Impact of Body Weight Reduction via Diet and Exercise on the Anti-Viral Effects of Pegylated Interferon Plus Ribavirin in Chronic Hepatitis C Patients with Insulin Resistance: A Randomized Controlled Pilot Trial

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Abstract

Objective Insulin resistance (IR) modifies the anti-viral effects of interferon (IFN) therapy in patients with chronic hepatitis C (CHC). This prospective study evaluated whether lifestyle interventions improve the anti-viral response to treatment with pegylated (PEG)-IFN plus ribavirin (RBV) in patients with CHC.

Methods The study cohort consisted of 60 patients chronically infected with a high viral load of hepatitis C virus genotype 1b and a homeostasis model assessment of IR (HOMA-IR) value above 2. The patients were divided into two groups, an intervention group (n=26) and a control group (n=34). The patients in the intervention group were prescribed diet and exercise treatment for 3-6 months to reduce their body weight by ≥5% before starting treatment with PEG-IFN plus RBV.

Results Diet and exercise significantly reduced the HOMA-IR values in the intervention group, from 3.4 to 2.5 (p=0.0009), especially among the 15 patients who achieved a body weight reduction of ≥5%. The viral disappearance rate at 12 weeks was significantly higher in the intervention group among the patients with a ≥5% weight reduction than in the control group (53.3% vs. 23.5%, p=0.01). However, the sustained viral response (SVR) rates were similar.

Conclusion Improvements in IR achieved through weight reduction via lifestyle interventions may enhance the early viral response to PEG-IFN plus RBV in patients with CHC. However, this intervention program has no effect on the SVR rate.

Key words: life style intervention, insulin resistance, pegylated interferon plus ribavirin, chronic hepatitis C

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Introduction

Insulin resistance (IR) and glucose intolerance are crucial and distinctive clinical manifestations in patients with chronic hepatitis C (CHC) (1-3). IR has been shown to impair the anti-viral effects of treatment with peginterferon (PEG-IFN) plus ribavirin (RBV) (4-7). Indeed, CHC pa-

tients infected with a high viral load of hepatitis C virus (HCV) genotype 1 and with IR show early and sustained viral response rates to PEG-IFN/RBV treatment of only 20%. Moreover, the addition of insulin sensitizers such as pioglitazone or metformin to PEG-IFN/RBV does not improve the viral response rate (8, 9).

Although HCV infection itself can induce IR in hepatocytes, visceral fat accumulation has been found to be more

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important for the onset of IR in CHC patients (10). This randomized controlled trial investigated whether lifestyle interventions achieved through diet and exercise enhance the anti-viral effects of PEG-IFN/RBV therapy in patients with CHC.

Materials and Methods

Study design

This was an open-label, prospective randomized pilot trial. Of 210 consecutive patients infected with HCV genotype 1b and exhibiting a high viral load (>5 logIU/mL, COBAS Taq-Man PCR, Roche Diagnostics, Tokyo, Japan) who visited Saga Medical School Hospital between June 2007 and December 2008, 194 were judged as requiring treatment and met the inclusion criteria for PEG-IFN plus RBV therapy, as follows: white blood cell count $>3,000/\text{mm}^3$, neutrophil count $>1,500/\text{mm}^3$, platelet count $>100,000/\text{mm}^3$ and hemoglobin concentration >10 g/dL. After excluding patients with other chronic liver diseases, such as autoimmune hepatitis, alcoholic hepatitis and decompensated cirrhosis, in addition to other conditions, including severe renal disorders, poorly controlled diabetes or treatment with an antidiabetic agent, poorly controlled hypertension, a previous medical history of interstitial pneumonia, pregnancy or the possibility of pregnancy, lactation, severe depression, a previous medical history of allergies to biological preparations such as vaccines, a previous medical history of allergies to interferon or ribavirin, 190 patients underwent 75-g oral glucose tolerance tests (OGTTs). Written informed consent was obtained from patients with a homeostasis model assessment of IR (HOMA-IR) score >2 on OGTT. Using a computer generated random number table, these patients were randomly allocated to an intervention group (Group A), who was prescribed lifestyle modifications to decrease body weight before PEG-IFN/RBV treatment, and a control group treated without intervention (Group B).

The primary endpoints of this study were the viral disappearance rate every four weeks during PEG-IFN/RBV treatment and the sustained viral response (SVR) rate, defined as the absence of the virus 24 weeks after the end of treatment.

