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Impact of Combination Interferon Therapy on the Body Weight, Body Fat and Lean Body Mass of Chronic HCV Infected Patients

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Abstract

Changes in body weight in HCV patients on interferon therapy are well established. However, these are not reported extensively in patients from developing societies, where the infection may have different dimensions. Also, most of the previous studies reported changes in body weight only but not in other compartments of body composition, which have numerous clinical implications. We, therefore, prospectively investigated these changes in current study. The study comprised 30 HCV positive patients, recruited from Khyber Teaching Hospital (KTH) Peshawar, Pakistan. Patients were screened for antibodies against HCV. The positive samples were subjected to polymerase chain reaction (PCR) analysis for detection of HCV-RNA and were entered into two groups: one group ('on therapy' (n=20) received Interferon (IFN) therapy, while the other group ('no therapy' (n=10) did not. Data were collected for weight, height, nutrition and other socio-demographic parameters. Body composition was assessed using bio-electric impedance analysis (BIA) and monitored for the six months of treatment. The major findings of this research study are significant ($p \leq 0.05$) reduction in body weight, body fat (BF) and lean body mass (LBM) in HCV patients on interferon-α (IFN-α) therapy. These parameters changed non-significantly (*p*, trends for all>0.05) in 'no therapy' group. The greatest effects of these changes were demonstrated in month 1-4 of treatment. In conclusion, interferon therapy causes significant reduction in compartments of body composition and that these changes may be considered to be used as surrogate indicators for monitoring the treatment efficacy.

Keywords: Body composition; Body fat; Interferon therapy; Hepatitis C

Introduction

Hepatitis C is a contagious disease of liver caused by the hepatitis C virus (HCV) [1] which is an enveloped ribo-nucleic acid (RNA) virus with a diameter of 50 nm and is classified as a separate genus (Hepacivirus) within the Flaviviridae family. The prevalence of HCV infection is estimated to be 2.2-3.0% (130-170 million people) worldwide [2].

About 15 to 20% of HCV infections progress to potentially serious cirrhosis and end-stage liver disease [3]. Patients with cirrhosis often have an abnormal body composition with clinical signs of protein-energy malnutrition and a relative increase in body weight due to ascites or edema [4-6]. Ascites is a condition that is becoming treatable with diuretics, albumin preparations, ascetic reperfusion, and transjugular intrahepatic portosystemic shunting, but the prognosis of patients with ascites remains poor [7,8]. According to all consensus guidelines (EASL 2011, NICE 2010, AASLD 2009), the current standard of care (SoC) for HCV is the combination of interferon (IFN) and/or ribavirin (RBV) for 24-48 weeks, depending primarily on the viral genotype, virological response (SVR) (defined as undetectable HCV RNA level at 6 months after treatment completion).

Interferon (IFN) has been extensively used for treatment of HCV. The current therapy for HCV infection in developing countries is combination of either Telaprevir or Boceprevir (Protease inhibitors) with Ribavirin (RBV) and Interferon (IFN) for genotype 1 patients. This therapy has shown improved cure rate (60-80 percent), a significant increase in compare to prior therapy with improved SVR and significant reduction in treatment time (12-36 weeks).

Approximately 10-15 % of patients are forced to discontinue IFN therapy due to side effects/adverse effects associated with the therapy/ The rate of treatment withdrawal has been reported to be substantially higher. In addition, dose reduction of IFN and/or RBV owing to side effects/adverse effects is in the range of 25-40 % of patients. Studies suggest that dose reduction should be implemented at the earliest possible stage, when slight signs of side effects/adverse effects are noted [9].

A large regional and global variability exists in the nature of side/adverse effects associated with HCV. There is also difference hence in the strategies employed to mitigate the impact of side/adverse effects during the treatment. The most common side/adverse effects include influenza-like symptoms (such as fatigue, headache, fever, and rigors). These occur in virtually all patients after the first doses of IFN, but usually subside after the first month of treatment. Dermatologic effects (alopecia, dermatitis) and gastrointestinal symptoms (nausea, diarrhea) are also very frequent. The most prevailing severe side effects/adverse effects are hematologic, neuropsychiatric and autoimmune [10].

