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Impact of Weight Loss in Overweight Patients Enrolled in Weight Management Program Prior to Hepatitis C Treatment on Early Virological Response

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Abstract

Background: Obesity is a risk factor for non-response to interferon-based hepatitis C therapy. We studied the effect of weight management program to induce weight loss in overweight patients prior to starting antiviral therapy on treatment response.

Methods: Overweight patients received a weight loss brochure and a 6-week nutrition and exercise program prior to PEG-IFN + Ribavirin therapy (n=25). Early virological response rates (EVR) were compared between overweight subjects with and without ≥ 3% weight loss and control lean subjects (n=11).

Results: Moderate to severe fibrosis was present in 41.7% and moderate to severe steatosis in 16.7% of patients. Most were Caucasians (90% and 72% for lean and overweight group, respectively). There was no statistical difference in age, sex or race between those who lost ≥ 3% of their body weight and those who didn't among overweight group. Overweight subjects who lost ≥ 3% of body weight at week 12 of CHC therapy had higher EVR vs. those without ≥ 3% weight loss, 69.2% vs. 33.3%, p=0.036.

Conclusion: Overweight patients enrolled into weight management program who achieved ≥ 3% body weight loss at 12 weeks of CHC therapy had higher EVR compared to those without 3% weight loss.

Keywords: Weight change; Hepatitis C; Treatment outcomes; Virological response

Abbreviations: CHC: Chronic Hepatitis C; EVR: Early Virological Response; peg-IFN: Pegylated Interferon; RVR: Rapid Virological Response; SVR: Sustained Virological Response; TNF: Tumor Necrosis Factor; HCV: Hepatitis C Virus

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Introduction

Obesity has been shown to be an independent negative predictor of CHC treatment response. Obesity defined as body weight above 75 kg [1], body surface area above 2 meters square [2] and BMI >30 kg/m^2 [3] were independent predictors of non-response to PEG-IFN based CHC therapy. Spontaneous weight loss as well as other markers such as cytopenias during IFN therapy were associated with higher treatment response [4-6] and blunted weight loss and cytopenia were associated with a null response to IFN based CHC therapy [7]. However, it is not clear if induction of weight loss prior to starting CHC therapy can improve HCV treatment response.

The most recent estimates of hepatitis C burden show an increase in seroprevalence over the last 15 years to 2.8%, equating to >185 million infections worldwide [8] Of those infected, 20% to 50% will develop cirrhosis and hepatocellular carcinoma. It has been estimated that approximately 20% of individuals infected with the hepatitis C virus (HCV) are obese and that obesity in these individuals is associated with steatosis and higher rate of progression of fibrosis [9, 10]. The past 18 months have witnessed significant advances in the pharmacotherapy of CHC with improved treatment response; however, PEG-IFN and Ribavirin

remain as component of CHC therapy [11]. Better understanding of strategies to improve treatment response may help improve CHC management.

Both rapid and early virological responses (RVR and EVR, respectively) are significantly associated with sustained virological response (SVR) (undetectable HCV RNA at 24 weeks after completion of therapy). Patients without an early virological response to PEG-IFN+Ribavirin have less than a 2 percent chance of achieving an SVR, compared with an SVR rate of 65 percent in patients with an EVR. Those who achieve RVR have a 90 percent chance of achieving SVR [12]. There are some predetermined factors associated with non-response such as patient race, age or HCV viral genotype [13]. On the other hand, potentially modifiable factors include obesity and other metabolic syndrome components, particularly insulin resistance. Several trials highlighted the inverse impact of obesity on outcome of CHC treatment [3, 14]. Suggested mechanisms include prevalence of associated steatosis and fibrosis [15, 16], insulin resistance [17-19], and increased systemic inflammatory responses such as high TNF [20]. It has been suggested that management of insulin resistance such as addition of metformin to HCV therapy may improve response to HCV therapy [21].

Spontaneous weight loss during PEG-IFN and Ribavirin therapy of CHC has been shown to correlate with better treatment response [22]. However, the impact of induced weight management prior to CHC therapy on treatment response of obese subjects remains to be established. In this study we evaluated the impact of weight management program to induce weight loss on virological response among overweight subjects.

