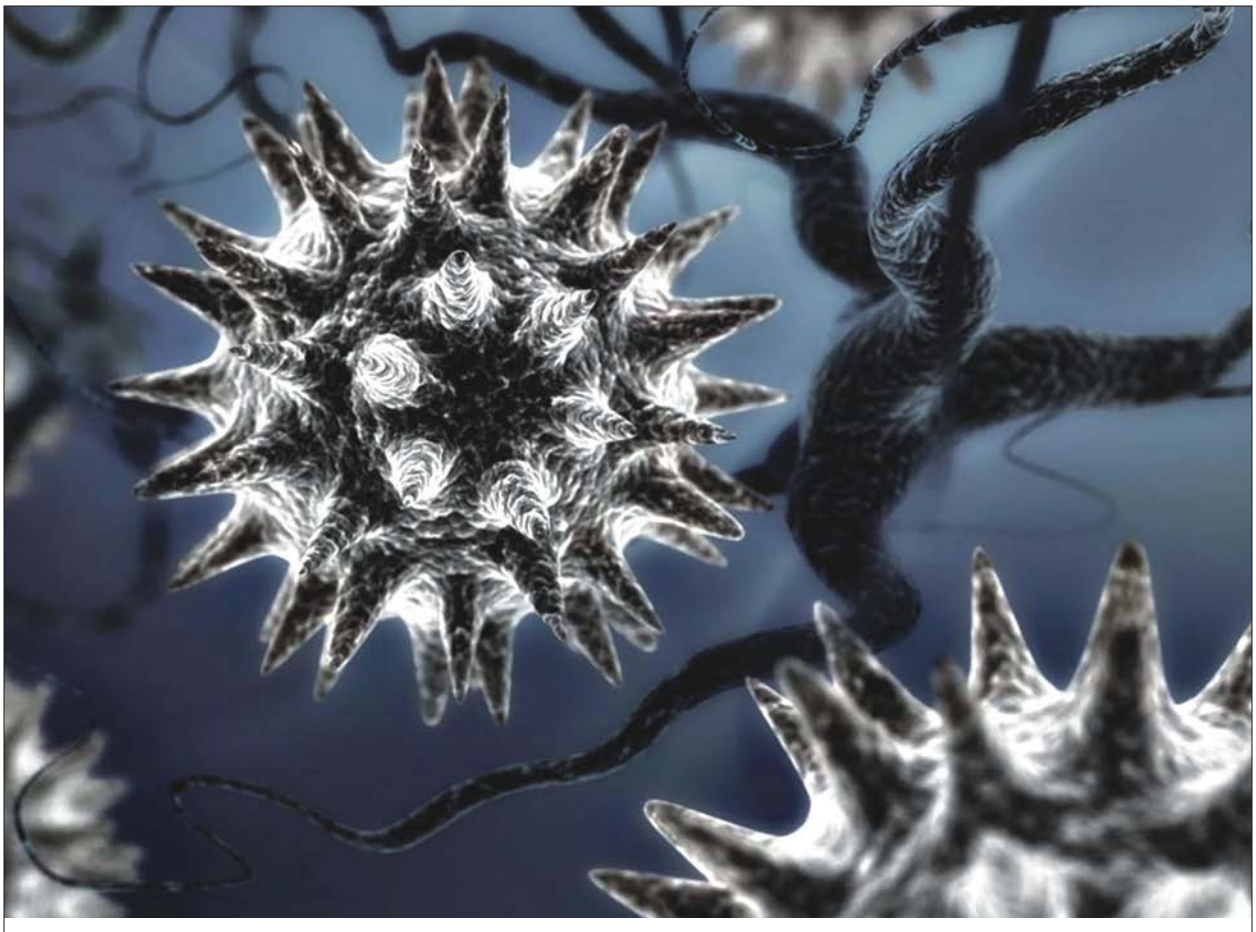

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# Nutritional Status and Body Composition Dynamics with Peginterferon Alpha and Ribavirin Combination Therapy in Chronic Hepatitis C Patients

