the predictive *cut-off* value, we compared the SVR rates between groups using *cut-off* values of BMI from 25 kg/m^2 by Chi–square and binary logistic regression tests and to assess the importance of BMI among other factors, multi logistic regression test. Values of $p \leq 0.05$ were considered statistically significant.

Results: From all patients 61.5% had SVR. Statistically significant results were achieved for the *cut-off* value of BMI 27 kg/m^2. Patients with BMI≥27 kg/m^2 were 2.6 times more likely than patients with BMI<27kg/m2 not to achieve SVR (OD: 2.58, CI95%:1.59-5.67). Also in the multivariable analysis, where we assessed the impact on SVR of BMI, age, sex, *baseline* HCVRNA, number of PLT and RVR, BMI≥27kg/m^2 resulted an important negative predictive factor for SVR (OD:4.16,Cl95%:1.08-5.84).

Conclusion: Overweight/obesity negatively influences treatment response in CHC patients. BMI ≥ 27kg/m2 is an independent negative predictive factor for SVR during treatment of these patients with standard scheme.

Key words: BMI, chronic hepatitis C, treatment, peginterferon/ribavirin.

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INTRODUCTION

Adipose tissue is generally considered as connective tissue without specific anatomy and is organized towards a large organ with specific vascular and nerve supply, complex cytology and high physiological plasticity (1). Obese patients have increased number of visceral adipocytes which will secrete pro inflammatory chemokines and cytokines causing systemic inflammation and increased secretion of free fatty acids (FFA) which can induce insulin resistance (IR) in skeletal muscles and liver (2, 3, 4). On the other hand visceral obesity synergically enhances hepatic steatosis and IR induced by HCV (5, 6, 7). The mechanisms by which HCV causes liver steatosis are associated precisely with viral proteins and insulin-resistance.

1. Studies have shown that HCV proteins (like core protein and NS5A protein) interact with cellular lipid metabolism by inhibiting the activity of triglycerides microsomal transfer protein which causes the accumulation of triglycerides in liver (8, 9, 10).

2. Insulin-resistance in CHC is a result of elevated FFAs, TNF-alfa and suppressor cytokine signaling family (SOCs) which cause the inhibition of insulin receptor substrate (IRS-1) (11, 12, 13) impairing in this way the translocation of glucose transporter GLUT-4 to the cell membrane, thus diminishing the cellular glucose uptake and increasing the level of blood glucose with compensatory elevation of insulinemia. As a result patients with CHC have a high prevalence of the disorders of carbohydrate metabolism like glucose intolerance in more than 40% of patients and diabetes mellitus in more than 17% of them (14, 15). On the other hand hyperinsulinemia can mediate important changes in lipid metabolism. It can induce hepatic steatosis by increasing influx of FFAs to the liver, owing to increased peripheral lipolysis and increased hepatic lipogenesis (16).

In this way overweight/obesity (BMI>25 kg/m2) is considered an independent risk factor for hepatic steatosis in patients with CHC meanwhile hepatic steatosis accelerates the progression of chronic hepatitis C, and is independently associated with hepatic fibrosis of stage III / IV in these patients (17).

Because of these influences in IR, steatosis and liver fibrosis the evaluation of overweight/obesity in the treatment response in these patients has been a topic of interest for several important studies. In fact many research studies are conducted about the impact of host and viral factors in treatment response in CHC patients where the most studied factors have been *baseline* host and viral factors like genotype of HCV, age, gender, HCVRNA, hematological profile (especially level of PLT), BMI, the stage of liver fibrosis and on- treatment factors where the most important factor reported was RVR (18-26). According to these studies genotype 2 and 3, younger age (< 45 years/ old), females, low HCVRNA at baseline (< 400000-800 000 UI/ml), normal values of PLT at

baseline, low BMI at baseline, and achieving RVR are all positive predictive factors of SVR. Another opinion about the influence of BMI in SVR is contradictory as pegylated interferon plus optimized weight-based ribavirin dosing negate the influence of weight and body mass index on sustained virological response (27, 28). Furthermore studies which confirm the impact of BMI in SVR have proposed different *cut-off* values of BMI with impact in treatment response. For these reasons it is of interest to study the impact and role of BMI among all these other important factors in our patients and to determine a *cut-off* value of BMI which may be used to predict success of treatment or sustained virological response (SVR) in our patients.

