Applied nutritional investigation

Weight loss and resting energy expenditure in patients with chronic hepatitis C before and during standard treatment

Milena Fioravante M.D.,* Sarah Monte Alegre M.D., Ph.D., Daniela Miguel Marin Ph.D., Sonia Leticia Silva Lorena M.D., Ph.D., Tiago Sevá Pereira M.D., Elza Cotrim Soares M.D., Ph.D.

*Department of Internal Medicine, Faculty of Medical Sciences, University of Campinas/UNICAMP, Sao Paulo, Brazil
Gastrocenter, University of Campinas/UNICAMP, Sao Paulo, Brazil

Objective: Infection with hepatitis C virus (HCV) is a serious public health problem worldwide. In clinical studies, weight loss has been reported in 11% to 29% of patients treated with pegylated interferon-α-2a/2b. Few reports have tried to explain such a weight loss. The aim of this study was to evaluate nutritional status, body composition, and resting energy expenditure (REE) in patients with chronic hepatitis C before and during treatment with pegylated interferon and ribavirin.

Methods: This was a prospective study with the evaluation of patients with hepatitis C virus before and after 12 wk of treatment with pegylated interferon and ribavirin. The evaluation consisted of anthropometry (weight, height, body mass index, and waist circumference), and body composition was determined by bioelectrical impedance analysis. The REE of each individual was obtained by indirect calorimetry. To compare the two phases of treatment, the Wilcoxon test was used. The significance level was 5%.

Results: Subjects had significant weight loss during treatment with a consequent decrease in body mass index. This weight decrease was accompanied by a significant decrease in body fat and no decrease in fat-free mass. There was a significant decrease in energy intake as assessed by 24-h recall. However, there was no change in REE and in REE corrected for fat-free mass.

Conclusion: Our study of patients with hepatitis C treatment showed that these patients had significant weight loss and this was not associated with changes in energy expenditure. However, we observed a significant decrease in energy intake, pointing to a possible need for intervention measures to decrease the damage.

Introduction

Infection with hepatitis C virus (HCV) is a serious public health problem worldwide [1] and is considered the major cause of chronic liver disease, cirrhosis, and death in the final stages of liver disease in the United States and in most Western countries. It is estimated that approximately 180 million people around the world are infected with HCV [2].

Currently, the standard treatment for chronic HCV infection is a combination of pegylated interferon (PEG-IFN) α-2a or α-2b and ribavirin. In clinical studies, weight loss has been reported in 13% to 20% of patients treated with PEG-IFN α-2a and 11% to 29% in patients treated with PEG-IFN α-2b [3–5], demonstrating an important and predictable biological response to treatment [6]. However, the actual mechanisms of these disorders have not yet been clarified; it is not known if chronic HCV infection affects energy expenditure or if PEG-IFN therapy affects the resting metabolic rate of these patients [7].

Several studies have demonstrated that patients on standard therapy have side effects, such as fatigue, influenzalike symptoms (fever, myalgia, headache), insomnia, nausea, alopecia, irritability, arthralgia, anorexia, weight loss, dermatitis, hematological abnormalities including neutropenia, and neuropsychiatric symptoms such as depression, many of which may affect nutritional status [3].

The few reports that have explained the weight loss often observed during the current standard treatment of chronic HCV with PEG-IFN and ribavirin led us to the necessity of designing
Materials and methods

Patients

This study prospectively evaluated the REE, nutritional status, and dietary intake of 42 patients with HCV referred to the viral hepatitis outpatient unit at the Gastrocenter (University of Campinas) and undergoing treatment with PEG-IFN and ribavirin.

The inclusion criteria adopted were those in the official protocol for HCV treatment from the Brazilian Ministry of Health. It is important to emphasize the homogeneity of the criteria, the cooperation of 79 y for inclusion, confirmation of the disease, and staging by liver biopsy.

The clinical exclusion criteria were the use of a weight-control dietary supplement, participating in a diet or weight-losing program or other medical treatment for weight loss, and having other chronic liver diseases such as hepatitis B, Wilson’s disease, hemochromatosis, autoimmune liver disease, decompensated cirrhosis, hepatocellular carcinoma, human immunodeficiency viral infection, severe heart disease, cancer, active thyroid disease, uncontrolled psychotic seizures, schizophrenia, severe depression without clinical control, pregnancy, alcohol abuse, and the active use of injected drugs.