The study protocol was developed in accordance with the Declaration of Helsinki, approved by the Ethics Committee of Saga Medical School in 2007 (approval ID number: 2007-07-02) and registered at UMIN-Clinical Trials Registry in 2010 (UMIN000003044).

Lifestyle intervention

The target of the intervention was a $\geq 5\%$ loss of initial body weight. During the three day run-in period, the contents of meals were recorded using a self-administered questionnaire, and a dietitian instructed each patient to maintain a total caloric intake of 25-35 kcal/ideal body weight/day according to their daily activity. The exercise intervention was based on the 'Exercise and Physical Activity Guide for

Health Promotion 2006,' published by the Ministry of Health, Labour and Welfare of Japan (11). Briefly, the patients were recommended to walk a minimum of 8,000 steps per day while wearing a pedometer. The patients were also instructed to record their weight and daily number of steps in diaries every day. Blood pressure was assessed and a physical examination was performed each month, and all patients received nutritional counseling regarding adequate caloric intake with a dietitian every three months. These lifestyle interventions were continued for 3-6 months.

PEG-IFN/RBV treatment

All patients received weekly subcutaneous injections of 1.5 $\mu\text{g/kg}$ of PEG-IFN $\alpha 2\text{b}$ (Pegintron, MSD, Tokyo, Japan) and oral RBV (Rebetol, MSD) every day. The daily dose of RBV was determined based on body weight: 600 mg for patients weighing up to 60 kg, 800 mg for those weighing 60-80 kg and 1,000 mg for those weighing more than 80 kg. The RBV dose was reduced from 600 to 400 mg, or from 800 or 1,000 to 600 mg, when the hemoglobin level was <10 g/dL. The PEG-IFN dose was halved when the leukocyte, neutrophil or platelet count was $<1,500/\mu\text{L}$, $<750/\mu\text{L}$ or $<50,000/\mu\text{L}$, respectively. Further dose reduction or discontinuation for other adverse events were made at the discretion of the attending physician.

The duration of treatment was 48 weeks for patients negative for HCV after 12 weeks and 72 weeks for patients negative for HCV between 13 and 36 weeks. All patients were followed up for 24 weeks after the completion of treatment completion, and those negative for the virus 24 weeks after treatment completion were judged as having achieved a SVR.

Laboratory assessments

All demographic and laboratory data were collected at the time of liver biopsy or OGTT. Data were collected for patients in the intervention group after the intervention and just before starting PEG-IFN plus RBV treatment. Venous blood samples were taken after a 12-h overnight fast for hematology, blood chemistry and 75 g OGTT.

IR was evaluated using the HOMA method (12) as follows: fasting plasma glucose (FPG) $\times$ fasting plasma insulin (FPI)/405. The whole-body insulin sensitivity index (WBISI) (13) was calculated as $10,000/(\text{FPG} \times \text{FPI} \times \text{mean PG } 0-120 \times \text{mean PI } 0-120)^{0.5}$.

Liver histology

Percutaneous liver biopsy samples were obtained under ultrasound guidance. A 15-mm-long liver biopsy specimen from each patient was fixed in 10% formalin, embedded in paraffin, sectioned and stained with hematoxylin-eosin and Azan for the histologic evaluation. Hepatic fibrosis and inflammation were scored histologically using the METAVIR scoring system (14). Based on the degree of lymphocyte infiltration and hepatocyte necrosis, the extent of inflammation was classified as A0 to A3, with higher scores indicating

Figure 1. Study participant flow. CHC: chronic hepatitis C, G1: genotype 1b

more severe inflammation. Fibrosis was graded as F0 (no fibrosis); F1 (portal fibrosis without septa); F2 (portal fibrosis with rare septa); F3 (numerous septa without cirrhosis) and F4 (cirrhosis). The degree of steatosis was quantified as the percentage of hepatocytes containing fat droplets, with the patients classified into two groups: namely, those with <10% and ≥10% hepatocytes containing fat droplets.

Statistical analysis

Categorical data were compared using the χ^2 test and continuous data were compared using the Mann-Whitney *U* test. The data are expressed as the mean $\pm$ SD, with a *p* value of <0.05 being considered statistically significant. All statistical analyses were performed using the SAS software program (SAS Institute, Cary, USA).