PATIENTS AND METHODS

In this retro-prospective study were enrolled 151 patients diagnosed with chronic hepatitis C in the service of Hepatology and Gastroenterology, UHC "Mother Teresa". All patients were treated with PegINF alfa-2a (180 μg s.c/week) or alfa-2b (150 μg s.c/week) and Ribavirin 800-1200 mg/day (according to genotype and body weight). Patients with genotype 1and 4 were treated in general for 48 weeks and for genotypes 2 and 3, 24 weeks but the duration of treatment varied from 24-48 to72 weeks according European Association for the Study of the Liver (EASL) recommendations depended also from the virological response during treatment. Success of treatment was considered HCVRNA negative during treatment and 24 weeks after the end of the treatment (SVR). HCVRNA negative were considered levels below 50 IU/ml. Patients were assessed for age, gender, height, weight, BMI, HCVRNA at baseline, PLT and RVR. For each patient BMI was estimated by formula BMI=weight (kg)/height ^{2} (m^2).

The patients included in the study had no absolute contraindications to long acting interferon and ribavirin therapy i.e. uncontrolled depression, psychosis or epilepsy; uncontrolled autoimmune disease; current liver decompensation; severe concurrent medical disease such poorly controlled hypertension, heart failure, poorly controlled diabetes, chronic obstructive medical disease.

In order to avoid possible confusion factors were excluded from the study patients with end stage renal disease, hemoglobinopathies and those with daily alcohol consumption of more than 40 g/day for men and 20 g/day for women.

To assess the impact of overweight and obesity in treatment response we evaluated several *cut-off* values of BMI, starting from BMI 25 kg/m^2, which represent the lower limit value of overweight/obesity. SVR rates were compared for each *cut-off* value of BMI by chi-square test and binary logistic regression. To assess the influence of BMI independently of other host and viral factors which in the literature can influence the response of treatment we used the multivariate logistic regression test. Values of $p \leq 0.05$ were considered statistically significant.

RESULTS

The distribution of genotypes in 151 patients with chronic hepatitis C who were involved in the study resulted: 1b (59%), 1a (1.3%), 2 (31.7%), 3 (6%), 4 (2%). The most prevalent genotype was 1b, nearly 60%.

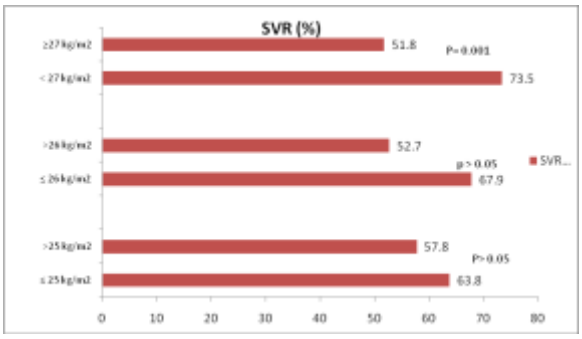
Of all patients, regardless of genotype, 93 achieved sustained virological response (SVR) so the rate of SVR was 61.5% while 58 (38.5%) patients didn't achieve SVR. According to genotypes the SVR rate in the group with genotypes 1 and 4 was 45.2% and in the group with genotypes 2 and 3 was 88%.

The study results showed that the average BMI in the SVR group was lower (25.1 ±4.5kg/m^2) than in the group without SVR (26.5 ± 3.7 kg/m^2) but without statistically significant difference.

There were no differences in SVR rate for the *cut-off* value of BMI of 25 kg/m^2. Thus the SVR rate in the group with BMI ≤ 25 kg / m^2 was 63.8% while in the group with BMI>25 kg / m^2 was 57.8%, without statistical differences between them (p>0.05) (Fig. 1).

