

# Impairment of health-related quality of life in patients with chronic hepatitis C is associated with insulin resistance

Takuya Kuwashiro · Toshihiko Mizuta · Yasunori Kawaguchi · Shinji Iwane · Hirokazu Takahashi · Noriko Oza · Satoshi Oeda · Hiroshi Isoda · Yuichiro Eguchi · Iwata Ozaki · Keizo Anzai · Kazuma Fujimoto

Received: 27 April 2012 / Accepted: 18 February 2013 / Published online: 16 March 2013  
© Springer Japan 2013

## Abstract

**Background** Although it has been reported that hepatitis C virus (HCV) infection is associated with a significant decline in health-related quality of life (HRQOL), the underlying causes and mechanisms are still unknown. Insulin resistance (IR) is recognized as a distinct aspect of chronic HCV infection. Therefore, we attempted to identify the factors including IR indices that are related to the HRQOL of patients with chronic hepatitis C (CHC).

**Methods** One hundred and seventy-five CHC patients (91 female, 84 male, mean age, 56.4 years) not using antidiabetic agents were included and underwent a 75-g oral glucose tolerance test (OGTT) and completed a self-administered HRQOL questionnaire, the Short Form 36 (SF-36), which is a well-validated questionnaire for assessing general QOL. Scale scores were standardized and summarized into physical and mental component summary (PCS and MCS). We investigated which clinical parameters, including homeostasis model assessment of insulin resistance (HOMA-IR), were associated with decline in PCS and MCS scores in CHC patients.

**Results** There were no significant differences in clinical parameters between high and low MCS, but there were significant differences in age, sex, hemoglobin, liver fibrosis, OGTT pattern, and HOMA-IR between high and low PCS. Multivariate analysis showed that HOMA-IR >2 was independently associated with lower PCS (OR 2.92,  $p < 0.01$ ).

**Conclusions** Our results suggest that impairment of HRQOL, especially physical domains, in CHC patients is associated with IR.

**Keywords** Chronic hepatitis C · Health-related quality of life · Insulin resistance

## Introduction

Chronic hepatitis C virus (HCV) infection is currently a major health problem that is estimated to affect 170 million people worldwide [1]. In a significant proportion of patients, infection leads to liver cirrhosis with potential complications, including impaired liver function, portal hypertension, and/or hepatocellular carcinoma. In addition to these serious complications, several studies have indicated that chronic HCV infection might be associated with considerable impairment of health-related quality of life (HRQOL) regardless of the disease stage [2–6]. However, the precise mechanism of decreased HRQOL in chronic hepatitis C (CHC) patients has not been elucidated, although there are some reports indicating an association with the degree of fibrosis, sex or age [7, 8].

Insulin resistance (IR) in CHC patients is often established early in the course of infection, and related to hepatic steatosis and fibrosis [9–11]. Regarding the mechanism of IR associated with HCV infection, Kawaguchi et al. [12] have reported that HCV core region can directly evoke downregulation of hepatic insulin receptor substrate (IRS)-1 and IRS-2. Moreover, Shintani et al. [13] have demonstrated using HCV core gene transgenic mice that tumor necrosis factor (TNF)- $\alpha$  induced by HCV infection can suppress insulin-induced tyrosine phosphorylation of

T. Kuwashiro · T. Mizuta (✉) · Y. Kawaguchi · S. Iwane · H. Takahashi · N. Oza · S. Oeda · H. Isoda · Y. Eguchi · I. Ozaki · K. Anzai · K. Fujimoto  
Department of Internal Medicine, Saga Medical School,  
5-1-1 Nabeshima, Saga 849-8501, Japan  
e-mail: mizutat@med.saga-u.ac.jp

IRS-1. Recent estimates have indicated that 30–70 % of patients with CHC display some evidence of IR [14, 15].

Therefore, the aim of this study was to investigate the relationship between HRQOL in CHC patients and clinical parameters focused on IR using the 36-item Short Form Health Survey (SF-36) [16].

SF-36 is a widely used self-administered questionnaire designed for use in clinical practice and research, health policy evaluations, and general population surveys. It has demonstrated consistently high reliability and validity in a variety of patient populations including CHC [2–4, 6–8, 16–20]. Although there are several questionnaires, such as Chronic Liver Disease Questionnaire (CLDQ) [21], Liver Disease Symptom Index (LDSI) [22], and Liver Disease Quality of Life (LDQOL) [23] for evaluation of QOL in chronic liver disease patients, we used SF-36 as a non-specific questionnaire to compare HRQOL in CHC patients with that in the general population.