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## ABSTRACT

Weight loss has been reported in patients treated with peginterferon alpha (Peg-IFN-") and ribavirin, however, the pathophysiological mechanism of this weight loss is unclear. We prospectively evaluated the nutritional status, body composition and dietary intake of 10 chronic hepatitis C patients treated with Peg-IFN-" and ribavirin, before, at the end of and at 6 months after treatment. Nutritional status and body composition were evaluated by using anthropometric analyses and Bioelectrical Impedance Analysis (BIA) with a body composition analyzer. Body weight, body mass index and total energy intake were significantly ($p<0.05$) reduced at the end of treatment compared with before treatment, however, at 6 months after treatment, they were recovered to before-treatment levels. In anthropometric analyses, percent Triceps Skinfold Thickness (TSF%) which represents body fat mass was significantly ($p<0.05$) decreased at the end of treatment compared with before treatment, whereas, percent Arm Muscle Circumference (AMC%) which represents body muscle was not. In the BIA, body fat mass was also significantly ($p<0.05$) decreased, whereas, skeletal muscle mass was not. There were no significant changes in grip strength and serum albumin level. Decreased TSF% and body fat mass were also recovered to before treatment values at 6 months after treatment. The body weight loss observed during Peg-IFN-"-2b and ribavirin was attributable to body fat mass decrease rather than skeletal muscle mass decrease. Decreased body weight and decreased body fat mass were recovered to before treatment values at 6 months after treatment without body composition change.

**Key words:** Nutritional status, body composition, weight loss, Peg-IFN and ribavirin, HCV

## INTRODUCTION

Hepatitis C Virus (HCV) infection is the major cause of chronic hepatitis, liver cirrhosis and hepatocellular carcinoma (Kiyosawa *et al*., 1990; Sata *et al*., 1998). Currently, it is estimated that there are ~180 million HCV-infected patients worldwide (Hanafiah *et al*., 2013), with the number being 1.5-2.0 million in Japan. Pegylated interferon alpha (Peg-IFN-") in combination with ribavirin, until recently has been the standard therapy for chronic hepatitis C patients

(Fried *et al*., 2002). Although recent therapeutic regimens with direct-acting antiviral agents have improved the therapeutic outcomes in HCV patients, Peg-IFN-" and ribavirin therapy is recommended for IFN-eligible patients (Limaye *et al*., 2011; Sherman *et al*., 2011; Osinusi *et al*., 2013; Afdhal *et al*., 2014; Drafting Committee for Hepatitis Management Guidelines, 2014).

Weight loss was reported in 11-29% of patients treated with Peg-IFN-"-2b and ribavirin (Manns *et al*., 2001; Fried, 2002; Seyam *et al*., 2005; Hamer, 2008; Suwantarat *et al*., 2010; Conjeevaram *et al*., 2011). However, the pathophysiological mechanism of this weight loss is unclear. Metabolism abnormality characterized by Protein Energy Malnutrition (PEM) is frequently observed in patients with decompensated liver cirrhosis and a rapid reduction of body weight may have greater influence on nutritional disorder in chronic hepatitis C patients than in healthy persons (Merli *et al*., 1996; Kondrup and Muller, 1997; Selberg *et al*., 1997). Most patients treated with Peg-IFN-" and ribavirin recovered their weight several months after the end of treatment, however, their body composition in terms of muscle and fat after weight recovery may not be same as compared with before treatment.

In the present study, we prospectively evaluated the nutritional status, on the basis of body weight and body composition, in patients receiving Peg-IFN-"-2b and ribavirin combination antiviral therapy for chronic hepatitis C, before, at the end of and at 6 months after treatment.

## MATERIALS AND METHODS

**Patients:** In this study, we prospectively evaluated the nutritional status and dietary intake of 10 chronic hepatitis C patients treated with Peg-IFN-"-2b and ribavirin combination therapy for 24-48 weeks from December 2007 to June 2011.

The inclusion criterion was serum HCV RNA-positive chronic hepatitis C patients receiving interferon therapy with Peg-IFN-" and ribavirin. The exclusion criteria were patients <20 years old and those with hepatocellular carcinoma, active thyroid disease, active collagen disease, severe hemorrhage in the fundus of the eye, uncontrolled depression and other hepatic diseases such as autoimmune hepatitis, chronic hepatitis B and primary biliary cirrhosis.