For the *cut-off* value of BMI 26 kg/m^2 the results showed that in the group of patients with BMI ≤ 26 kg/m^2 SVR rate was higher than in the group with BMI>26 kg/m^2 (63.8% vs. 52.7%), but still there were no statistically significant differences between groups (Fig. 1).

Figure 1. SVR rates according *cut-off* values of BMI



Important results were achieved when compared SVR rates in groups of patients with BMI <27kg/m^2 and ≥ 27kg/m^2. The SVR rates were respectively 73.5% vs 51.8% (p=0.001) (Fig 1). Through the technique of binary logistic regression was found a causal link, statistically significant between non-SVR and BMI ≥ 27 kg/m2 (Tab.1); so it can be said that patients with BMI ≥ 27 kg/m^2 are 2.6 times more likely than patients with BMI<27kg / m^2 not to achieve SVR (OD: 2:58, CI95%: 1.59-5.67) (Tab. 1).

Table 1. The impact of BMI (*cut-off* value of 27 kg/m2) in treatment response

BMI	**HCVRNA_post therapy**		**OD**	**CI95%**
	Pos (without SVR) n=58 (%)	neg (with SRV) n=93 (%)		
≥ 27 kg/m^2	40 (69.0)	43 (46.2)	2.58	1.59-5.67
< 27 kg/m^2	18 (31.0)	50 (53.8)	reference	

Similarly, in the multivariate logistic regression test adjusted for important host and viral factors known in the literature like age, gender, HCVRNA *at baseline* with *cut off* value 400 000 UI/ml, number of platelets at *baseline* (PLT) and RVR at week 4, BMI with *cut–off* value 27 kg/m^2 resulted an important predictive factor of SVR (Tab. 2). Statistically significant predictive factor of SVR in this multivariate analyze were also the number of PLT at *baseline* and RVR while age, gender and HCVRNA at *baseline* with *cut-off* value of 400000UI/ml didn't show important impact on treatment response. So, in the group of patients with SVR the number of PLT at *baseline* was significantly greater than in the group without SVR (219827.06 ± 80966.55/mm^3 vs 179145.37 ± 64504.51/mm^3 (OD: 1.12, CI 95% 1.01-1.65). In the group of patients who achieved RVR, 80% of them had SVR and 20% non-SVR. In the group of patients who didn't achieved RVR at week 4 of treatment, 63.6% of them had non-SVR and only 36.4% of them had SVR after treatment. The differences in the scale of SVR between the two groups with RVR and without RVR are statistically significant (OD: 8.1, CI95% 2.3-12.3).

Table 2. The multivariate logistic regression analyze

Variables		HCVRNA_post therapy		OD	CI95%
		Pos, (non SVR) n=58 (%)	Neg, SRV n=93 (%)		
Age		43.95 ± 13.96	43.17 ± 12.30	1.03	0.98-1.09
Gender	male	49 (59.8%)	33 (40.2%)	1.75	0.16-3.07
	female	44(63.8%)	25 (36.2%)	reference	
BMI	≥ 27 kg/m^2	40 (69.0)	43 (46.2)	4.16	1.08-5.84
	< 27 kg/m^2	18 (31.0)	50 (53.8)	reference	
HCVRNA *baseline*	>400 000 UI/ml	13 (22.41)	45 (77.59)	3.03	0.92-9.9
	≤ 400 000 UI/ml	45 (48.39)	48 (51.61)	reference	
PLT (nr/mm^3)		179145.37 ± 64504.51	219827.06 ± 80966.55	1.12	1.01-1.65
RVR	with RVR	8 (20.0)	32 (80.0)	8.1	2.3-12.3
	without RVR	28 (63.6)	16 (36.4)	reference	