## Patients and methods

### Study population

We included 190 consecutive patients with CHC diagnosed by HCV antibody test and polymerase chain reaction, who attended Saga Medical School Hospital between January 2005 and December 2008. They were not taking, or had not recently (within 6 months) taken, any antiviral medication. Patients were excluded if they fulfilled the following criteria: (1) hepatitis B virus surface antigen positivity; (2) autoimmune liver disease, alcoholic liver disease (20 g/day alcohol), and/or medication-associated liver damage; (3) taking insulin-sensitizing or antidiabetic medication; and (4) extremity disorders, and/or other significant problems including chronic renal and heart failure. These criteria led to exclusion of 15 patients, which left 175 who were eligible for inclusion. Liver biopsy was performed in 162 of the 175 patients (within 12 months of the study). All 175 patients gave informed consent, and the study was approved by the ethics committee of Saga Medical School in accordance with the Declaration of Helsinki (approved ID number: 2004-04-04 and 2007-04-02).

### Assessment of HRQOL

HRQOL of CHC patients was assessed using the SF-36, a 36-item self-administered questionnaire encompassing eight physical and mental health domains and two physical and mental summary scales [24]. We used a Japanese-validated version of SF-36, and the data of the present study were compared to the Japanese normative sample score of SF-36 in 2966 individuals [25]. The eight subscales: physical

functioning (PF), role-physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role-emotional (RE) and mental health (MH), were calculated from the questionnaires as described previously [26–28]. Patients completed SF-36, and the resulting scores were transformed into a scale of 0 (worst possible score) to 100 (best possible score), as recommended by the questionnaire's originators. Physical and mental summary measures were obtained from the sum scores of the corresponding subscales, that is, PF, RP, BP and GH for the physical component summary (PCS) and VT, SF, RE and MH for the mental component summary (MCS). According to the recommendations given in the manual, subscale scores were calculated if at least half of the items on the respective scale were answered. Transformation of the raw scores was performed using Microsoft Excel (Redmond, WA, USA).

### Clinical and laboratory assessments

All venous blood samples were taken after a 12-h overnight fast. For the oral glucose tolerance test (OGTT), patients ingested a solution containing 75 g glucose, and venous blood samples were collected at 0, 30, 60, 90 and 120 min for the measurement of plasma glucose and serum insulin concentrations. Glucose was determined by a glucokinase method and insulin was measured using a chemiluminescent enzyme immunoassay kit (Abbott Japan, Tokyo, Japan). Glucose tolerance was categorized into 3 groups according to the criteria of the World Health Organization [29] as follows: (1) normal glucose tolerance (NGT; fasting plasma glucose level <110 and 2-h plasma glucose level <140 mg/dL); (2) impaired glucose tolerance (IGT; fasting glucose level  $\leq$ 126 mg/dL and 2-h glucose level  $\geq$ 140 and  $\leq$ 200 mg/dL); and (3) diabetes mellitus (DM; fasting glucose level  $\geq$ 126 mg/dL or 2-h glucose level  $\geq$ 200 mg/dL).

IR was evaluated by the homeostasis model assessment of insulin resistance (HOMA-IR) method, which was calculated as follows:  $\text{HOMA-IR} = \text{fasting plasma glucose} \times \text{fasting serum insulin}/405$ . Body mass index (BMI) was calculated as  $\text{kg}/\text{m}^2$ . Serum HCV-RNA levels were identified by 2 different quantitative polymerase chain reaction (PCR) assays: one was Amplicore HCV Monitor version 2.0 and the other was COBAS Taq-Man HCV Monitor Test (both Roche Diagnostics, Tokyo, Japan). High viral load was defined as  $\geq 100$  kIU/mL by Amplicore method and  $\geq 5.0$  logIU/mL by Taq-Man method. The HCV genotype was determined on the basis of the sequence of the core region [30].

### Liver histology

Percutaneous liver biopsy was performed under ultrasound imaging within 12 months before SF-36. Histological

hepatic fibrosis and inflammation were scored using the METAVIR scoring system [31]. Grade of fibrosis was classified from F0 to F4, with varying degrees of fibrosis as follows: F0, no fibrosis; F1, portal fibrosis without septa; F2, portal fibrosis with rare septa; F3, numerous septa without cirrhosis; and F4, cirrhosis. Based on the degree of lymphocyte infiltration and hepatocyte necrosis, activity was classified from A0 to A3, with higher scores indicating more severe inflammation.

#### Statistical analysis

Comparisons between groups were made using the Mann–Whitney *U* test for continuous variables and the  $\chi^2$  or Fisher's exact probability test for categorical data. Multivariate analysis was performed using logistic regression analysis. Relationships between continuous variables were analyzed by Pearson's correlation coefficient test. Data are expressed as mean  $\pm$  SD.  $P < 0.05$  was considered statistically significant. All statistical analyses were performed using SAS software (Cary, NC, USA).

