*Acta Medica et Biologica*
*Vol.56, No.1, 1-9, 2008*

# Regular Exercise Improves Insulin Sensitivity, Physical Activity, and Psychosocial Status in Patients with Chronic Liver Diseases

**Makoto KOBAYASHI[1], Takeshi SUDA[1], Masao HASHIBA[2], Koji NAGASAKI[2], Aiko ADACHI[2], Minoru NOMOTO[1], Masaaki ARAKAWA[2] and Yutaka AOYAGI[1]**

[1]Department of Gastroenterology and Hepatology, Graduate School of Medical and Dental Sciences, Niigata University; [2]Niigata Health Promotion and Sports Medicine Center, Niigata, Japan

*Received November 9, 2007; accepted December 17, 2007*

**Summary. Limitations to physical activity lead to impairments of insulin sensitivity and deterioration of health related quality of life (HRQOL) in patients with chronic liver diseases (CLD). The effects of regular exercise on physical and psychosocial factors were prospectively evaluated in CLD. Five patients with various etiologies and stages were enrolled. Daily aerobic and resistance trainings were conducted for a course of five months with an oral intake of branched-chain amino acids (BCAA) starting one month prior to the exercise. Various biochemical, physical parameters, and profile of mood states (POMS) were measured before and after the course. Statistical significance was evaluated using a resampling method. No event was marked during the course to require additional treatments. A significant improvement in insulin sensitivity was observed as reductions of fasting blood glucose and serum insulin levels. Physical capability was significantly improved in both strength and endurance as increments of grasping and knee extension powers, and ventilatory threshold. The fatigue score was significantly reduced in accordance with a decreasing tendency of all other negative aspects in POMS. While significant decreases in serum concentrations of cholinesterase and prealbumin, platelet count, and bone mass were observed, serum concentrations of transferrin and BCAA as well as prothrombin activity showed increasing tendency. Regular exercise could be a promising alternative to improve insulin sensitivity and HRQOL in CLD, though medications and close evaluation should be conducted for possibilities of osteoporosis and hemorrhagic events.**

**Key words**— liver diseases; exercise; insulin resistance; quality of life; branched-chain amino acids.

## INTRODUCTION

Hepatocellular carcinoma (HCC) is one of major causes of cancer deaths all over the world.[1)] The development of HCC is generally associated with chronic liver cell damage due to various etiologies.[2)] To date, hepatitis B and C infections have been the most common agents, but pandemic obesity is likely to become the most frequent cause of liver diseases, especially in developed countries.[3)] Interestingly, accumulating evidence suggests that insulin resistance plays a key role in both liver cell damage and hepatocarcinogenesis by inducing oxidative stress in various liver diseases including viral infections and calorie excess.[4,5,6)] Because the liver is a major target organ for insulin action to control blood glucose level, over 70% of patients with liver cirrhosis also exhibit insulin resistance, regardless of the etiologies.[7)] In general, calorie restriction is a first line prescription for insulin resistance. However, a restriction of calorie intake works against maintaining the functional reserve of the

**Correspondence:** Takeshi Suda, Department of Gastroenterology and Hepatology, Graduate School of Medical and Dental Sciences, Niigata University, Asahimachi 1-757, Chuo-ku, Niigata 951-8122, Japan.

**Abbreviations** – BCAA, branched-chain amino acids; CLD, chronic liver diseases; HCC, hepatocellular carcinoma; HRQOL, health-related quality of life; TNF-α, tumor necrosis factor-α; γ-GTP, γ-glutamyltranspeptidase.

liver in patients with chronic liver diseases (CLD). Thus, the treatment for insulin resistance in accordance with liver cell damage is necessary but rather challenging for a physician.