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Fellay et al. [11] has reported that anemia as an adverse effect of IFN therapy, is common in as much as 30% of the treated patients. For evaluation of anemia, usually the lowest hemoglobin (Hb) values are recorded 6-8 weeks after treatment has been started and stay at the same level throughout the remaining therapy period. There are higher chances of severe anemia to occur, with hemoglobin levels as much below as<10 g/dL and approximately 10-15 % of patients suffer from severe anemia [11].

In most clinics and health care centers, patients are weighed almost at every visit. However measuring weight alone can be a misleading indicator of nutritional status, particularly in HCV patients, because lean body mass is lost in preference to fat and in addition to it, there is no way to distinguish between body fat (BF), and lean body mass (LBM) when weight measurements alone are used [12]. Serial weight measurements have been used by the Centers for Disease Control and Prevention (CDC) as a way to identify the wasting syndrome and predict the development of AIDS [13]. However, measurement of body weight alone failed to identify dramatic losses in body cell mass and other body composition parts [14]. Thus, further measures of body composition are also needed, to identify losses or gains of lean body mass, body fat or body cell mass associated with increased mortality [13]. The present study was aimed to prospectively evaluate effects of combination antiviral therapy on total body weight, body fat and lean body mass of HCV infected adult individuals.

To investigate the effect of antiviral therapy, we carried out a cross-sectional prospective study, to evaluate changes in various parameters of body composition such as body weight, body fat (BF) and lean body mass (LBM).

Material and Methods

The present study was conducted at the Institute of Biotechnology and Genetic Engineering (IBGE) KPK Agricultural University, Peshawar and Khyber Teaching Hospital (KTH), Peshawar, Khyber Pakhtunkhwa of Pakistan.

Inclusion criteria were: adult male, having HCV, non-diabetic with no other reported infectious and/or non-infectious diseases, non-smoker and non-drug-users. In addition only those patients were included who had no recent history of intentional or unintentional weight loss or changes in other body composition parameters. All those subjects were excluded who had a recent history of any metabolic complications and/or medical disorder. A total of 30 subjects of local Pashtun ethnicity participated willingly in the study. The subjects were divided into two groups. One group started with IFN-combination (On therapy group) while the other group did not take any therapy during the study period. IFN-α 2b dose was 3 mU thrice a week plus Ribavirin 1000 mg/day. All the patients of the study, who visited the OPD were assessed and interviewed thoroughly. The following procedures were adapted for data collection.

- Screening for diagnosis to make sure they are suffering from HCV
- 24-hours Dietary Recall (Performa)
- Biochemical Tests and differential blood counts.
- Body composition Assessment using Bio-electric Impedance (BIA)

Screening

Initially all the subjects were screened for anti-Hepatitis C virus antibodies by Immuno-Chromatographic Tests (ICT) (Abbot and Awrate). Samples diagnosed as positive by ICT technique were further evaluated using ELISA (BIOKIT, S.A, Barcelona-Spain) according to the manufacturer's instructions. All the ELISA positive samples were processed for RNA extraction. According to manufactures' instructions we extracted HCV RNA from 200 µl sample of serum by using Ana-gen RNA extraction Kit (Ana-gen, USA). Qualitative HCV RNA extraction and HCV genotyping was carried out according to our previous work [15]. All the products of PCR (1st and 2nd rounds) were analyzed on 1.8% agarose gel prepared in 0.5% TBE buffer, stained with Ethedium bromide. Using Alpha quant (Alpha Innotech) gels were photographed.

Assessment of body composition and determination of blood chemistry

BIA is recommended in measurement of body composition in healthy as well as individuals with chronic disease conditions [16]. Bioelectrical impedance analysis (BIA) was performed to measure body weight, body fat and lean body mass of the study subjects by using Bodystat® Quanscan 4000 Hydration/Body composition Monitoring Unit, Isle of man, UK [17].

Routine blood chemistry for albumin, ALT (Alanin Aminotransferase) and hemoglobin were determined.

The study was approved by the Board of Studies, IBGE, AUP. Written consents of willing to participate in the study were obtained from all patients.

Statistical analysis

The data were statistically analyzed using SAS (Version 7.0. SAS, USA). Data were expressed in mean (STD). Student's t-test was performed to explore the difference between means of variables of interest. A p value of ≤ 0.05 was considered as significant.