## Results

#### Patient characteristics

Clinical, biochemical, virological and histological characteristics of all 175 CHC patients are summarized in Table 1. Forty-four (25 %) patients were considered obese, with BMI  $>25$  kg/m<sup>2</sup>, and 64 (37 %) patients were evaluated for IR, with HOMA-IR  $>2$ . About one-third of the patients showed abnormal glucose tolerance; with respect to degrees of glucose tolerance, 67, 21 and 12 % of patients showed NGT, IGT and DM, respectively. A large majority of HCV was genotype 1b (76 %). Liver biopsy samples were obtained from 162 patients, and 152 (94.4 %) indicated minimal to moderate necroinflammatory activity, although 10 patients had severe activity. Regarding fibrosis in the biopsy samples, F1, F2, F3 and cirrhosis (F4) were seen in 83 (51 %), 51 (31 %), 22 (14 %) and 6 (4 %) patients, respectively. Liver biopsy was not performed in the remaining 13 of the 175 patients because of refusal.

One woman had a low serum albumin level of 2.7 g/dL, but her other hepatic function tests were well preserved, such as 80 % of prothrombin activity and 1.5 mg/dL of total bilirubin level. Therefore, we included her in this study as compensated liver cirrhosis. One woman showed a high serum level of total bilirubin of 2.7 mg/dL. However, her liver histology showed a METAVIR fibrosis stage of F2. Her indirect bilirubin level was 2.2 mg/dL; therefore, we assumed that her bilirubinemia was constitutional

**Table 1** Patient characteristics ( $n = 175$ )

	<i>n</i> or mean $\pm$ SD (range)
Age (years)	56.4 $\pm$ 9.9 (24–74)
Male/female	84/91
Body weight (kg)	59.1 $\pm$ 9.5 (39.4–91.5)
BMI (kg/m <sup>2</sup> )	23.0 $\pm$ 2.9 (15.6–30.3)
>25/<25	44/131
WBC (/ $\mu$ L)	5,031 $\pm$ 1,622 (2,400–15,900)
Hemoglobin (g/dL)	13.8 $\pm$ 1.5 (9.4–17.8)
Platelets ( $\times 10^4$ / $\mu$ L)	15.9 $\pm$ 5.1 (6.0–30.5)
Albumin (g/dL)	4.1 $\pm$ 0.3 (2.7–5.2)
Total bilirubin (mg/dL)	1.0 $\pm$ 0.3 (0.4–2.8)
AST (IU/L)	52 $\pm$ 34 (15–233)
ALT (IU/L)	63 $\pm$ 52 (9–395)
$\gamma$ -GT (IU/L)	52 $\pm$ 52 (11–341)
Total cholesterol (mg/dL)	173 $\pm$ 31 (94–263)
Fasting glucose (mg/dL)	88.8 $\pm$ 14.0 (68–220)
Fasting insulin ( $\mu$ U/mL)	8.7 $\pm$ 5.3 (1.6–33.3)
HOMA-IR	1.9 $\pm$ 1.2 (0.3–6.8)
>2/<2	64/111
OGTT pattern: NGT/IGT/DM	118/37/20
Viral load: high/low	165/8
HCV genotype: 1/2/unknown	133/38/4
Histology ( $n = 162$ )	
Necroinflammatory: A1/A2/A3	93/59/10
Fibrosis: F1/F2/F3/F4	83/51/22/6

Data are expressed as mean  $\pm$  SD (range). Histological necroinflammation grade and fibrosis stage were scored according to the METAVIR scoring system

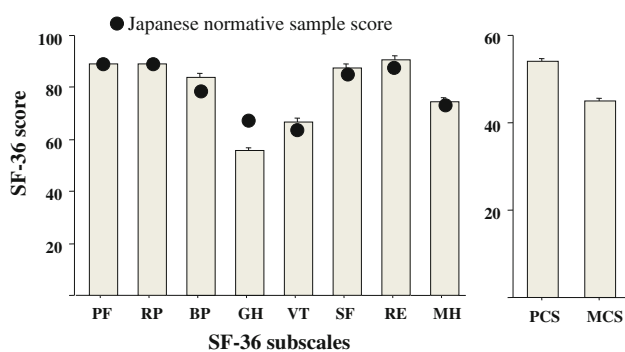
AST aspartate aminotransferase, ALT alanine aminotransferase, BMI body mass index, DM diabetes mellitus,  $\gamma$ -GT gamma-glutamyl transpeptidase, HOMA-IR homeostasis model assessment of insulin resistance, IGT impaired glucose tolerance, NGT normal glucose tolerance, OGTT oral glucose tolerance test, WBC white blood cell

jaundice, such as Gilbert disease. Therefore, we included her in the F2 group.

#### Assessment of HRQOL

We compared the HRQOL scores in CHC patients in our study with those in the Japanese normative sample, and there was no difference except for evaluation of GH (Fig. 1).