Health-related quality of life (HRQOL) is another key issue in managing CLD. Because in cases with chronic diseases, survival is not at risk for a long time and the goal of treatments is to maintain patients in symptom-free and community-living,[8] physicians have to consider HRQOL as a key component to evaluate therapeutic interventions. It is reported that, rather than psychiatric and active medical comorbidities, the severity of liver diseases determines HRQOL in CLD,[9] and that fatigue and depression are strong indicators for impaired HRQOL.[10] Unfortunately, however, it is hard for physicians to respond to such symptoms of fatigue because of their inherent subjectivity and the lack of quantitative objectivity in the symptom.

It is reported that exercise improves insulin sensitivity even in non-obese and non-diabetic subjects in the absence of significant changes in body mass index (BMI).[11] Furthermore, a substantial body of literature attests to the benefits associated with habitual exercise on physiological wellbeing.[12,13,14] In this study, we aimed to clarify if regular exercise has an advantage in terms of metabolic, physical, and psychosocial problems in CLD. Indicators associated with those problems were evaluated before and after aerobic and resistance training conducted regularly for five months with an oral intake of branched-chain amino acids (BCAA). Efficacy and safety issues of regular exercise on CLD are also discussed.

## MATERIALS

### Patients

The patient's characteristics are summarized in Table 1. Five CLD due to various etiologies and stages were enrolled, with the exception of acute events, edema, and ascites detectable by physical examination, jaundice, risky esophageal varices, overt encephalopathy of grade II or more, and viable hepatocellular carcinoma proven or suspected by ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI), and/or abnormal values of α-fetoprotein or des-γ-carboxyprothrombin. All subjects gave their informed consent to participate. The ethical committees of participating institutes approved the study under the title of Efficacy of Exercise in Patients with Chronic Liver Diseases.

### Exercise and nutritional support

Both regular aerobic and resistance training were conducted for five months. An oral intake of BCAA (Aminoleban EN, Otsuka Pharmaceutical Co.,Ltd., Tokyo) was started one month prior to the exercise with a dose of one pack (200 kcal including 2.037 g of L-leucine, 1.9225 g of L-isoleucine, and 1.602 g of valine) a day as a late evening snack. Patients were directed to do habitual exercise at home and were supervised once a week at our affiliated facility. Aerobic training was performed using a cyclic ergometer at the facility or by walking at home with less intensity than the target heart rate, which was defined as the heart rate at the ventilatory threshold point. When an electrocardiogram taken during the exercise using a cyclic ergometer revealed an abnormal profile, the patient was excluded from the study according to a cardiologist's instruction. Weight-bearing exercise and/or resistance training using equipments were indicated to be at an intensity less than 15 repetition maximum. In both aerobic and resistance training, the rate of perceived exertion was cushy or slightly sweaty in all cases at these intensities. Physical activity and intensity at home were monitored by special instructions based on self-report measures and a computer-assisted pedometer.

### Measurement of physical parameters

Before and after the course, several physical parameters were measured. BMI was calculated from body length and body weight. Using whole body dual energy X-ray absorptiometry (whole body DEXA), bone mineral content, fat-free mass, and fat mass were quantified for the entire body. By monitoring exhaled gas during exercise on a treadmill, maximum oxygen uptake and ventilatory threshold point were determined. Perceptive intensity of each exercise was graded as a rate of perceived exertion in 20 steps from easiest to hardest by interviews during each exercise.

### Profile of Mood States (POMS)

Before and after the course of exercise, patients were requested to fill in POMS psychometric scale[15] to assess their psychosocial state. As it is temporary, the mood state was asked to be reported for the previous five days. POMS consists of five negative mood scales; anger, anxiety, fatigue, confusion, and depression; and one positive scale; vigor. The score of each scale was calculated along the instruction by standardizing age and gender effects for each subject.

### Statistical analysis

For comparison of each value before and after the course of exercise, the statistical difference was evaluated by a resampling method[16, 17] using Resampling Stats version

**Table 1.** Patient characteristics

| Case | Gender | Age | Etiology | Child-Pugh | PH of HCC† |
|---|---|---|---|---|---|
| 1 | F | 66 | AIH | 6 | No |
| 2 | F | 57 | LC(B) | 6 | Yes |
| 3 | F | 65 | LC(C) | 7 | Yes |
| 4 | F | 59 | AIH | 5 | No |
| 5 | M | 72 | CH(C) | 6 | No |

†, Past history of development of hepatocellular carcinoma; F, female; M, male; AIH, autoimmune hepatitis; LC, liver cirrhosis; CH, chronic hepatitis; (B), type B; (C), type C.