We investigated the patients' background including age, sex, alcohol consumption, medical history, serum albumin, HCV RNA titer and HCV serotype before interferon treatment. In addition, we also investigated Peg-IFN-" and ribavirin dose reduction, treatment period and therapeutic effect. Sustained Viral Response (SVR) was defined as undetectable serum HCV RNA at 24 weeks after the end of therapy.

**Ethical considerations and informed consent:** This study was approved by the ethics committee of the National Hospital Organization Tokyo Medical Center and written informed consent was obtained from each patient after the purpose of the study has been fully explained.

**Assessment of nutritional status and body composition:** Anthropometric analyses and body composition measurements were performed three times for each patient, i.e., before treatment, at the end of treatment and at 6 months after treatment. We measured body height and weight and then calculated the Body Mass Index (BMI) as follows:

$$\text{Weight (kg)/height (m)}^2$$

It is measured that, the Arm Circumference (AC) and Triceps Skinfold Thickness (TSF) by using a flexible tape and a caliper. Arm Muscle Circumference (AMC) was calculated by using the following equation:

$$AMC\ (cm) = AC - B \times (TSF/10)$$

The AMC% and TSF% were determined by comparing the measured AMC and TSF with the Japanese anthropometric reference data. In addition, the grip strength of both hands was measured (Hosoya *et al*., 2002).

Body composition measurement was performed by means of Bioelectrical Impedance Analysis (BIA) with a body composition analyzer (InBody S20; Biospace Japan Inc., Tokyo, Japan). A personal computer was connected to the analyzer to calculate the body composition, i.e., skeletal muscle mass, body fat mass, waist-hip ratio, Body Cell Mass (BCM) and Total Body Water (TBW). Measurements were performed with the patient in supine position in the morning after fasting an overnight fast.

**Nutritional counseling and energy intake:** Nutritional counseling in the hospital was performed by nutritionists at three clinical time points with anthropometric analyses, body composition measurement and serum albumin measurement.

The total calories were calculated on the basis of the basal energy expenditure which was calculated by using the Harris-Benedict equation.

The nutritionists also estimated the energy and macronutrient intake at the same time by interviewing the patients about their daily diet.

**Statistical analysis:** The patients' basic characteristics were expressed as Mean±Standard deviation for continuous data. The Wilcoxon signed-rank test was used to compare the data between the different time points, i.e., before, at the end of and at 6 months after treatment.

The correlation between energy intake and body weight change was analyzed by using Pearson's correlation coefficient.

The significance level for all analyses was set at $p<0.05$. We used IBM SPSS Statistics version 20 for statistical analysis.

## RESULTS

**Patient characteristics:** A total of 10 patients with chronic hepatitis C treated with Peg-IFN-"-2b and ribavirin participated in this study, including seven male and three female patients with age ranging from 42-71 years. The patients' BMI ranged from 17.2-27.5; two patients had a BMI of >25 and one patient had a BMI of <18. Serum albumin ranged from 3.8-4.6 g dLG$^{1}$ and none of the patients had a serum albumin level of <3.5 g dLG$^{1}$. Two patients were serotype 1, five were serotype 2 and three were of undeterminable serotype. The titer of serum HCV RNA ranged from 5.1-7.4 log copies mLG$^{1}$. The treatment period was 24 or 48 weeks and 4 of 10 patients achieved SVR after the therapy. The characteristics of the patients are shown in Table 1.

**Anthropometric assessment:** Body weight and BMI were significantly ($p<0.05$) reduced at the end of treatment compared with before treatment, however, at 6 months after treatment, they were recovered to before-treatment levels.