We evaluated factors associated with HRQOL scores in CHC patients. Dividing PCS and MCS score into 2 groups by each median score (PCS 57, MCS 46), univariate and multivariate analysis were performed. Univariate analysis showed that older age, female sex, low hemoglobin, high fasting insulin level, high HOMA-IR value, and impaired glucose tolerance were significant factors associated with lower PCS. In contrast, there was no significant factor



**Fig. 1** SF-36 mean subscale scores in CHC patients. *Dots* are Japanese normative sample mean scores. In physical and mental component summary (PCS and MCS), mean score was 50, calculated from Japanese normative sample scores. *BP* bodily pain, *GH* general health, *MH* mental health, *PF* physical functioning, *RE* role-emotional, *RP* role-physical, *SF* social functioning, *VT* vitality

associated with MCS (Table 2). Multivariate analysis after adding fibrosis factor to the significant factors by univariate analysis indicated that high HOMA-IR value was the only significant factor associated with lower PCS (OR 2.92,  $p < 0.01$ , 95 % CI 1.37–6.18) (Table 3).

Correlations between SF-36 subscale, PCS and MCS scores and HOMA-IR

The correlation coefficients between eight subscales of SF-36 and HOMA-IR are shown in Table 4. RP and GH scores associated with PCS were strongly and negatively correlated with HOMA-IR. Relationships between PCS, MCS and HOMA-IR are shown by scatter plots (Fig. 2). PCS had a negative correlation with HOMA-IR value ( $r = -0.234$ ,  $p = 0.018$ ) (Fig. 2a); meanwhile, MCS was not associated with HOMA-IR ( $r = 0.09$ ,  $p = 0.48$ ) (Fig. 2b). Similar results were obtained for analysis of patients ( $n = 152$ ) excluding F4 stage fibrosis or DM pattern in 75 g OGTT, which might have influenced their HRQOL or insulin resistance (Fig. 2c for PCS:  $r = -0.224$ ,  $p = 0.02$  and Fig. 2d for MCS:  $r = 0.084$ ,  $p = 0.58$ ).

## Discussion

This cross-sectional study regarding HRQOL of Japanese CHC patients indicated that the impairment of the physical aspect of HRQOL was significantly related to IR evaluated by HOMA-IR, but was not associated with the demographic factors, inflammatory activity, fibrosis stage or viral factors.

IR or abnormal glucose metabolism are known to be clinical characteristics of HCV-infected patients [9–13]. Previous reports have indicated that eradication of HCV by

interferon (IFN) therapy improves IR [32] and HRQOL scores [33, 34]. We have previously shown that sustained viral disappearance induced by IFN treatment improves systemic as well as hepatic insulin sensitivity, and decreases serum levels of soluble TNF receptor [35]. Lecube et al. [36] have demonstrated that serum levels of proinflammatory cytokines in CHC patients are higher than those in patients with chronic liver disorder due to other causes. Moreover, it has also been reported that the levels of circulating inflammatory cytokines such as interleukin (IL)-1, IL-6, IL-8 and TNF- $\alpha$  are related to fatigue in patients with acute myelogenous leukemia and myelodysplastic syndrome [37]. Judging from these reports, we assume that HCV infection increases systemic IR and production of inflammatory cytokines, which lead to impairment of HRQOL.

However, the limitation of this study was that there was no comparison of the relationship of QOL with IR between CHC and other chronic liver disease patients, including hepatitis B or fatty liver disease, and no data regarding inflammatory cytokines in the present study. A previous study has indicated that there was a significant association between declined physical functioning and elevated HOMA-IR in the general elderly population, not related to HCV or liver disease [38]. Therefore, we cannot conclude whether the association of HRQOL and IR is characteristic of HCV-infected patients, and whether it is mediated via cytokines. It should be clarified whether this association is dependent on disease etiology.

Our study indicated that IR was only associated with the physical component of HRQOL and not with the mental component. Meanwhile, Tillman et al. [39] have reported that MCS of SF-36, but not PCS, in CHC patients was significantly lower than that in patients with non-HCV liver disease such as chronic hepatitis B, primary biliary cirrhosis, primary sclerosing cholangitis, and autoimmune hepatitis. Although that study had some differences in age, race and the setting of the control group from our study, these are not enough to explain the discrepancies in the results. Bonkovsky et al. [7] have reported that there is a significant difference in BMI between high and low scores of PCS but not MCS in CHC patients. Moreover, a systematic review has indicated that PCS in CHC patients with sustained virological response by IFN treatment was improved [40]. These reports support our results. At present, however, it is controversial which component, mental and/or physical, in QOL is impaired by HCV infection.

The causal relationship between HRQOL and IR remains largely speculative because our study was cross-sectional. Although it has been reported that glucose intolerance or high plasma glucose level might cause weak muscle strength and impair physical function [41], it is possible that impairment of physical aspects influences IR.