**Table 2.** Body composition related factors

| | Before | After |
|---|---|---|
| Cr (mg/dl)* | 0.63 ± 0.08 | 0.68 ± 0.12 |
| CPK (IU/l) | 192 ± 102 | 214 ± 116 |
| U-3-MH (μmol/day) | 247.6 ± 183.6 | 201.3 ± 63.6 |
| Ccr (ml/min) | 122.5 ± 33.6 | 134.8 ± 33.7 |
| Fasting glucose (mg/dl)** | 96.2 ± 5.4 | 92.2 ± 8.1 |
| Fasting insulin (μU/ml)* | 16.0 ± 8.8 | 12.8 ± 7.1 |
| HOMA | 3.8 ± 2.1 | 3.0 ± 1.7 |
| HbA1c (%) | 5.1 ± 0.7 | 5.1 ± 0.6 |
| BMI | 25.5 ± 1.3 | 25.6 ± 0.6 |
| Bone mineral content (g)** | 1765.4 ± 377.8 | 1724.8 ± 387.5 |
| Fat-free mass (kg) | 37.7 ± 5.1 | 38.2 ± 4.7 |
| Fat mass (kg) | 18.2 ± 5.0 | 18.0 ± 4.2 |

Mean ± SD; *, $P < 0.001$; **, $P = 0.03$; Cr, creatinine; U-3-MH, urinary extraction of 3-methyl-histidine; CPK, creatine phosphokinase; Ccr, creatinine clearance; HOMA, homeostasis model assessment score; BMI, body mass index.

5.0 software with the assumption of a null hypothesis: the exercise does not affect each value. First, each value before the exercise was subtracted from the value after the exercise in each case, and the average was calculated. Second, the subtracted value was randomly converted into a negative or positive value with the original absolute value, and the average was calculated. Next, the frequency of when the average calculated in the second step was larger than the average calculated in the first step, if it was positive; or smaller than the average calculated in the first step, if it was negative, was determined by repeating the second step a thousand times. Finally, the average of the frequencies was calculated by performing all steps five times and was defined as a probability. When the probability was less than 0.05, we rejected the null hypothesis and decided that the value was significantly different before and after the exercise.

## RESULTS

### Regular exercise was feasible in patients with chronic liver diseases

In this study we applied regular aerobic exercise and resistance training for five months with intensity up to the target heart rate and strength repeatable more than