Results

Written informed consent was obtained from 60 of the 64 patients with a HOMA-IR score >2 on OGTT. Although 30 patients were allocated to Group A, four patients rejected the intervention after randomization due to the required alterations in their social or home environment and were therefore included in Group B. Finally, 26 and 34 patients were assigned to Groups A and B, respectively (Fig. 1).

The patient characteristics prior to treatment with PEG-IFN plus RBV are shown in Table 1. There were no significant differences in age, sex or histological findings between the intervention (Group A) and control (Group B) groups. Before the start of the lifestyle interventions, there were no significant differences between the two groups in body composition, hematological findings, hepatic function parameters, lipid profiles, insulin sensitivity or viral load, although the fasting glucose concentrations were higher in Group A than in Group B.

Following the lifestyle interventions, although prior to the

start of PEG-IFN/RBV treatment, the patients in Group A showed decreases in body weight, visceral fat, white cell count, hemoglobin, platelet count, serum albumin, GGT, triglycerides, fasting glucose, insulin and HOMA-IR. These subjects also showed increases in HDL-cholesterol and the insulin sensitivity index. However, there were no significant differences between Group A after intervention and Group B.

The rates of disappearance of serum HCV-RNA after starting PEG-IFN/RBV treatment are shown in Fig. 2. The rates of HCV-RNA negativity in Groups A and B were 0.0% and 2.9%, respectively, at 4 weeks, 19.2% and 11.8%, respectively, at 8 weeks, 42.3% and 23.5%, respectively, at 12 weeks, 88.5% and 70.6%, respectively, at the end of treatment and 34.6% and 29.4%, respectively, six months after treatment. However, none of the differences at any time point were statistically significant.

The intervention group was divided into two subgroups, 15 patients who lost ≥5% of their weight after the intervention (Group A1) and 11 who lost <5% of their weight (Group A2) (Fig. 1). These two subgroups were similar before the intervention, except for the platelet count and fibrosis stage. After the intervention, the fasting plasma insulin levels and HOMA-IR values were significantly lower in Group A1 than in Group B; however, but did not differ between Group A2 and Group B. The plasma insulin levels were lower in Group A1 than in Group A2 after the intervention, although the difference was not statistically significant (Table 2).

The rates of disappearance of serum HCV-RNA after the beginning of PEG-IFN/RBV treatment in Groups A1, A2 and B were 0.0%, 0.0%, 2.9%, respectively, at 4 weeks, 20.0%, 18.2%, and 11.8%, respectively, at 8 weeks 53.3%, 27.3%, and 23.5%, respectively, at 12 weeks, 93.3%, 81.8%, and 70.6%, respectively, at the end of treatment and 33.3%, 36.4%, and 29.4%, respectively, six months after the end of

Table 1. Characteristics of Patients who Underwent Lifestyle Intervention Prior to Treatment with PEG-IFN/RBV (Group A, before and after Intervention) and Those Treated with PEG-IFN/RBV without Lifestyle Intervention (Group B).