Materials Methods

Patients

All Patients with chronic hepatitis C confirmed by HCV-RNA who had been referred to the University of Pittsburgh Medical Center (UPMC) for hepatitis C management and provided informed consent were enrolled. Out of 64 patients referred for HCV genotype 1 management who provided consent to the study, 36 completed at least 1 month of HCV therapy and were included in the analysis. Data were missing in patients due to inability to start CHC therapy (n=11) or refusal to participate with nutrition intervention (n=17). The study was approved by the Institutional Review Board of UPMC. Treatment naïve HCV Genotype 1 infected patients were divided into 2 groups; Lean patients, BMI <25 (n=11) and Overweight, BMI ≥ 25 (n=25). The latter received a one-time 15-minute weight loss instruction and pamphlet and enrolled into weight management program with 6 weekly one-hour nutrition and physical exercise educational sessions immediately after initial evaluation followed by monthly follow up. All patients started CHC therapy 6 weeks after initial evaluation **(Figure 1)**.

Data analysis included demographics (gender, races, age) HCV genotypes, Interferon types (α 2a and α 2b), rates of viral responses by PCR, age, pre-treatment weight (within 6 weeks prior to HCV treatment). Body weight was measured and BMI calculated at time of first appointment, at start of CHC therapy 6 weeks after the initial appointment and 12 weeks after the start of CHC therapy. Weight change was calculated as the change compared to the weight at initial visit. A cutoff point of 3% weight loss was chosen as an indicator of significant weight loss, consistent with the guidelines recommendation to improve steatosis [23]. Body mass index (BMI) was calculated as weight in kg divided by square meter of the height (kg/m^2). Overweight was defined as BMI ≥ 25 for both in men and women.

Treatment duration, pre-treatment HCV RNA, liver fibrosis grade, pre-treatment ALT and AST were also documented. Records for different variables were taken at exact time plus or minus 1 month.

Hepatitis C therapy

Hepatitis C therapy consisted of weekly subcutaneous injections of pegylated IFN-α2a or IFN-α2b and daily oral Ribavirin. RVR was defined as undetectable HCV RNA levels after 4 weeks of therapy. EVR was defined as a greater than 2-log10 decline in serum HCV RNA from the pretreatment baseline or an undetectable serum HCV RNA at treatment week 12. All patients received weight based Ribavirin+Pegasys 150 mcg, 6 weeks after their initial evaluation.

HCV genotyping was performed by sequence analysis of a portion of the 5'untranslated region of the viral genome using Inno-Lipa HCV2 Line Probe Assay (Innogenetics, Ghent, Belgium). Cobas amplicor HCV test (version 2.0; Roche Diagnostics, Branchbrugh, NJ) was used to detect HCV RNA. Quantitative assessment of HCV RNA was done by in-house quantitative real-time RT-PCR assay, Cobas Amplicor HCV Test (version 2.0; Roche Diagnostics, Branchburg, NJ) was used to detect HCV RNA.

Nutrition and exercise interventions

Overweight and obese patients were offered an interventional program including diet and physical activity education. The interventions were based on The Group Lifestyle BalanceTM (GLB) Program [24]. The GLB is a comprehensive lifestyle behavior change program adapted directly from the successful lifestyle intervention used in the National Institutes of Health Diabetes Prevention Program. Each patient was given a weight loss goal of 3% of current body weight and was given a personal calorie goal as well as target fat grams per day. Diet and physical activity education classes were conducted by a Registered Dietitian. Candidates received up to 6 weekly classes followed by remedial educational sessions monthly for a total of 6 months. Each class lasted 1 hour for all participants. Each patient was provided a pedometer and a dietary logs to keep a record of daily dietary intake and physical activity. The dietitian checked dietary logs, discussed any related issues, reinforced and encouraged compliance to the dietary and exercise recommendations in the follow up sessions. The dietary education included healthy food selection, methods and strategies to decrease calorie and fat intake and methods to help achieve and maintain weight loss. The participants were asked to do 2½ hours of brisk physical activity each week by starting with 10 minutes of physical activity such as walking or cycling then gradually increase the activity duration up to 30 minutes. Exercises were done at home or outdoor.