DISCUSSION

According to our study results, overweight patients with a BMI 27-30 kg/m^2 and those obese with BMI> 30 kg/m^2 had a lower response to treatment, a result similar to that of many other studies about the impact of overweight and obesity in treatment response (29-36). One of the most important studies on BMI and SVR was that conducted by Bressler (29) which has

identified obesity with the *cut-off* value of BMI of 30 kg/m^2 as an independent factor for non-response to treatment. Some other studies propose the *cut-off* value of BMI 25 kg/m^2 (37). In fact the *cut-off* value of BMI that was found in our study with impact in treatment response was similar with that of large important studies conducted by Di Bisceglie (38) and Mitchel L. Shiffman (39). This result was also confirmed in the multivariate analyze where in addition to BMI, important predictive factors of SVR were also RVR and the number of PLT at *baseline*. Similarly with other studies we found that RVR is a strong positive predictive factor of SVR (22, 23) and low number of PLT at *baseline* is a negative predictive factor of SVR (24, 40). HCVRNA at baseline doesn't seem an important predictive factor in the multivariate analyze because the lack of HCVRNA negative at week 4 (RVR) perhaps is the best predictor of treatment failure independently of HCVRNA > 400 000 UI/ml at *baseline* (40).

Two mechanisms explain why thrombocytopenia at baseline predict non-SVR: it usually accompanies advanced stages of hepatic disease and thus the response to treatment will be low because the advanced fibrosis itself constitutes a significant negative predictive factor for SVR (24, 41) and at the same time thrombocytopenia may be associated with antiviral therapy as an important side effect of Peg interferon, inducing dosage reduction during treatment, which is another factor that could reduce the chances of SVR (42).

In the multivariate analyze age and gender didn't influence treatment response, a result similar to those of large studies where despite the fact that invariable analysis found significant negative correlation between older age, male gender and SVR, this did not result in multivariable analyzes (20, 21, 43, 44).

Thereby we can say that in our study high BMI at *baseline* was an important negative predictive factor of SVR both in univariable and in multivariable analysis. Although the exact mechanisms of how obesity interferes with the response to treatment are not fully explained some of the mechanisms by which it may affect the treatment of CHC are: the altered level of cytokines in obesity i.e. increased levels of pro-inflammatory and reduced level of anti-inflammatory cytokines (30) the reduced bioavailability of interferon alpha (31), the insulin resistance and hepatic steatosis which cause an increase in fatty droplets in hepatocytes which can function as a barrier, preventing the interaction between antiviral medications and hepatocytes (33, 33), the poor lymphatic circulation seen in obese patients which this can lead to suboptimal levels of PegINF absorbed through this circulation (34) and finally obesity may also affect the antiviral response modulating the interferon signaling pathway. Obese subjects infected with HCV genotype 1 had increased hepatic expression of SOCS-3, a factor that has been shown to inhibit IFN-alfa signaling pathway (35). In patients with genotype 3 infection, fatty liver can occur in the

absence of obesity and insulin resistance and is called viral steatosis (36). Individuals infected with genotype 3, despite having hepatic steatosis in the absence of obesity may have a good response to the antiviral therapy and liver steatosis disappears with the disappearance of viremia (45). The good response to treatment of patients with genotype 3a shows that viral steatosis does not prevent the good response to treatment while the effect of steatosis in SVR is evident in non 3a genotypes (46, 47, 48).

Studies have shown that weight loss in patients with chronic hepatitis C will reduce blood level of transaminases, reduce blood level of insulin and will lead to improvement of liver steatosis and fibrosis and thus improving treatment response (41, 49, 50).

Although the topic of this study is not new, the strength of it lies in the fact that for the first time it reports the influence of BMI, an important pretreatment predictor of response, in Albanian patients with chronic HCV infection treated with Peginterferon and ribavirin. BMI is a strong valuable factor because it represents a modifiable host factor at *baseline*. As a result weight optimization will improve liver steatosis and fibrosis and also significantly will improve treatment response in chronic hepatitis C patients. One limitation of this study is the absence of liver biopsy prior treatment which could accurately correlate the overweight/obesity with the stade of liver steatosis and fibrosis at *baseline*.

CONCLUSIONS

Overweight/obesity increase hepatic steatosis and insulin resistance and negatively influence treatment response in CHC patients. BMI ≥ 27 kg/m2 is an important predictive factor for non-response during treatment of these patients with PegINF/RBV. *Baseline* weight optimization is highly recommended in chronic hepatitis C patients treated with standard scheme in order to increase the chances for treatment success (SVR).

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