**Table 2** Univariate analysis of factors associated with PCS and MCS

	PCS			MCS		
	<57 (n = 89)	>57 (n = 86)	p value	<46 (n = 89)	>46 (n = 86)	p value
Age (years)	58.1 ± 9.3	54.6 ± 10.3	0.02	55.6 ± 9.5	57.2 ± 10.1	0.26
Male/female	35/54	49/37	0.02	41/48	43/43	0.60
Body weight (kg)	59.3 ± 9.5	58.9 ± 9.6	0.83	58.8 ± 9.2	59.7 ± 9.8	0.47
BMI (kg/m <sup>2</sup> )	23.3 ± 3.0	22.7 ± 2.8	0.16	22.8 ± 2.9	23.1 ± 2.9	0.45
WBC (/ $\mu$ L)	5,124 ± 1,990	4,932 ± 1,100	0.74	4,998 ± 1,881	5,065 ± 1,322	0.20
Hemoglobin (g/dL)	13.6 ± 2.2	14.0 ± 2.1	0.04	13.8 ± 2.0	13.8 ± 1.4	0.67
Platelets ( $\times 10^4$ / $\mu$ L)	15.6 ± 5.2	16.2 ± 5.0	0.45	16.4 ± 5.2	15.4 ± 5.0	0.17
Albumin (g/dL)	4.1 ± 0.36	4.1 ± 0.4	0.43	4.1 ± 0.37	4.1 ± 0.39	0.07
Total bilirubin (mg/dL)	0.9 ± 0.30	0.9 ± 0.35	0.47	0.9 ± 0.35	1.0 ± 0.29	0.05
AST (IU/L)	53 ± 33	52 ± 35	0.84	51 ± 31	54 ± 37	0.53
ALT (IU/L)	61 ± 43	65 ± 61	0.62	62 ± 56	64 ± 49	0.86
$\gamma$ -GT (IU/L)	50 ± 52	54 ± 54	0.61	48 ± 50	56 ± 55	0.32
Total cholesterol (mg/dL)	175 ± 31	172 ± 31	0.54	177 ± 31	170 ± 30	0.19
Fasting glucose (mg/dL)	89.8 ± 16.8	87.7 ± 10.3	0.36	87.4 ± 9.4	90.1 ± 17.5	0.50
Fasting insulin ( $\mu$ U/mL)	9.7 ± 6.1	7.7 ± 4.0	0.009	9.3 ± 6.2	8.1 ± 4.1	0.50
HOMA-IR	2.1 ± 1.3	1.6 ± 1.0	0.001	1.9 ± 1.3	1.8 ± 1.0	0.37
OGTT pattern: NGT/IGT + DM	53/36	65/21	0.02	59/30	59/27	0.74
Viral load: high/low	83/5	82/3	0.50	83/6	82/2	0.16
HCV genotype: 1/2	66/21	67/17	0.79	64/23	69/15	0.26
Histology						
A1/A2,3	41/36	52/30	0.19	47/32	46/34	0.80
F1,2/F3,4	62/18	72/10	0.08	68/13	66/15	0.67

Data are presented as mean ± SD. PCS was divided into 2 groups by median value: PCS <57 and PCS >57. MCS was divided into 2 groups by median value: MCS <46 and MCS >46

AST aspartate aminotransferase, ALT alanine aminotransferase, BMI body mass index, DM diabetes mellitus,  $\gamma$ -GT gamma-glutamyl transpeptidase, HOMA-IR homeostasis model assessment of insulin resistance, IGT impaired glucose tolerance, NGT normal glucose tolerance, OGTT oral glucose tolerance test, WBC white blood cell

**Table 3** Multivariate analysis of factors associated with decline in physical component summary in CHC patients

	PCS <57		
	OR	p value	95 % CI
Age >60 years	1.87	0.07	0.93–3.78
Sex: female	1.53	0.33	0.64–3.68
Liver fibrosis: F3–4	1.22	0.68	0.46–3.25
IGT + DM	1.78	0.13	0.82–3.82
Hemoglobin <14	1.71	0.23	0.70–4.14
HOMA-IR >2	2.92	<0.01	1.37–6.18

DM diabetes mellitus, HOMA-IR homeostasis model assessment of insulin resistance, IGT impaired glucose tolerance

Longitudinal studies are needed to verify the detailed mechanism of this relationship.