Table 1: Patients' background

| Age | Sex | Height (cm) | Weight (kg) | BMI (kg mG$^2$) | Alb (g dLG$^1$) | HCV serotype | RNA (logIU mLG$^1$) | Treatment period (weeks) | INF dose reduction | RBV dose reduction | Treatment effect |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 58 | M | 182.9 | 80.0 | 23.9 | 4.5 | 1 | 5.1 | 48 | No | Yes | SVR |
| 62 | M | 172.6 | 70.4 | 23.6 | 4.6 | 1 | 7.0 | 48 | Yes | No | NR |
| 68 | M | 166.1 | 65.0 | 23.6 | 4.5 | 2 | 5.7 | 48 | No | No | NR |
| 42 | M | 166.0 | 75.8 | 27.5 | 3.8 | 2 | 5.8 | 24 | No | No | SVR |
| 60 | F | 150.2 | 38.8 | 17.2 | 3.9 | 2 | 6.7 | 24 | No | Yes | SVR |
| 65 | M | 156.1 | 66.0 | 27.1 | 4.3 | 2 | 6.6 | 24 | Yes | Yes | NR |
| 71 | M | 167.5 | 65.5 | 23.3 | 3.9 | 2 | 5.1 | 24 | No | No | SVR |
| 50 | M | 174.7 | 75.0 | 24.6 | 4.5 | Undeterminable | 5.8 | 24 | No | No | Relapse |
| 56 | F | 160.3 | 55.3 | 21.5 | 4.3 | Undeterminable | 7.4 | 24 | No | Yes | NR |
| 64 | F | 152.7 | 49.9 | 21.4 | 4.2 | Undeterminable | 6.1 | 24 | Yes | Yes | Relapse |

BMI: Body mass index, Alb: Albumin, HCV: Hepatitis C virus, SVR: Sustained viral response, NR: No response

Table 2: Anthropometric, body composition, grip strength and serum albumin changes in chronic hepatitis C patients

| Parameters | Before treatment (n = 10) | End of treatment (n = 10) | Before vs. end of treatment at p | Six months after treatment (n = 8) | Before vs. 6 months after treatment p |
|---|---|---|---|---|---|
| Weight (kg) | 64.50±12.1 | 60.70±12.1 | 0.008 | 61.60±14.5 | 0.09 |
| BMI (kg mG$^2$) | 23.50±2.60 | 22.10±2.60 | 0.008 | 22.30±3.10 | 0.09 |
| Anthropometric analysis | 103.80 | | | | |
| AMC% | 101.00±6.50 | 98.00±6.30 | 0.200 | 99.90±8.40 | 0.09 |
| TSF% | 122.90±49.6 | 101.80±34.0 | 0.030 | 115.60±48.1 | 0.46 |
| **Body composition with BIA** | | | | | |
| Skeletal muscle mass (kg) | 25.60±4.80 | 25.20±6.10 | 0.680 | 24.50±6.80 | 0.33 |
| Body fat mass (kg) | 17.60±5.70 | 14.30±3.90 | 0.020 | 16.40±4.90 | 0.48 |
| Waist-hip ratio | 0.95±0.06 | 0.90±0.03 | 0.008 | 0.91±0.03 | 0.18 |
| BCM (kg) | 30.30±5.40 | 29.60±6.30 | 0.240 | 29.10±7.40 | 0.33 |
| TBW (L) | 34.60±6.10 | 34.20±7.30 | 0.650 | 33.40±8.40 | 0.36 |
| **Hand grip strength** | | | | | |
| Right | 35.50±7.90 | 33.60±5.40 | 0.580 | 35.50±10.0 | 0.89 |
| Left | 31.90±7.70 | 31.70±7.00 | 0.880 | 32.50±9.10 | 0.48 |
| **Blood chemistry** | | | | | |
| Albumin (g dLG$^1$) | 4.30±0.30 | 4.10±0.30 | 0.140 | 4.30±0.20 | 0.58 |

Values are presented as Mean±Standard deviation. BMI: Body mass index, AMC: Arm muscle circumference, TSF: Triceps skinfold thickness, BIA: Bioelectrical impedance analysis, BCM: Body cell mass, TBW: Total body water

In the anthropometric analysis, TSF% was significantly ($p<0.05$) decreased at the end of treatment compared with before treatment, whereas, AMC% was not. The decreased TSF% was recovered to before treatment level at 6 months after treatment (Table 2).

**Body composition:** In the body composition analysis by using InBody S20, body fat mass and waist-hip ratio were also significantly ($p<0.05$) decreased at the end of treatment compared with before treatment, whereas skeletal muscle mass, BCM and TBW were not. The decreased body fat mass was also recovered to before-treatment level at 6 months after treatment. There was no significant change in grip strength and serum albumin at the three time points for 6 months (Table 2).