	Group A (n=26)		Group B (n=34)	p value		
	Pre-intervention	Post-intervention		A pre vs. A post	A pre vs. B	A post vs. B
Male / Female	15 / 11	—	19 / 15	—	0.89 [†]	—
Age (y)	55.9 ± 9.7	—	56.5 ± 8.3	—	0.78 ^{†††}	—
Body weight (kg)	67.4 ± 10.7	64.1 ± 10.4	63.8 ± 11.3	<0.0001 ^{††}	0.21 ^{†††}	0.91 ^{†††}
BMI (kg/m ²)	25.2 ± 2.8	24.0 ± 2.6	24.3 ± 2.7	<0.0001 ^{††}	0.18 ^{†††}	0.67 ^{†††}
VFA (cm ²)	108.0 ± 48.0	87.5 ± 41.8	98.2 ± 32.7	0.0001 ^{††}	0.39 ^{†††}	0.31 ^{†††}
WBC (×10 ³ /μL)	5.4 ± 1.1	4.9 ± 1.4	5.2 ± 1.4	0.04 ^{††}	0.64 ^{†††}	0.37 ^{†††}
Hemoglobin (g/dL)	14.6 ± 1.3	14.2 ± 1.3	14.0 ± 1.9	0.02 ^{††}	0.15 ^{†††}	0.62 ^{†††}
Platelet (×10 ³ /μL)	16.3 ± 4.6	14.9 ± 4.3	16.4 ± 5.4	0.003 ^{††}	0.96 ^{†††}	0.26 ^{†††}
Total protein (g/dL)	7.6 ± 0.5	7.3 ± 0.5	7.4 ± 0.5	0.002 ^{††}	0.44 ^{†††}	0.51 ^{†††}
Albumin (g/dL)	4.3 ± 0.3	4.1 ± 0.3	4.1 ± 0.5	0.0003 ^{††}	0.02 ^{†††}	0.48 ^{†††}
AST (IU/L)	62.5 ± 41.6	62.3 ± 40.9	56.4 ± 30.0	0.97 ^{††}	0.51 ^{†††}	0.52 ^{†††}
ALT (IU/L)	78.7 ± 60.5	77.8 ± 65.6	62.4 ± 34.1	0.94 ^{††}	0.19 ^{†††}	0.24 ^{†††}
GGT (IU/L)	50.3 ± 28.4	43.3 ± 22.2	59.2 ± 51.2	0.02 ^{††}	0.43 ^{†††}	0.15 ^{†††}
Total cholesterol (mg/dL)	182.5 ± 32.7	176.2 ± 30.7	174.1 ± 32.4	0.11 ^{††}	0.33 ^{†††}	0.80 ^{†††}
LDL-cholesterol (mg/dL)	115.4 ± 30.2	107.9 ± 26.1	104.2 ± 33.2	0.17 ^{††}	0.33 ^{†††}	0.72 ^{†††}
HDL-cholesterol (mg/dL)	44.9 ± 15.1	47.8 ± 17.0	46.1 ± 16.5	0.02 ^{††}	0.78 ^{†††}	0.70 ^{†††}
Triglyceride (mg/dL)	123.7 ± 49.5	99.5 ± 41.4	107.1 ± 31.0	0.003 ^{††}	0.12 ^{†††}	0.42 ^{†††}
FPG (mg/dL)	98.2 ± 9.2	90.1 ± 9.0	92.0 ± 10.0	0.0001 ^{††}	0.02 ^{†††}	0.44 ^{†††}
FPI (μU/mL)	13.8 ± 4.0	11.0 ± 5.3	13.9 ± 6.3	0.004 ^{††}	0.91 ^{†††}	0.06 ^{†††}
HOMA-IR	3.4 ± 1.2	2.5 ± 1.3	3.1 ± 1.3	0.0009 ^{††}	0.46 ^{†††}	0.06 ^{†††}
WBISI	3.2 ± 1.2	4.3 ± 2.1	3.8 ± 1.3	0.0007 ^{††}	0.30 ^{†††}	0.30 ^{†††}
Viral load (log IU/mL)	6.6 ± 0.5	6.5 ± 0.5	6.5 ± 0.3	0.693 ^{††}	0.42 ^{†††}	0.41 ^{†††}
Interferon adherence (%)	—	93.1 ± 11.6	86.2 ± 23.6	—	0.09 ^{†††}	—
Ribavirin adherence (%)	—	88.9 ± 12.7	79.8 ± 28.9	—	0.08 ^{†††}	—
Histological findings*						
Inflammation (A0,1 / A2,3)	15 / 11	—	14 / 15	—	0.49 [†]	—
Fibrosis (F0-2 / F3,4)	10 / 16	—	13 / 16	—	0.63 [†]	—
Steatosis (<10% / ≥ 10%)	21 / 5	—	19 / 10	—	0.38 [†]	—

Results are shown as number or mean ± SD.

*: n=54 (n=26 in group A, n=28 in group B)

†: chi-squared test, ††: paired *t*-test, †††: Mann-Whitney U test

BMI: body mass index, VFA: visceral fat area, WBC: white blood cell, AST: aspartate aminotransferase, ALT: alanine aminotransferase, GGT: gamma glutamyl transpeptidase, LDL: low density lipoprotein, HDL: high density lipoprotein, FPG: fasting plasma glucose, FPI: fasting plasma insulin, HOMA-IR: homeostasis model assessment of insulin resistance, WBISI: whole body insulin sensitivity index, PEG-IFN/RBV: pegylated interferon plus ribavirin

Figure 2. Rates of serum HCV RNA negativity during the observation period. White bars indicate the intervention group (Group A) and black bars indicate the control group (Group B). There were no significant differences between these two groups in the HCV RNA negativity rates at any time point. ETR: end-of-treatment response, SVR: sustained virologic response

treatment. At 12 weeks, the early virologic response rate was significantly higher in Group A1 than in Group B ($p=0.01$), although there were no differences in the SVR rates (Fig. 3).