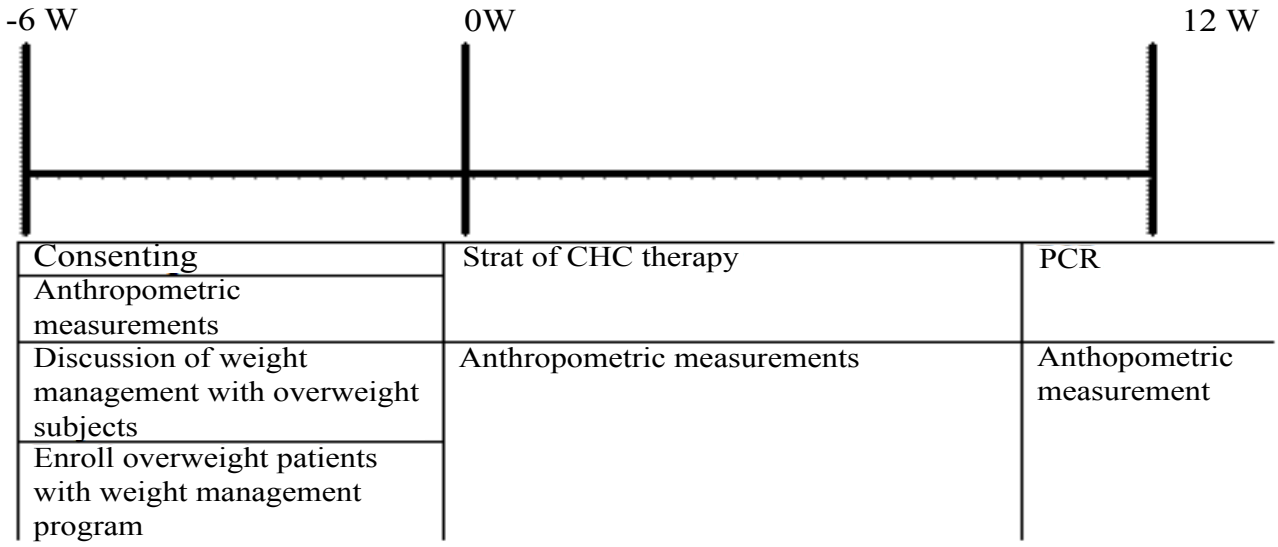

Figure 1 Research timeline.

Statistical analysis

Statistical analysis was carried out using SPSS for Windows (version 17) (SPSS Inc. Chicago, IL). Descriptive statistics are presented as mean ± standard deviation for quantitative variables and as percentages for qualitative variables. Intent to treatment analysis included data of all patients who received at least one dose of hepatitis C therapy. The categorical variables were compared using Fisher exact test as appropriate. Statistical significance was set at $p \leq 0.05$ (two-tailed).

Results

36 patients completed at least 1 month of HCV therapy and were included in the analysis. 69% of participants had BMI ≥ 25. Mean initial BMI in Lean and overweight groups were 22.3 ± 2.84 and 30.3 ± 3.55, respectively, **(Table 1A)**. Lean group was significantly younger than overweight group with 63.6% and 20% <50 years old, respectively, p=0.011. 42% were males, 77.8% Caucasians, 21.8% African American **(Table 1A)**. There was no statistical difference in age, sex or race between those who lost ≥ 3% of their body and who didn't among overweight group **(Table 1B)**.

The mean weight change at start of (week 0), and at 12 weeks of CHC therapy (week 0) compared to weight at initial appointment are summarized in **Table 2**. Overweight group lost 0.33 kg ± 5.61 during the 6 weeks prior to CHC therapy compared to a loss of 1.95 kg ± 6.41 for lean subjects. At 12 weeks the mean weight loss for overweight and lean groups were 3.44 ± 4.12 and 1.44 kg ± 3.82, respectively. 18% and 20% of lean and overweight groups lost ≥ 3% of their initial body weight at the start of CHC treatment. At week 12, 60% and 27.3% of overweight and lean groups lost ≥ 3% of their weight **(Table 3)**.

Effect of weight loss on early virological response

EVR for lean and overweight groups 82% vs. 52%, respectively, p=0.092. EVR was compared between overweight subjects who achieved ≥ 3% weight loss and those who didn't ≥ 3% weight loss at week 12 of CHC therapy in overweight patients was associated with a higher EVR, 69% vs. 33.3%, p=0.036 **(Table 4)**.

Table 1A Baseline demographic and clinical characteristics for lean and overweight subjects.

	Lean N=11	Overweight N=25	P value	N=36
Age >50 years	36%	80%	0.020	24
Females	64%	56%	0.729	21
Caucasians A.A	91%	72%	0.388	28
DM	0%	28%	0.534	7
HTN	0%	40%	0.141	10
ALT (IU)	88.60 ± 64.15	80.06 ± 55.78	0.728	36
BMI (IU)	22.30 ± 2.84	30.03 ± 3.55	0.000	36
Weight (Kg)	68.08 ± 10.72	88.19 ± 13.60	0.000	36

Table 1B Baseline demographic and clinical characteristics for overweight subjects with and without 3% weight loss.