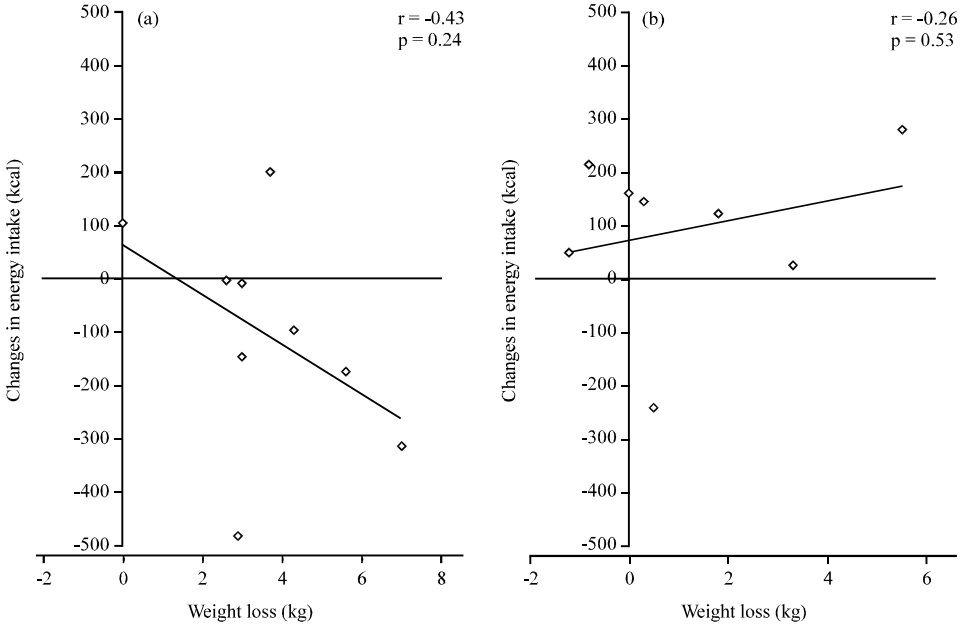


Fig. 1(a-b): Relation between energy intake and body weight in chronic hepatitis (a) Befor vs. End of treatment and (b) End of treatment vs. 6 months after treatment

Table 3: Nutrient intake and macronutrient changes in chronic hepatitis C patients

| Parameters | Before treatment | End of treatment | Before treatment vs. end of treatment p | Six months after treatment | Before treatment vs. 6 months after treatment p |
|---|---|---|---|---|---|
| Energy intake (kcal) | 1715.2±169.8 (n = 9) | 1569.2±257.3 (n = 9) | 0.03 | 1731.9±245.4 (n = 8) | 0.67 |
| Protein (%) | 17.6±1.7 (n = 8) | 18.2±2.0 (n = 8) | 0.77 | 18.3±1.6 (n = 8) | 0.67 |
| Fat (%) | 37.5±8.9 (n = 8) | 40.2±8.9 (n = 8) | 0.78 | 37.9±9.3 (n = 8) | 0.58 |
| Carbohydrate (%) | 56.1±6.9 (n = 9) | 54.0±8.1 (n = 9) | 0.78 | 54.9±6.0 (n = 8) | 0.67 |

Value are presented as Mean±Standard deviation

**Dietary intake:** The total energy intakes were significantly reduced at the end of treatment compared with before treatment and were recovered at 6 months after treatment in nine patients whose nutritional intake data were available. In the macronutrient analysis, the proportion of protein, fat and carbohydrate did not change at the three time points (Table 3, Fig. 1).

## DISCUSSION

**Statement of principal findings:** Peg-IFN-" and ribavirin treatment was reported to have the variety of adverse effects such as fatigue, influenza-like symptoms, gastrointestinal disturbances, neuropsychiatric symptoms and hematologic abnormalities (Manns *et al*., 2001; Fried *et al*., 2002; Hadziyannis *et al*., 2004). Although weight loss was also frequently observed in patients treated with Peg-IFN-" and ribavirin, the pathophysiological mechanism remains to be elucidated (Seyam *et al*., 2005; Suwantarat *et al*., 2010; Conjeevaram *et al*., 2011; Afdhal *et al*., 2014).