Discussion

This prospective study assessed whether lifestyle interventions may improve IR in CHC patients and subsequently influence the anti-viral effects of PEG-IFN/RBV treatment. The results indicated that a diet and exercise intervention for 3-6 months can reduce the plasma glucose levels and increase insulin sensitivity in CHC patients with IR. Moreover, these interventions may enhance the early viral response to PEG-IFN/RBV treatment in patients with adequate ($\geq 5\%$) weight reduction. To our knowledge, this report is the first to prospectively show the effects of body weight reduction with diet and exercise on the anti-viral response to IFN-based treatment for CHC.

Table 2. Characteristics of Patients who Underwent Lifestyle Intervention Prior to Treatment with PEG-IFN/RBV (Group A, before and after Intervention) who Did (Group A1) and Did Not (Group A2) Achieve $\geq 5\%$ Body Weight Reduction and Patients Treated with PEG-IFN/RBV without Lifestyle Intervention (Group B).

	Group A1 n=15				Group A2 n=11				Group B n=34				p value			
	Pre-intervention		Post-intervention		Pre-intervention		Post-intervention		A1 pre		A1 post		A1 pre		A1 post	
	vs.	vs.	vs.	vs.	vs.	vs.	vs.	vs.	vs.	vs.	vs.	vs.	vs.	vs.	vs.	vs.
male / female	10 / 5		—	—	5 / 6		—	—	19 / 15		—	—	—		—	—
Age (yrs)	56.3 $\pm$ 8.5		—	—	55.4 $\pm$ 11.5		—	—	56.5 $\pm$ 8.3		—	—	56.5 $\pm$ 8.3		—	—
Body weight (kg)	67.7 $\pm$ 8.9		62.7 $\pm$ 8.5		67.1 $\pm$ 13.3		65.9 $\pm$ 12.8		63.8 $\pm$ 11.3		0.92 ^{††}	0.72 ^{††}	63.8 $\pm$ 11.3		0.91 ^{††}	0.45 ^{††}
BMI (kg/m ²)	24.2 $\pm$ 2.9		23.4 $\pm$ 2.5		25.2 $\pm$ 2.6		24.8 $\pm$ 2.6		24.3 $\pm$ 2.7		0.24 ^{††}	0.30 ^{††}	24.3 $\pm$ 2.7		0.99 ^{††}	0.16 ^{††}
VFA (cm ²)	112.3 $\pm$ 52.8		81.6 $\pm$ 39.0		102.1 $\pm$ 42.1		95.5 $\pm$ 46.0		98.2 $\pm$ 32.7		0.27 ^{††}	0.76 ^{††}	98.2 $\pm$ 32.7		0.60 ^{††}	0.41 ^{††}
WBC ($\times 10^3/\mu\text{L}$)	5.2 $\pm$ 1.2		4.6 $\pm$ 1.5		5.6 $\pm$ 1.0		5.3 $\pm$ 1.1		5.2 $\pm$ 1.1		0.30 ^{††}	0.35 ^{††}	5.2 $\pm$ 1.1		0.18 ^{††}	0.24 ^{††}
Hemoglobin (g/dL)	14.9 $\pm$ 1.1		14.3 $\pm$ 1.2		14.2 $\pm$ 1.4		14.0 $\pm$ 1.4		14.0 $\pm$ 1.9		0.91 ^{††}	0.29 ^{††}	14.0 $\pm$ 1.9		0.54 ^{††}	0.62 ^{††}