The present study failed to demonstrate the difference in HRQOL defined by SF-36 scores between healthy individuals and CHC patients, except for general health score. This result was different from previous studies that have

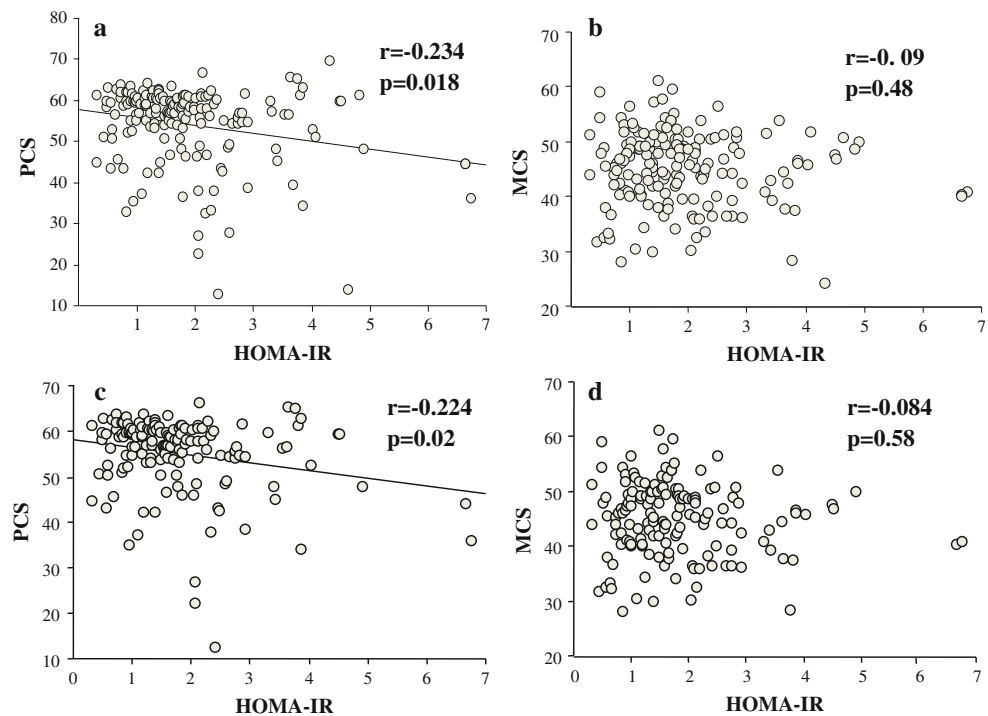
**Table 4** Correlation coefficient between eight subscale scores of SF-36 (PF, RP, GH, VT, SF, RE, MH) and HOMA-IR

	Correlation coefficient	p value
PF	−0.143	0.06
RP	−0.252	0.0007
BP	−0.093	0.2
GH	−0.258	0.0005
VT	−0.110	0.1
SF	−0.158	0.04
RE	−0.181	0.02
MH	−0.076	0.3

BP bodily pain, GH general health, MH mental health, PF physical functioning, RE role-emotional, RP role-physical, SF social functioning, VT vitality

indicated that CHC patients have a diminished HRQOL compared with healthy controls across all SF-36 scores [2–6]. The reason for this discrepancy is outlined below. First, almost all the patients were willing to visit our tertiary

**Fig. 2** Correlations between physical component summary (PCS) score and homeostasis model assessment of insulin resistance (HOMA-IR) (a, c). Correlations between mental component summary (MCS) score and HOMA-IR (b, d). PCS was associated with HOMA-IR in all patients (a  $r = -0.234$ ,  $p = 0.018$  by Pearson's correlation coefficient test) and in those excluding F4 stage fibrosis or diabetes mellitus (DM) pattern in 75 g OGTT (c,  $r = -0.224$ ,  $p = 0.02$ ). MCS was not associated with HOMA-IR in all patients (b  $r = 0.09$ ,  $p = 0.48$ ) and in those excluding F4 stage fibrosis or DM pattern in 75 g OGTT (d  $r = 0.084$ ,  $p = 0.58$ )



hospital for IFN treatment in the future, so their QOL might be better than that in the general HCV-infected patients. Second, a previous large cross-sectional survey of unselected HCV-positive patients contained many with low household income, untreated diabetes, or a history of intravenous drug use, which were shown to be independent predictors of reduced HRQOL [42]. Our study did not include such patients.

Previous reports suggest that advanced liver fibrosis, especially cirrhosis, is strongly associated with decline of QOL [7, 8]. In the present study, we could not find a significant difference in HRQOL score between mild (F0–F2) and severe (F3, F4) fibrosis. However, we cannot deny the association between QOL and liver fibrosis, because our result might have been due to the small number of cases of liver cirrhosis ( $n = 6$ ). Liver fibrosis evokes IR, therefore, further studies are necessary to elucidate the relationship between fibrosis and IR and QOL.

In conclusion, this study shows that diminished HRQOL, especially physical domains, in CHC patients is associated with IR. Improvement in IR due to weight reduction by diet and/or exercise, or using insulin sensitizers, might improve HRQOL in CHC patients, following good adherence to IFN treatment, although the relationship between IR and HRQOL warrants further exploration.

**Acknowledgments** The authors would like to thank Ms Yukie Watanabe, Ms Chieko Ogawa, and all the medical staff at Saga Medical School Hospital for their assistance and excellent advice.