	Overweight >3% weight loss N=15	Overweight <3% weight loss N=10	P value	N=25
Age >50 years	73.3%	90%	0.307	24
Females	46.7%	70%	0.250	21
Caucasians	80%	60%	1.190	28
DM	33%	20%	0.529	7
HTN	46.7%	30%	0.649	10

Table 2 Summary of weight changes at different times of CHC therapy (Kg).

	Lean (A)	Overweight (B)	P value	N
Week 0	-1.95 ± 6.41	-0.33 ± 5.61	0.467	11
Week 12	-1.44 ± 3.82	-3.44 ± 4.11	0.273	25

CHC: Chronic Hepatitis C; Week 0: Start of CHC Therapy; Overweight group underwent 15 minutes nutrition discussion, given nutrition procure and enrolled into 6 weeks nutrition and exercise program

Table 3 Percentage of patients who achieved 3% weight loss at different times of CHC treatment.

	Week 0	12 weeks
Lean (11)	18.2% (2)	27.3% (3)
Overweight (25)	20% (5)	60% (15)

CHC: Chronic Hepatitis C; Week 0: Start of CHC Therapy; Overweight group underwent 15 minutes nutrition discussion, given nutrition procure and enrolled into 6 weeks nutrition and exercise program

Table 4 Early Virological Response (EVR) rates in overweight subjects with and without 3% weight loss.

	EVR	
	EVR Responsive	EVR Non-responsive
>3% weight loss	69.2% 9	30.8% 4
<3% weight loss	33.3% 4	66.7% 8

P=0.036

Discussion

In our study, overweight and obese subjects with CHC had a 15 minutes discussion about nutrition, provided a weight management procure and invited to enroll into a weight management program for 6 weeks prior to starting CHC therapy. Our data revealed that patients enrolled into weight management program prior to IFN based CHC therapy who achieved 3% weight loss at week 12 of PEG-IFN + Ribavirin therapy had significantly higher EVR compared to those without 3% weight loss. The mechanisms of the impact of obesity and potential beneficial role of weight loss on response to IFN bases CRC therapy have not been clearly defined. Possible mechanisms include the effect on hepatic steatosis [25-30], insulin resistance and altered immune response. Weight management has been shown not only to a decrease in steatosis but also improvement in fibrosis severity [25, 26]. Weight reduction in obese patients has been shown to dramatically improve the liver histology and biochemistry of patients with steatosis and results in reversal of steatosis and a reduction of fibrosis level in the liver [27, 28]. A loss of at least 3-5% of body weight appears necessary to improve steatosis, but a greater weight loss (up to 10%) may be needed to improve necroinflammation [23].

The development of insulin resistance in HCV-infected patients is thought to be due to a combination of both host and virus-mediated pathways. Host-related factors typically seen in patients with NAFLD, including overweight/obesity decreased physical activity, older age, and diets high in saturated and trans-fatty acids or fructose, are thought to contribute to insulin resistance. Insulin resistance is a significant component of metabolic syndrome and is significantly associated with obesity. In addition, HCV infection is associated with an idiosyncratic relationship with glucose metabolism with negative affects on the response to IFN-based CHC therapy [29]. Insulin resistance is a significant component of metabolic syndrome and is significantly associated with obesity. Improved virological response to IFN based therapy has been reported when patients received metformin in addition to PEG-IFN and Ribavirin [21].

Conclusion

Overweight and obese subjects with chronic hepatitis C who had a 3% weight loss on weight management program starting prior to initiation of antiviral therapy had higher EVR. Weight management programs including diet and exercise regimen before beginning PEG-IFN + Ribavirin therapy of CHC may improve IFN based CHC treatment response and may provide an important adjunct treatment strategy for overweight patients with chronic hepatitis C.

Statement of Authorship

Hossam Kandil and Hany Elwakeel designed and conceived the study, developed the overall research plan and provided the database essential for research. Sherif Elbehiry wrote the first draft. Hossam Kandil, Sherif Elbehiry, Laura Matarese, Hany Elwakeel, Kareem Kandil and Eslam Ali helped with statistical analysis, interpreted the data and reviewed the manuscript for submission. All authors have read and approved the final manuscript. The data were collected at University of Pittsburgh. Data analysis and manuscript preparation were done at East Carolina University.

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