All subjects were evaluated before treatment, i.e., when the start of treatment was determined by the medical team, and reassessed after 12 wk of therapy. The patients had weekly injections of PEG-IFN α-2a (180 μg) or α-2b (1.5 μg/kg) plus ribavirin (1000 to 1250 mg/d).

No patients had any clinical evidence of ascites or fluid retention.

Data collection was conducted from March 2009 to December 2010.

Ethical considerations

The study was approved by the research ethics committee at the Faculty of Medical Sciences, University of Campinas and written informed consent was obtained from each participant after the purpose of the study was fully explained.

Assessment of nutritional status

Anthropometric analysis was done under fasting conditions. Body height and weight were measured and body mass index (BMI) was calculated [8]. A flexible tape was used to measure the circumference of the arm (midarm circumference) while the arm was hanging relaxed. The measurement was taken midway between the tip of the acromion and the olecranon process. Triceps skinfold thickness was measured to the nearest millimeter using a Lange caliper (Santa Cruz, CA, USA). These were measured on the dominant side of the body, with the patient standing in a relaxed position. Muscular midarm circumference was calculated by the formula: muscular midarm circumference (cm) = midarm circumference – skinfold thickness/10. The abdominal circumference was measured at the midpoint between the iliac crest and the last rib.

Body composition

Body composition was measured by bipolar bioelectrical impedance analysis with an alternating electric current (50 μA) at two frequencies, 1 MHz and 5 kHz, as previously described and validated by Boulier et al. [9].

A portable impedance analyzer (Biodynamics 310, Seattle, WA, USA) was equipped with a microprocessor; a computer was used to calculate the impedance and body composition. Measurements were taken in the morning, under fasting conditions. The subjects had been supine for 10 min, with their arms relaxed at the sides but not touching the body. Fat-free mass (FFM) was expressed in kilograms and total body fat in percentages.

Resting energy expenditure

The resting energy expenditure (REE) of each participant was obtained by indirect calorimetry in the metabolic unit of the Department of Clinical Medicine, Faculty of Medical Sciences, University of Campinas. The procedure was performed in the morning in a room with controlled temperature, low light, and no noise. After a 30-min rest in the supine position, measurements were taken using a canopy, open-circuit indirect calorimeter (model 29N, Medics Vmax, Yorba Linda, CA, USA). After equilibrium was reached (about 10 min), respiratory exchanges were monitored continuously over a 30-min period; data were obtained every minute and averaged over the 30 min. The system was calibrated immediately before each measurement with two standard gases. The REE was calculated from the oxygen consumption rate and the carbon dioxide production rate. The REE was also expressed as a ratio of FFM (REE/FFM) in kilocalories per kilogram of FFM and for 24-h.

Nutritional counseling/food intake

All subjects were free-living and were instructed to consume their habitual diets during the treatment. However, before the start of treatment, a 24-h recall was performed by the nutritionist responsible for this study and who had general guidelines on healthy eating. Patients were followed up monthly. Four of the eutropic patients began during the study to have severe weight loss, and thus, for ethical reasons, were instructed to improve their alimentation. As a result, by the end of the study none of these patients were malnourished.

The 24-h recall was performed before and after 12 wk of starting treatment. The diet composition was quantified by NutWin 1.5 (Federal University of São Paulo, São Paulo, Brazil). To minimize inaccuracies in the 24-h recall, the interviewer was always the nutritionist responsible for this study. The researcher attempted to clarify the information provided by the subjects and all 24-h recalls were analyzed by the same researcher.

Statistical analysis

All data are expressed as mean ± standard deviation. The comparison of data between the two times of treatment (before treatment and at 12 wk) was performed using the Wilcoxon test. The Mann-Whitney test was used to compare the variables between two groups (liver fibrosis stages 1 to 2 and 3 to 4). The analysis of correlation between weight loss and energy intake was performed by the Spearman correlation coefficient.