**Table 3.** Serum biochemistries and blood cell counts

| | Normal range | Before | After |
|---|---|---|---|
| ALT (IU/l) | 10 - 20 | 49.0 ± 13.4 | 51.2 ± 13.1 |
| AST (IU/l) | 5 - 45 | 48.4 ± 17.7 | 48.2 ± 15.4 |
| LDH (IU/l) | 140 - 245 | 225.2 ± 82.3 | 243.8 ± 54.7 |
| ALP (IU/l) | 104 - 318 | 389.4 ± 165.1 | 369.4 ± 133.8 |
| γ-GTP (IU/l)* | 16 - 73 | 84.8 ± 69.1 | 65.0 ± 48.2 |
| T. Bil (mg/dl) | 0.2 - 1.0 | 0.8 ± 0.2 | 0.8 ± 0.1 |
| D. Bil (mg/dl) | < 0.4 | 0.3 ± 0.1 | 0.3 ± 0.1 |
| ChE (IU/l)* | 3500 - 8000 | 4037 ± 1737 | 3874 ± 1721 |
| Total protein (g/dl) | 6.5 - 8.2 | 8.1 ± 0.7 | 7.9 ± 0.6 |
| Albumin (g/dl) | 3.7 - 5.5 | 3.9 ± 0.4 | 4.0 ± 0.4 |
| Prealbumin (mg/dl)* | 22.0 - 40.0 | 19.5 ± 6.4 | 18.1 ± 7.0 |
| PA (%) | 80.0 - 100 | 70.0 ± 16.2 | 82.5 ± 12.5 |
| Transferrin (mg/dl) | 190 - 320 | 288.0 ± 96.8 | 303.6 ± 104.2 |
| TC (mg/dl) | 150 - 219 | 178.0 ± 41.0 | 174.2 ± 34.4 |
| $NH_3$ (μg/dl) | 18 - 70 | 75.6 ± 42.0 | 63.2 ± 16.8 |
| BCAA/Tyrosine | 4.99 - 9.45 | 4.6 ± 1.4 | 5.0 ± 1.8 |
| BCAA (μmol/l) | 379 - 688 | 394.6 ± 44.2 | 427.4 ± 68.8 |
| WBC (/$mm^3$) | 3500 - 9700 | 6700 ± 3726 | 6658 ± 4650 |
| RBC ( × $10^4$/$mm^3$) | 376 - 577 | 466.8 ± 20.5 | 460.8 ± 19.4 |
| Hemoglobin (g/dl) | 11.2 - 18.3 | 14.3 ± 0.9 | 14.1 ± 1.2 |
| Ht (%) | 34.3 - 51.9 | 44.7 ± 2.5 | 45.1 ± 2.8 |
| Platelet ( × $10^4$/$mm^3$)** | 14.0 - 37.9 | 16.8 ± 7.6 | 13.0 ± 5.5 |

Mean ± SD; *, $P < 0.001$; **, $P = 0.03$; PA, prothrombin activity; TC, total cholesterol; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; ALP, alkaline phosphatase; T. Bil, total bilirubin; D. Bil, direct bilirubin; ChE, cholinesterase; BCAA, branched-chain amino acids; WBC, white blood cell; RBC, red blood cell; Ht, hematocrit.

**Table 4.** Physical capabilities

| | Before | After |
|---|---|---|
| Grasping power (kg)** | 21.6 ± 6.3 | 24.3 ± 7.2 |
| Knee extension (watt/kg)* | 9.8 ± 3.3 | 10.9 ± 3.4 |
| VT (sec)* | 139.2 ± 25.0 | 157.2 ± 18.9 |
| %HR (%) | 48.7 ± 16.9 | 43.5 ± 10.9 |

Mean ± SD;*, $P < 0.001$; **, $P = 0.03$; VT, ventilatory threshold point; %HR, proportion of heart rate against maximum heart rate with the exercise at ventilatory threshold point.

**Table 5.** Profile of Mood States (POMS) psychometric scale

| | Before | After |
|---|---|---|
| Anxiety | 53.4 ± 4.3 | 48.4 ± 6.2 |
| Depression | 62.6 ± 5.6 | 53.4 ± 10.5 |
| Anger | 55.6 ± 6.7 | 50.6 ± 4.0 |
| Confusion | 56.2 ± 4.3 | 51.4 ± 4.9 |
| Fatigue* | 54.6 ± 7.6 | 49.2 ± 7.5 |
| Vigor | 51.6 ± 3.4 | 49.8 ± 9.9 |

Mean ± SD;*, $P < 0.001$.

15 times, respectively, to CLD patients with various etiologies. During the course of five months of exercise, no major events demanding additional treatments were observed, such as rupture of esophageal varices, overt encephalopathy, edema and/or ascites, or hepatocellular carcinoma development. Nor were any severe complaints documented, such as muscle pain or cramps. Although serum concentration of creatinine (Cr) was significantly increased after the course from 0.63 ± 0.08 mg/dl to 0.68 ± 0.12 mg/dl ($P < 0.001$), creatinine clearance (Ccr) was stable during the course ($P = 0.12$, the upper section of Table 2). Neither serum concentration of creatine phosphokinase (192 ± 102 IU/l vs. 214 ± 116 IU/l) nor urinary excretion level of 3-methyl-histidine (247.6 ± 183.6 μmol/day vs. 201.3 ± 63.6 μmol/day) showed significant differences before and after the course as well ( $P = 0.25$ and $P = 0.25$, respectively).