Results

The current study was conducted to investigate the changes in body composition as a result of interferon (IFN) therapy in HCV positive patients. A total of 30 male patients participated in the study. These patients were divided into two distinct groups i.e. 'on therapy' group (N, 20) and 'no therapy' group (N, 10). HCV positive patients 'on therapy' used the IFN treatment and were followed for the 6 months of treatment. As a control, HCV positive patients on 'no therapy' were also followed for the 6 months after they were first diagnosed.

The age and other characteristics of the patients are presented in Table 1. The mean age (p=0.39), weight (p=0.64), and BMI (p=0.56) of the two groups of HCV positive patients at baseline did not differ significantly. Table 1 also shows the mean body fat, lean body mass, intracellular and extracellular body water and phase angle of HCV positive patients which shows a homogeneous population of the study with respect to age and body weight. As clear from Table 1, these values did not differ significantly for the two groups (p, for all trends>0.05).

Tables 2 and 3 show respectively, the mean values of nutrient intake (energy and protein), selected blood biochemistry (albumin, ALT, hemoglobin) and differential blood counts of the HCV positive patients at baseline. As can be seen, these figures did not differ significantly for the two groups of HCV positive patients (i.e. on therapy and no therapy) (p, for all trends>0.05).

The mean difference in body weight of HCV patients 'on therapy' and on 'no therapy' are shown in Figure 1. As shown, there was a

Characteristics	HCV[1] Positive Patients		*p*-value
	On therapy (20)	No therapy (10)	
Age (years)	33.1 ± 9.97	36.1 ± 7.54	0.35
Weight (Kg)	62.9 ± 8.27	61.3 ± 12.83	0.84
BMI	22 ± 3.1	21 ± 4.2	0.46
Body Fat (Kg)	11.35 ± 6.57	9.41 ± 5.33	0.12
Lean Body Mass (Kg)	51.6 ± 8.93	51.8 ± 11.12	0.53
ICW[2] (Liters)	22.28 ± 4.20	19.8 ± 2.42	0.08
ECW[3] (Liters)	18.6 ± 3.87	17.8 ± 2.45	0.55
Phase Angle[4]	5.98 ± 0.23	5.88 ± 0.19	0.14

Significantly different if $p \leq 0.05$
HCV[1] Genotype 2b; ICW[1]=Intracellular Water; ECW[2]=Extracellular Water; Phase Angle[3]=The phase angle is defined as the relation between the two vector components of impedance: resistance and reactance. It may be interpreted as an indicator of water distribution between the extra- and intracellular spaces [27]

Table 1: Baseline means of age, anthropometric and body composition characteristics of chronic HCV positive patients.

Characteristics	HCV Positive Patients		p-value
	On therapy (20)	No therapy (10)	
Protein intake (g)	73 ± 4	73.8 ± 3.8	0.62
Energy intake (Kcal)	2114.9 ± 274	2051 ± 151	0.46
Albumin	2.9 ± 0.06	v2.8 ± 0.74	0.75
ALT[1]	55.05 ± 11.98	56 ± 13.64	0.87
Hemoglobin	13.1 ± 2.18	12.6 ± 1.52	0.51

Significantly different if $p \leq 0.05$
[1]ALT=Alanin Aminotransferase

Table 2: Baseline Daily Nutrient intake and Blood Chemistry of the Patients.

Blood cells/components	HCV Positive Patients		p-value
	On therapy	No therapy	
White Blood Cell (10^3/µL)	6.0 ± 1.52	5.75 ± 1.00	0.23
Red Blood Cells (10^6/µL)	4.72 ± 0.83	4.15 ± 1.11	0.31
Platelets (10^3/µL)	235.85 ± 64.52	224.67 ± 79.49	0.69
Lymphocyte (10^3/µL)	1.84 ± 0.46	1.87 ± 0.61	0.91
Neutrophile (10^3/µL)	2.57 ± 0.73	2.62 ± 0.71	0.35

Difference significant at p=0.05

Table 3: Baseline differential blood counts of the patients.

significant ($p \leq 0.05$) reduction in Body Weight (62.93 ± 8.27 Kg at baseline vs. 57.13 ± 7.54 Kg at month 6) in HCV patients 'on therapy' group, whereas, a non-significant decrease in body weight in HCV patients on 'no therapy' (61.31 ± 11.73 Kg at baseline vs.60.72 ± 13.81 Kg at month 6).