All analyses were carried out using SAS 9.1.3 for Windows (SAS Institute, Cary, NC, USA) and statistical significance was accepted at P < 0.05.

Results

Fourty-two patients with chronic hepatitis C treated with PEG-IFN and ribavirin participated in this study.

At the baseline of the study, 40.5% were eutrophic, 33.3% were overweight, and 26.2% were obese. The characteristics of the study population are listed in Table 1.

The differences in nutritional status, energy intake, and REE of the patients before and during drug therapy for the treatment of hepatitis C are presented in Table 2. The subjects had significant weight loss during the treatment with a consequent decrease in BMI. This weight decrease was accompanied by a significant decrease in body fat and no decrease in FFM.

Table 1

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Values</th>
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<tbody>
<tr>
<td>Gender, n (%)</td>
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</tr>
<tr>
<td>Male</td>
<td>30 (71.4)</td>
</tr>
<tr>
<td>Female</td>
<td>12 (28.6)</td>
</tr>
<tr>
<td>Age (y)</td>
<td>46.3 ± 10.8</td>
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<tr>
<td>Interferon, n (%)</td>
<td></td>
</tr>
<tr>
<td>α-2a</td>
<td>23 (54.8)</td>
</tr>
<tr>
<td>α-2b</td>
<td>19 (45.2)</td>
</tr>
<tr>
<td>Genotype, n (%)</td>
<td></td>
</tr>
<tr>
<td>1/4a</td>
<td>1 (2.4)</td>
</tr>
<tr>
<td>1a</td>
<td>9 (22)</td>
</tr>
<tr>
<td>1a1b</td>
<td>1 (2.4)</td>
</tr>
<tr>
<td>1b</td>
<td>13 (31.7)</td>
</tr>
<tr>
<td>3a1</td>
<td>17 (41.5)</td>
</tr>
<tr>
<td>Staging, n (%)</td>
<td></td>
</tr>
<tr>
<td>1–2</td>
<td>17 (40.5)</td>
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<tr>
<td>3–4</td>
<td>25 (59.5)</td>
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</tbody>
</table>

Nutritional status according to BMI, n (%)

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<table>
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<tbody>
<tr>
<td>Eutrophic</td>
<td>17 (40.5)</td>
</tr>
<tr>
<td>Overweight</td>
<td>14 (33.3)</td>
</tr>
<tr>
<td>Obesity I</td>
<td>8 (19)</td>
</tr>
<tr>
<td>Obesity II</td>
<td>2 (4.8)</td>
</tr>
<tr>
<td>Obesity III</td>
<td>1 (2.4)</td>
</tr>
</tbody>
</table>

BMI, body mass index.
Weight loss is a side effect commonly seen in patients on therapy with PEG-IFN and ribavirin, ranging from 12% to 29% [4, 5], which can reach 90% of individuals [10], with probable recovery after treatment [11]. However, the mechanisms of these disorders have not yet been elucidated, including the influence of therapy on REE. Therefore, we attempted in this study to contribute to a better understanding of this phenomenon.

Hamer [10] reported that 93% of patients had weight loss and decreased energy intake during therapy with PEG-IFN α-2a and ribavirin. In comparison, in the present study, 88% of patients had weight loss and a decreased energy intake in the 12-wk period, with no changes in REE.

In a randomized trial, Manns et al. [4] evaluated patients who received PEG-IFN α-2b 1.5 μg/kg each week plus ribavirin 800 mg/d or PEG-IFN α-2b 1.5 μg/kg per week for 4 wk and then had weight loss and a decreased energy intake (Fig. 1).

There was a significant decrease in energy intake assessed by the 24-h recall (Table 3), without a significant change in the percentage of the distribution of macronutrients but with a significant decrease in the consumption of proteins and fat (Table 4). However, there were no changes in REE and REE corrected for FFM (Table 2).

A slightly significant correlation was found between weight loss and a decrease in energy intake (Fig. 1).

From the standpoint of the degree of hepatic fibrosis, i.e., the stage of hepatitis C, compared with the weight, REE and REE adjusted for FFM, and the energy intake of patients before and during drug therapy, we observed no differences for the variables analyzed (Table 5).