**Conflict of interest** The authors declare that they have no conflict of interest.

## References

1. Shepard CW, Finelli L, Alter MJ. Global epidemiology of hepatitis C virus infection. *Lancet Infect Dis.* 2005;5:558–67.
2. Foster GR, Goldin RD, Thomas HC. Chronic hepatitis C virus infection causes a significant reduction in quality of life in the absence of cirrhosis. *Hepatology.* 1998;27:209–12.
3. Rodger AJ, Jolley D, Thompson SC, Lanigan A, Crofts N. The impact of diagnosis of hepatitis C virus on quality of life. *Hepatology.* 1999;30:1299–301.
4. Kramer L, Bauer E, Funk G, Hofer H, Jessner W, Steindl-Munda P, et al. Subclinical impairment of brain function in chronic hepatitis C infection. *J Hepatol.* 2002;37:349–54.
5. Strauss E, Dias Teixeira MC. Quality of life in hepatitis C. *Liver Int.* 2006;26:755–65.
6. Younossi Z, Kallman J, Kincaid J. The effects of HCV infection and management on health-related quality of life. *Hepatology.* 2007;45:806–16.
7. Bonkovsky HL, Snow KK, Malet PF, Back-Madruga C, Fontana RJ, Sterling RK, et al. Health-related quality of life in patients with chronic hepatitis C and advanced fibrosis. *J Hepatol.* 2007;46:420–31.
8. Teuber G, Schäfer A, Rimpel J, Paul K, Keicher C, Scheurlen M, et al. Deterioration of health-related quality of life and fatigue in patients with chronic hepatitis C: association with demographic factors, inflammatory activity, and degree of fibrosis. *J Hepatol.* 2008;49:923–9.
9. Petit JM, Bour JB, Galland-Jos C, Minello A, Verges B, Guiguert M, et al. Risk factors for diabetes mellitus and early insulin resistance in chronic hepatitis C. *J Hepatol.* 2001;35:279–83.