Platelet ($\times 10^3/\mu\text{L}$)	14.8 $\pm$ 3.7		13.1 $\pm$ 4.0		18.4 $\pm$ 5.0		17.5 $\pm$ 3.5		16.4 $\pm$ 5.4		0.07 ^{††}	0.77 ^{††}	16.4 $\pm$ 5.4		0.13 ^{††}	0.92 ^{††}
AST (IU/L)	68.3 $\pm$ 44.5		70.0 $\pm$ 49.0		54.6 $\pm$ 38.0		51.7 $\pm$ 25.0		56.4 $\pm$ 30.0		0.31 ^{††}	0.29 ^{††}	56.4 $\pm$ 30.0		0.04 ^{††}	0.008 ^{††}
ALT (IU/L)	87.3 $\pm$ 69.4		93.0 $\pm$ 79.8		66.8 $\pm$ 46.0		57.1 $\pm$ 31.9		62.4 $\pm$ 34.1		0.27 ^{††}	0.88 ^{††}	62.4 $\pm$ 34.1		0.42 ^{††}	0.27 ^{††}
GGT (IU/L)	55.2 $\pm$ 30.0		46.9 $\pm$ 24.3		43.6 $\pm$ 26.5		38.5 $\pm$ 19.0		59.2 $\pm$ 51.2		0.10 ^{††}	0.73 ^{††}	59.2 $\pm$ 51.2		0.40 ^{††}	0.17 ^{††}
Total cholesterol (mg/dL)	176.2 $\pm$ 33.3		169.3 $\pm$ 31.0		191.0 $\pm$ 31.4		185.6 $\pm$ 28.9		174.1 $\pm$ 32.4		0.78 ^{††}	0.34 ^{††}	174.1 $\pm$ 32.4		0.31 ^{††}	0.35 ^{††}
HDL-cholesterol (mg/dL)	42.1 $\pm$ 12.3		43.9 $\pm$ 13.9		48.5 $\pm$ 17.9		53.1 $\pm$ 20.0		46.1 $\pm$ 16.5		0.84 ^{††}	0.14 ^{††}	46.1 $\pm$ 16.5		0.26 ^{††}	0.19 ^{††}
Triglyceride (mg/dL)	122.1 $\pm$ 48.4		103.5 $\pm$ 49.8		126.0 $\pm$ 53.2		94.2 $\pm$ 27.6		107.1 $\pm$ 31.0		0.43 ^{††}	0.69 ^{††}	107.1 $\pm$ 31.0		0.31 ^{††}	0.18 ^{††}
FPG (mg/dL)	100.3 $\pm$ 7.5		90.8 $\pm$ 9.5		95.5 $\pm$ 10.8		89.1 $\pm$ 8.5		92.0 $\pm$ 10.0		0.20 ^{††}	0.15 ^{††}	92.0 $\pm$ 10.0		0.85 ^{††}	0.58 ^{††}
FPI ($\mu\text{U/mL}$)	13.0 $\pm$ 2.6		9.3 $\pm$ 3.3		14.8 $\pm$ 5.3		13.2 $\pm$ 6.8		13.9 $\pm$ 6.3		0.007 ^{††}	0.34 ^{††}	13.9 $\pm$ 6.3		0.19 ^{††}	0.64 ^{††}
HOMA-IR	3.2 $\pm$ 0.8		2.1 $\pm$ 1.3		3.5 $\pm$ 1.6		2.9 $\pm$ 1.7		3.1 $\pm$ 1.3		0.58 ^{††}	0.67 ^{††}	3.1 $\pm$ 1.3		0.01 ^{††}	0.07 ^{††}
Viral load (log IU/mL)	6.5 $\pm$ 0.6		6.5 $\pm$ 0.6		6.6 $\pm$ 0.4		6.5 $\pm$ 0.5		6.5 $\pm$ 0.3		0.78 ^{††}	0.37 ^{††}	6.5 $\pm$ 0.3		0.009 ^{††}	0.10 ^{††}
Histological findings *											0.88 ^{††}	0.10 ^{††}			0.88 ^{††}	0.74 ^{††}
Inflammation (A0, I / A2, 3)	8 / 7		—		8 / 3		—		14 / 15		0.92 [†]	0.17 [†]	14 / 15		0.31 [†]	—
Fibrosis (F0-2 / F3,4)	3 / 12		—		7 / 4		—		13 / 16		0.10 [†]	0.29 [†]	13 / 16		0.02 [†]	—
Steatosis (%) (<10 / $\geq$ 10)	13 / 2		—		8 / 3		—		19 / 10		0.94 [†]	0.10 [†]	19 / 10		0.37 [†]	—

Results are shown as number or mean $\pm$ SD.