### Discussion

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### Table 2

Differences in nutritional status and resting energy expenditure of patients before and during hepatitis C treatment

<table>
<thead>
<tr>
<th></th>
<th>Baseline/before treatment</th>
<th>Week 12 of treatment</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>79.1 ± 15.6</td>
<td>75.7 ± 15</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.5 ± 5.2</td>
<td>26.3 ± 5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body fat (%)</td>
<td>29 ± 8.2</td>
<td>26.7 ± 7.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FFM (kg)</td>
<td>55.6 ± 10</td>
<td>55 ± 10.2</td>
<td>0.210</td>
</tr>
<tr>
<td>Abdominal circumference (cm)</td>
<td>97.8 ± 14.3</td>
<td>95.5 ± 14.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triceps skinfold (mm)</td>
<td>18 ± 8.1</td>
<td>15.6 ± 7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Muscular midarm circumference</td>
<td>27 ± 2.9</td>
<td>26.5 ± 2.8</td>
<td>0.008</td>
</tr>
<tr>
<td>REE (kcal)</td>
<td>1168.2 ± 303</td>
<td>1151.3 ± 249</td>
<td>0.670</td>
</tr>
<tr>
<td>REE (kcal)/FFM (kg)</td>
<td>20.9 ± 3.7</td>
<td>21.1 ± 3.7</td>
<td>0.864</td>
</tr>
</tbody>
</table>

BMI, body mass index; FFM, fat-free mass; REE, resting energy expenditure

* Wilcoxon test. Statistical significance was accepted at P < 0.05.

### Table 3

Dietary intake of patients before and during hepatitis C treatment

<table>
<thead>
<tr>
<th></th>
<th>Baseline/before treatment</th>
<th>Week 12 of treatment</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy intake (kcal)</td>
<td>2131 ± 890</td>
<td>1834 ± 699</td>
<td>0.012</td>
</tr>
<tr>
<td>Carbohydrate (%)</td>
<td>50.6 ± 6</td>
<td>52.8 ± 6.2</td>
<td>0.06</td>
</tr>
<tr>
<td>Protein (%)</td>
<td>16.3 ± 4.6</td>
<td>16.2 ± 3.4</td>
<td>0.98</td>
</tr>
<tr>
<td>Fat (%)</td>
<td>33.1 ± 5.5</td>
<td>31 ± 5.8</td>
<td>0.12</td>
</tr>
</tbody>
</table>

* Wilcoxon test. Statistical significance was accepted at P < 0.05.

### Table 4

Macronutrient intakes of patients before and during hepatitis C treatment

<table>
<thead>
<tr>
<th></th>
<th>Baseline/before treatment</th>
<th>Week 12 of treatment</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbohydrate (g)</td>
<td>270.3 ± 116.6</td>
<td>243.2 ± 88</td>
<td>0.194</td>
</tr>
<tr>
<td>Protein (g)</td>
<td>84 ± 35.6</td>
<td>75.5 ± 34.1</td>
<td>0.040</td>
</tr>
<tr>
<td>Fat (g)</td>
<td>80.7 ± 38.2</td>
<td>65.3 ± 29.7</td>
<td>0.009</td>
</tr>
</tbody>
</table>

* Wilcoxon test. Statistical significance was accepted at P < 0.05.

0.5 μg/kg per week plus ribavirin 1000 to 1200 mg/d for 48 wk, and the percentages of patients who had weight loss were 29% and 17%, respectively.

Seyam et al. [6] observed that 91.2% of patients treated with PEG-IFN α-2b lost weight at 4 wk, 93.7% at 12 wk, and 94.7% at 24 wk.

Conjeevaram et al. [11] found decreases in BMI and homeostasis model assessment (HOMA-IR) values in non-responder patients, those with relapse, and patients who achieved a sustained virologic response (SVR). However, these values rebounded after the end or the suspension of treatment mainly in non-responders and those who relapsed. This was probably because there was a decrease in the inflammatory process of the liver with a consequent decrease of inflammatory cytokines during treatment and maintenance in those with SVR. A similar result was observed by Suwantarat et al. [12], in which patients who achieved SVR had significant weight loss compared with those without SVR, but this association is controversial. The weight loss was maintained during drug therapy, but these patients began to gain weight once therapy was stopped.