The PEM is a frequently observed nutritional disorder, characterized by decreases in serum albumin and the respiratory quotient (Miwa and Moriwaki, 2004). The PEM represented serum albumin decrease and skeletal muscle reduction in patients with decompensated liver cirrhosis. Moreover, rapid weight loss during Peg-IFN-" and ribavirin treatment may induce serious

metabolic disorders in hepatitis C patients. In this study, body weight and BMI were significantly decreased at the end of treatment in 10 participants. In anthropometric analyses, TSF% which represents body fat mass was decreased, whereas, AMC% which represents body muscle was not decreased. In the body composition analysis by means of BIA, body fat mass was also significantly decreased, whereas, skeletal muscle mass was not. There were no changes in BCM and TBW which reflect the amount of protein plus intracellular water content and total amount of water, respectively (Plauth *et al*., 2006).

The body weight loss observed during the Peg-IFN-" and ribavirin therapy was attributable to body fat mass decrease rather than skeletal muscle mass decrease. The grip strength which correlated with body muscle mass, also did not change because the skeletal mass did not decrease (Kallman *et al*., 1990; Alvares-da-Silva and da Silveira, 2005). Because there was no significant change in serum albumin during the therapy, we found that the nutritional condition in patients receiving Peg-IFN and ribavirin therapy was different from the lack of protein and energy shortage observed in persons with PEM. Therefore, most of the patients did not show decreased performance status although they complained about appetite loss and fatigue.

Body weight loss with significant decrease in body fat mass and no decrease in fat-free mass was reported in chronic hepatitis C patients with Peg-IFN-" and ribavirin combination therapy (Fioravante *et al*., 2012). However, body weight loss with not only body fat mass decrease but also fat-free mass decrease has also been reported in HCV patients with conventional interferon and ribavirin therapy (Jonas *et al*., 2012; Alam *et al*., 2013). These studies, however, it did not evaluate the recovery of body weight and the body composition change after the therapy (Fioravante *et al*., 2012; Alam *et al*., 2013). The recovery of body fat mass, TSF% and age-to-body weight ratio at 6 months after Peg-IFN and ribavirin therapy was reported in a study in children (Jonas *et al*., 2012). The BIA method was used in these studies to evaluate body composition (Yanovski *et al*., 1996). In anthropometric analyses, the AMC% and TSF% estimate whole-body data by using measurements from only one side of the arm, however, in BIA analysis, the analyzer measures the whole body and, therefore, the nutritional assessment is more accurate.

A significant reduction in caloric intake was observed during the therapy. This caloric intake reduction tended to be correlated with the body weight loss observed in this study. Body weight loss with a significant decrease in body fat was due to energy intake decrease during the treatment, as previously reported. The proportion of protein, fat and carbohydrate did not change during the therapy although the total calorie intake was reduced. The nutritional counseling provided by nutritionists may have influenced the macronutrient change. Most of the patients recovered their body weight at 6 months after the treatment, however, five patients became overweight compared with before therapy (patient No. 1, 3, 4, 7 and 9). Although nutritional intervention should be required to minimize dietary intake reduction during Peg-IFN-" and ribavirin therapy, nutritional intervention after the therapy may also be needed to prevent rapid weight gain and an overweight status.

The limitation of this study is the small sample size. Although all 10 patients received Peg-IFN-" and ribavirin, the treatment periods were varied depending on the viral serotype. Furthermore, we did not have data on HCV patients without IFN therapy as controls. The reduction of nutritional adverse effects may have occurred because the patients were monitored and their energy intake estimated, by nutritionists at our hospital during the therapy.

In conclusion, we found that body weight loss with a significant decrease in body fat mass and no decrease in skeletal muscle mass was related to a reduction in caloric intake in chronic hepatitis

C patients with Peg-IFN-"-2b and ribavirin combination therapy. In addition to careful medical monitoring by physicians, nutritional counseling by nutritionists also seems to be important in these patients.

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