10. Hui JM, Sud A, Farrell GC, Bandara P, Byth K, Kench JG, et al. Insulin resistance is associated with chronic hepatitis C virus infection and fibrosis progression. *Gastroenterology*. 2003;125:1695–704.
11. Camma C, Bruno S, Di Marco V, Di Bona D, Rumi M, Vinci M, et al. Insulin resistance is associated with steatosis in nondiabetic patients with genotype 1 chronic hepatitis. *Hepatology*. 2006;43:64–71.
12. Kawaguchi T, Yoshida T, Harada M, Hisamoto T, Nagao Y, Ide T, et al. Hepatitis C virus down-regulates insulin receptor substrates 1 and 2 through up-regulation of suppressor of cytokine signaling 3. *Am J Pathol*. 2004;165:1499–508.
13. Shintani Y, Fujie H, Miyoshi H, Tsutsumi T, Tsukamoto K, Kimura S, et al. Hepatitis C infection and diabetes: direct involvement of the virus in the development of insulin resistance. *Gastroenterology*. 2004;126:840–8.
14. Shaheen M, Echeverry D, Oblad MG, Montoya MI, Teklehaimanot S, Akhtar AJ. Hepatitis C, metabolic syndrome, and inflammatory markers: results from the Third National Health and Nutrition Examination Survey [NHANES III]. *Diabetes Res Clin Pract*. 2007;75:320–6.
15. Imazeki F, Yokosuka O, Fukai K, Kanda T, Kojima H, Saisho H. Prevalence of diabetes mellitus and insulin resistance in patients with chronic hepatitis C: comparison with hepatitis B virus-infected and hepatitis C virus-cleared patients. *Liver Int*. 2008;28:355–62.
16. Ware JE, Snow KK, Kosinski M, Gandek B. SF-36 Health Survey Manual and Interpretation Guide. Boston: The Health Institute, New England Medical Center; 1993.
17. Stewart AL, Hays RD, Ware JE Jr. The MOS short-form general health survey. Reliability and validity in a patient population. *Med Care*. 1988;26:724–35.
18. Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36): I. Conceptual framework and item selection. *Med Care*. 1992;30:473–83.
19. McHorney CA, Ware JE, Raczek AE. The MOS 36-item short-form health survey: II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. *Med Care*. 1993;31:247–63.
20. McHorney CA, Ware JE Jr, Lu JF, Sherbourne CD. The MOS 36-item Short-Form Health Survey (SF-36): III. Tests of data quality, scaling assumptions, and reliability across diverse patient groups. *Med Care*. 1994;32:40–66.
21. Younossi ZM, Guyatt G, Kiwi M, Boparai N, King D. Development of a disease specific questionnaire to measure health related quality of life in patients with chronic liver disease. *Gut*. 1999;45:295–300.
22. Van der Plas SM, Hansen BE, De Boer JB, Stijnen T, Passchier J, De Man RA, et al. The Liver Disease Symptom Index 2.0; validation of a disease-specific questionnaire. *Qual Life Res*. 2004;13:1469–81.
23. Gralnek IM, Hays RD, Kilbourne A, Rosen HR, Keeffe EB, Artinian L, et al. Development and evaluation of the Liver Disease Quality of Life Instrument in persons with advanced, chronic liver disease—the LDQOL 1.0. *Am J Gastroenterol*. 2000;95:3552–65.
24. Ware JE, Kosinski M, Keller SD. SF-36 Physical and Mental Summary Scales: a user's manual. Boston: The Health Institute, New England Medical Center; 1994.
25. Fukuhara S, Suzukamo Y. Manual of SF-36v2 Japanese version: Institute for Health Outcomes and Process Evaluation Research, Kyoto; 2004.
26. Aaronson NK, Acquadro C, Alonso J, Apolone G, Bucquet D, Bullinger M, et al. International quality of life assessment (IQOLA) project. *Qual Life Res*. 1992;1:349–51.
27. Ware JE Jr, Gandek B. Overview of the SF-36 Health Survey and the International Quality of Life Assessment (IQOLA) Project. *J Clin Epidemiol*. 1998;51:903–12.
28. Fukuhara S, Bito S, Green J, Hsiao A, Kurokawa K. Translation, adaptation and validation of the SF-36 Health Survey for use in Japan. *J Clin Epidemiol*. 1998;51:1037–44.
29. Alberti KG, Zimmer PZ. Definition, diagnosis and classification of diabetes mellitus and its complications Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabetes Med*. 1998;15:539–53.
30. Ohno O, Mizokami M, Wu RR, Saleh MG, Ohba K, Orito E, et al. New hepatitis C virus (HCV) genotyping system that allows for identification of HCV genotypes 1a, 1b, 2a, 2b, 3a, 3b, 4, 5a, and 6a. *J Clin Microbiol*. 1997;35:201–7.
31. Bedossa P, Poynard T. An algorithm for the grading of activity in chronic hepatitis C. The METAVIR Cooperative Study Group. *Hepatology*. 1996;24:289–93.
32. Conjeevaram HS, Wahed AS, Afdhal N, Howell CD, Everhart JE, Hoofnagle JH, Virahep-C Study Group. Changes in insulin sensitivity and body weight during and after peginterferon and ribavirin therapy for hepatitis C. *Gastroenterology*. 2011;140:469–77.
33. Bonkovsky HL, Woolley JM. Reduction of health-related quality of life in chronic hepatitis C and improvement with interferon therapy. The Consensus Interferon Study Group. *Hepatology*. 1999;29:264–70.
34. Hassanein T, Cooksley G, Sulkowski M, Smith C, Marinos G, Lai MY, et al. The impact of peginterferon alfa-2a plus ribavirin combination therapy on health-related quality of life in chronic hepatitis C. *J Hepatol*. 2004;40:675–81.
35. Kawaguchi Y, Mizuta T, Oza N, Takahashi H, Ario K, Yoshimura T, et al. Eradication of hepatitis C virus by interferon improves whole-body insulin resistance and hyperinsulinaemia in patients with chronic hepatitis C. *Liver Int*. 2009;29:871–7.
36. Lecube A, Hernández C, Genescà J, Simó R. Proinflammatory cytokines, insulin resistance, and insulin secretion in chronic hepatitis C patients: a case-control study. *Diabetes Care*. 2006;29:1096–101.
37. Meyers CA, Albitar M, Estey E. Cognitive impairment, fatigue, and cytokine levels in patient with acute myelogenous leukemia or myelodysplastic syndrome. *Cancer*. 2005;104:788–93.
38. Schlotz W, Ambery P, Syddall HE, Crozier SR, Sayer AA, Cooper C, et al. Specific associations of insulin resistance with impaired health-related quality of life in the Hertfordshire Cohort Study. *Qual Life Res*. 2007;16:429–36.
39. Tillmann HL, Wiese M, Braun Y, Wiegand J, Tenckhoff S, Mössner J, et al. Quality of life in patients with various liver diseases: patients with HCV show greater mental impairment, while patients with PBC have greater physical impairment. *J Viral Hepat*. 2011;18:252–61.
40. Spiegel BM, Younossi ZM, Hays RD, Revicki D, Robbins S, Kanwal F. Impact of hepatitis C on health related quality of life: a systemic review and quantitative assessment. *Hepatology*. 2005;41:790–800.
41. Sayer AA, Dennison EM, Syddall HE, Gilbody HJ, Phillips DI, Cooper C. Type 2 diabetes, muscle strength, and impaired physical function: the tip of the iceberg? *Diabetes Care*. 2005;28:2541–2.
42. Helbling B, Overbeck K, Gonvers JJ, Malinverni R, Dufour JF, Borovicka J, et al. Host-rather than virus-related factors reduce health-related quality of life in hepatitis C virus infection. *Gut*. 2008;57:1597–603.