This decline in nutritional status may be related to the effect of the side effects of the treatment, which include fatigue, loss of appetite, and nausea.

Therefore, weight loss in patients during the treatment of chronic hepatitis C with PEG-IFN and ribavirin, besides being a frequent symptom [6, 10–12], is an ongoing concern for experts who monitor these patients during the therapy cited [13].

In our study, although weight loss occurred, we observed that none was classified as malnourished according to the BMI in the nutritional assessment (data not shown), possibly because they...
were being monitored by medical staff and a nutritionist who provided guidance on how to deal with the symptoms during treatment, with the aim of decreasing damage.

Regarding body composition, although there was no decrease in FFM, a significant loss in body fat was observed. We observed a decrease of approximately 14% of caloric intake, but with a proper proportional distribution of macronutrients (Table 3), i.e., there was no restriction on a specific macronutrient, which probably contributed to the preservation of FFM. Also, at the baseline, i.e., before starting treatment, all patients received general guidelines on how to eat healthily. None of the patients practiced physical activity during the treatment. The main reason for non-physical activity was the presence of side effects such as anemia, fatigue, and arthralgia, which are very common during PEG-INF use.

From the standpoint of the body composition data, similar results have been described by other investigators. Iwasa et al. [14] reported a significant decrease in visceral fat and total body fat percentage in patients with chronic hepatitis C after 3 and 6 mo of calorie restriction (Table 3). Further, Redman et al. [15] found a significant decrease in body fat and FFM in individuals after 3 and 6 mo of calorie restriction (calorie decreases of 17.8% and 19.5%, respectively) with or without exercise.

However, there are no other studies that explain the significant loss of body fat in these patients. Because most patients were overweight or obese, the calorie restriction likely caused this decrease.

Another point to consider is the possible decrease of inflammation characterized by a decrease in alanine aminotransferase [14,16] during treatment that may reflect the decrease in circulating inflammatory cytokines [17], which in turn could contribute to decreased total body fat.

Although in our study there was no change in REE, there was a decrease in energy intake, which partly explains the weight loss (Fig. 1). Other studies showing the relation of inflammatory cytokines to weight loss and a decrease in body fat (lipolysis) need to be carried out in patients with chronic hepatitis C.

The weight loss may be related to the adverse effects of treatment, such as a loss of appetite, with the consequent decrease in energy intake and disease progression rather than changes in REE.

Patients receiving treatment with PEG-INF plus ribavirin for chronic hepatitis C must be monitored closely for side effects. These events can be managed effectively to maximize the patients’ adherence and thus the chance for treatment success [18].

The addition of the direct-acting antiviral agent to standard treatment seems to have the potential to double the sustained response rate compared with that recorded with standard treatment alone in treatment-naïve patients with genotype-1 [19]. However, these gains will be partly offset by new challenges in viral resistance and increased adverse events [20], especially in weight loss.

A limitation in the study is the potential inaccuracies associated with the 24-h recall. This method depends on the memory of the interviewee who may not recall information precisely. Conversely, it is a quick and easy questionnaire response, the patients do not need to be literate as they are interviewed, and the test does not influence the feeding patterns of the patient. However, any estimation of intake and portion sizes may have a degree of error.

The finding obtained in our study is of great significance, because we cannot attribute the changes in REE to the drugs used. The fact that we demonstrated a decrease in energy intake in the subjects of this study reinforces the need for greater support for these individuals from a nutritional standpoint, emphasizing the inclusion of the nutritional professional in the team who follows these patients.

The results have an important consequence from the clinical point of view, because the standard treatment will used for several years, even after the advent of direct-acting antivirals such as the protease inhibitors recently approved for clinical use [21].

In conclusion, our study of patients with hepatitis C treatment showed that these patients had a significant weight loss and this was not associated with changes in energy expenditure. However, we observed a significant decrease in energy intake, pointing to a possible need for intervention measures to decrease the damage.

Acknowledgments

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References