*: n=54 (n=15 in group A1, n=11 in group A2, n=28 in group B)

†: Chi-squared test, ††: Mann-Whitney U test

BMI: body mass index, VFA: visceral fat area, WBC: white blood cell, AST: aspartate aminotransferase, ALT: alanine aminotransferase, GGT: gamma glutamyl transpeptidase, HDL: high density lipoprotein, FPG: fasting plasma glucose, FPI: fasting plasma insulin, HOMA-IR: homeostasis model assessment of insulin resistance, WBIS: whole body insulin sensitivity index, PEG-IFN/RBV: pegylated interferon plus ribavirin

Figure 3. Rates of serum HCV RNA negativity during the observation period. White bars indicate the intervention group with a $\geq 5\%$ loss of body weight (Group A1), gray bars indicate the intervention group with a $< 5\%$ decrease in body weight (Group A2) and black bars indicate the control group (Group B). The HCV RNA negativity rates at 12 weeks differed significantly in Groups A1 and B ($p=0.01$). ETR: end-of-treatment response, SVR: sustained virologic response

Although IR is an important clinical manifestation in HCV-infected patients, its mechanism of onset remains unclear. HCV-associated IR results from two types of hepatic insulin resistance: direct inhibition of the insulin signal in hepatocytes by the HCV core protein and an inadequate insulin action due to hepatic fibrosis (15, 16). However, the accumulation of visceral fat owing to obesity has been found to induce greater IR in patients with CHC than in those with non-alcoholic fatty liver (10). The results presented here suggest that metabolic factors may be a major cause of IR in CHC patients. Because hyperinsulinemia or hyperglycemia due to IR can cause hepatic fibrosis (1) or hepatocarcinogenesis (17-19), lifestyle interventions may improve the prognosis of HCV-infected patients.

We also found that the lifestyle interventions reduced the serum albumin levels and platelet counts. Interventions may reduce excess calorie and protein consumption, thus reducing the serum albumin levels. An increased platelet count is often accompanied by systemic inflammatory reactions. Visceral fat tissues secrete several proinflammatory cytokines and induce systemic inflammatory reactions. Therefore, visceral fat reduction achieved via diet and exercise may restore the platelet count to a normal level.

The molecular mechanisms by which IR influences the effects of IFN are not fully understood. Suppressors of cytokine signaling (SOCS) are candidate substances that link IR to IFN resistance. SOCS-1 and -3 are able to inhibit the insulin signaling pathway by inhibiting the tyrosine phosphorylation of insulin receptor substrate (IRS) proteins, thereby promoting the proteasomal degradation of IRS proteins and inhibiting insulin receptor kinase activity (20). In addition, these two SOCS proteins inhibit JAK/STAT signaling, a major signaling pathway of IFN, thus reducing the expression of the anti-viral proteins 2,5-OAS and MxA (21). Although HCV infection contributes to the increased expres-

sion of SOCSs (22, 23), adipocytokines, such as tumor necrosis factor- α and interleukin-6, have been reported to increase the expression of SOCSs (24). Taken together, body fat reduction achieved through diet and exercise can induce the inhibition of the SOCS expression, even in HCV-infected hepatocytes, following improvements in insulin sensitivity and the anti-viral effects of IFN. However, further research is needed to elucidate this mechanism, especially because the adipocytokine levels were not measured in this study.

Although the ETR rate was higher in Group A than in Group B, the SVR rates were similar. Relapse has been reported to be affected by adherence to RBV administration (25). However, there were no significant differences between Groups A and B in the rate of adherence rate to RBV (89% vs. 80%) or IFN (93% vs. 86%). Because the current study population was rather small, a larger number of patients may be needed to determine differences in the SVR rates.

One limitation associated with this study is that the patients were not evaluated for interleukin-28B (IL-28B) gene polymorphisms. These polymorphisms modify the anti-viral effects of PEG-IFN/RBV treatment. However, this study was planned in 2007, before the effects of IL-28B gene polymorphisms had been discovered. Because the IL-28B genotype may be associated with IR in CHC patients, this issue must be resolved in the future.

The development of direct-acting anti-viral agents (DAAs) has brought about a major breakthrough in the treatment of CHC. However, IFN-based methods remain the predominant form of treatment for CHC in most countries, as treatment with DAAs in the absence of IFN continues to be associated with many unresolved issues, including the existence or appearance of drug-resistant mutations in targeted sequences and the higher cost of DAAs. In addition, although IFN therapy has been shown to inhibit hepatocarcinogenesis, evidence for this inhibition with DAAs is lacking. Therefore, the results of this study may provide suggestions on the use of anti-viral treatments in HCV-infected patients in the future.

In conclusion, this prospective study showed that lifestyle interventions to reduce body weight in CHC patients with IR may improve the early viral response to PEG-IFN/RBV treatment in these subjects. However, other additive or alternative approaches are likely required to achieve final viral eradication.

The authors state that they have no Conflict of Interest (COI).

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