As evident from Figure 2 there was significant ($p \leq 0.05$) reduction in body fat (11.4 ± 6.57 Kg at baseline vs. 9.1 ± 6.36 Kg at month 6) observed in HCV patients 'on therapy', whereas, a non-significant increase occurred in HCV patients on 'no therapy' (body fat 9.02 ± 2.8 Kg at baseline vs. 9.41 ± 2.55 Kg at month 6; p=0.213).

Figure 3 shows the changes in LBM in the HCV patients 'on therapy' (blue line) and HCV patients on 'no therapy' (red line). There was a significant ($p \leq 0.05$) mean reduction in LBM in HCV patients on therapy (51.6 ± 8.93 Kg LBM at baseline vs. 48.0 ± 8.64 Kg LBM at month 6) (Figure 3). In HCV patients on 'no therapy', there was a non-significant difference between the LBM at baseline (51.86 ± 10.16 Kg) and at month 6 (51.87 ± 11.14 Kg) (Figure 3).

Discussion

Hepatitis C is highly prevalent in Pakistan [15]. Treatment options for Hepatitis C include conventional IFN alone or in combination with Ribavirin. However, IFN-based therapy has several diverse effects (manifested in the form of weight loss etc) due to which, most often the treatment is discontinued [9]. As has been considered previously, beside body weight body fat (BF), lean body mass (LBM), extracellular and intracellular water (ECW and ICW), phase angle, and body cell mass (BCM) are some important parameters for assessing the health and nutritional status of individuals [18-20].

Data on changes in body composition in patients with HCV infection before and during treatment are not reported extensively, particularly in developing countries, where the infection may have different dimensions of prevalence and therapeutic approaches. This study was conducted on HCV patients in order to investigate the

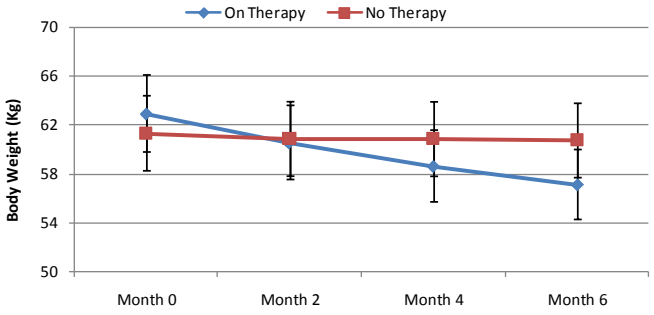

Figure 1: Mean Body Weight (Kg) of the HCV patients patients 'on therapy' group (blue line) and HCV patients on 'no therapy' group (red line) at different time points of the study period i.e. at baseline, at month 2, month 4 and month 6.

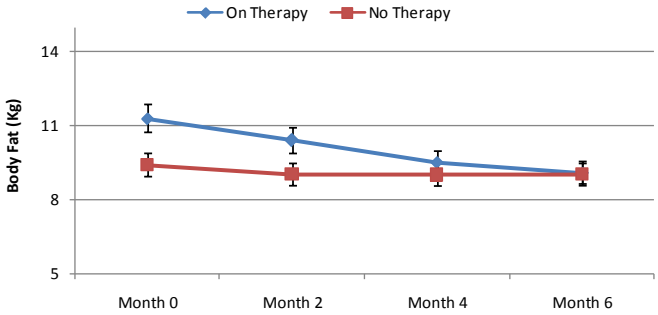

Figure 2: Mean Body Fat (Kg) of the HCV patients 'on therapy' group (blue line) and HCV patients on 'no therapy' group (red line) at different time points of the study period i.e. at baseline, at month 2, month 4 and month 6.

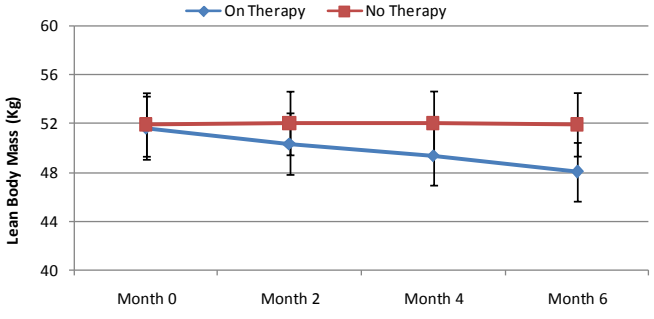

Figure 3: Mean lean body mass (Kg) of the HCV patients 'on therapy' group (blue line) and HCV patients on 'no therapy' group (red line) at different time points of the study period i.e. at baseline, at month 2, month 4 and month 6.

immediate effects of interferon-α (IFN-α) therapy on some selected parameters of body composition. Data on body composition is an important factor for treatment decisions, especially if supplemental therapy is needed. IFN-α and/or ribavirin treatment in HCV has been reported to be very often associated with fatigue, cephalgia, weight loss, flu-like syndromes, and anorexia [21]. All these contraindication may have adverse implications for changes in nutritional status and body composition [22].

HCV infection may adversely affect energy balance of the body leading to a reduction of both somatic proteins of fat-free mass (FFM) and of visceral proteins in the elderly patients. In addition, body composition is altered in patients with HCV because of protein-energy malnutrition, altered micronutrient status, and variable fluid homeostasis [22].

In our study the percentage of individuals that experienced a reduction in total body weight during interferon therapy are higher than the 11-29%, reported by other studies [21,23]. The original studies mainly relied on patients for reporting of weight reduction rather than on prospective measurement, this may result in the difference in the percentage of subjects that experienced weight loss. Alternatively, a loss more than a pre-specified mass or percentage of baseline in some analysis is defined as weight loss. The observations prepared by other studies are, however, reliable with our own. As an example, an experiment of eleven children that were on interferon therapy for HCV showed a weight reduction and nutritional status was impaired in all of the subjects [24]. Another study reported that a reduction of body weight was observed; at the end of 4 weeks 91.2% of the patients showed a reduction in weight, at 12 weeks 93.7%, at 24 weeks 94.7% and at the end of 48 weeks of treatment a reduction in weight was observed in 89.6% of the patients. At 4 weeks median weight losses were 2.3% of pretreatment weight, at 12 weeks 4.6%, at 24 weeks 6.3%, at 52 weeks 8.9% of the treatment. Median weight had increased to 96.4% of the pre-treatment 12 weeks after the completion of the treatment, and this had increased to 99% by 24 weeks [25].

As can be seen in our study (Figures 1-3), changes in body weight and other body compartments (i.e. body fat and lean body mass) occurred mostly in the first four months of the treatment. These results are consistent with those reported by Gottrand et al. [24] and Lebensztjen et al. [26]. The former reported weight loss in HCV patients during the first three months of IFN therapy, while the latter reported these changes mainly in the second month of therapy. The onset and timing of weight loss is important as decisions regarding continuation, cessation, or modification in the dose and treatment regimen depend on the time when and how changes in body weight start.

In our study, all patients 'on therapy' lost weight with the greatest effect being demonstrated early in treatment (months 2 - 4) (Figure 1). All patients 'on therapy' lost body fat and again the greatest effect being demonstrated early in treatment (months 2 - 4) (Figure 2). The loss in lean body mass (LBM) was also experienced by all patients 'on therapy'; however, the loss in LBM was uniform throughout the study period (Figure 3). In the HCV positive subjects who were on 'no therapy', the mean body weight loss was 0.59 (± 0.018) Kg and the difference between mean body weight at month 6 (60.72 ± 12.80) and mean body weight at baseline (61.31 ± 12.86 SD) was not statistically significant (p=0.20). Similarly, no significant changes in body fat and lean body mass were recorded for patients with 'no therapy' (Figures 2 and 3, respectively).

Winding up, interferon therapy (IFN) results in weight loss as a side effect in hepatitis C infected individuals. Adding together, the therapy affects other compartments of body composition adversely. The study is limited in that it could recruit male patients only with relatively smaller sample size. Future studies based on the finding of the present study will include female subjects from possibly all segment of population to generalize the results.

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