**Liver cell damage and functional reserve of the liver were not affected by exercise**

Serum concentrations of enzymes associated with liver cell damage or destruction of the biliary system are summarized in the upper section of Table 3. The values of each enzyme were not significantly different during the course, with the exception of γ-GTP, which significantly decreased from 84.8 ± 69.1 IU/l to 65.0 ± 48.2 IU/l ($P < 0.001$).

The values reflecting the functional reserve of the liver and blood cell counts are summarized in the middle and lower sections of Table 3, respectively. Although serum concentrations of cholinesterase and prealbumin as well as platelet counts were significantly decreased from 4037 ± 1737 IU/l, 19.5 ± 6.4 mg/dl, and 16.8 ± 7.6 $\times 10^4/mm^3$ to 3874 ± 1721 IU/l, 18.1 ± 7.0 mg/dl, and 13.0 ± 5.5 $\times$ $10^4/mm^3$, respectively ($P < 0.001$, $P < 0.001$ and $P = 0.03$, respectively), all other values including serum concentrations of total cholesterol, total bilirubin, and $NH_3$, and BCAA/tyrosine ratio showed no significant differences after the course, compared with those just before starting the exercise. Moreover, serum concentrations of transferrin and BCAA and prothrombin activity tended to be increased from 288.0 ± 96.8 mg/dl, 394.6 ± 44. μmol/l, and 70.0 ± 16.2% to 303.6 ± 104.2 mg/dl, 427.4 ± 68.8 μmol/l and 82.5 ± 12.5%, respectively ($P = 0.06$, $P = 0.10$, and $P = 0.06$, respectively). The decrease in platelet counts was associated with neither anemia nor leukopenia.

**Physical capabilities were improved both in muscle strength and endurance**

Physical capabilities were improved in both muscular strength and endurance as shown in Table 4. Grasping power of 21.6 ± 6.3 kg at the beginning significantly increased to 24.3 ± 7.2 kg at the end of course ($P = 0.03$). Maximal voluntary force production for knee extension measured using isokinetic dynamometry was also significantly increased from 9.8 ± 3.3 watt/kg to 10.9 ± 3.4 watt/kg ($P < 0.001$). Furthermore, ventilatory threshold point, an indicator of capacity for aerobic exercise, was significantly increased from 139.2 ± 25.0 sec to 157.2 ± 18.9 sec ($P < 0.001$). Consistent with the increase in the ventilatory threshold point, the proportion of heart rate against maximum heart rate revealed a tendency to decrease from 48.7 ± 16.9% to 43.5 ± 10.9% when exercise stress reached the ventilatory threshold point ($P = 0.07$).

**Insulin sensitivity was restored without alteration of body mass composition**

As an indicator for insulin resistance, the levels of fasting glucose, insulin, and HbA1c were measured before and after the course (the middle section of Table 2). The homeostasis model assessment score was calculated from fasting glucose and insulin. In the results, while HbA1c was not significantly changed, fasting glucose and insulin

were significantly reduced from 96.2 ± 5.4 mg/dl and 16.0 ± 8.8 μU/ml to 92.2 ± 8.1 mg/dl and 12.8 ± 7.1 μU/ml, respectively ($P = 0.03$ and $P < 0.001$, respectively). Along with this reduction, the homeostasis model assessment score was also significantly decreased from 3.8 ± 2.1 to 3.0 ± 1.7 ($P < 0.001$). As summarized in the lower section of Table 2, BMI and fat-free mass did not show significant differences before and after the course (25.5 ± 1.3 vs. 25.6 ± 1.0 and 37.7 ± 5.1 kg vs. 38.2 ± 4.7 kg, respectively). Whole body bone mineral content was the only parameter among body composition indicators changing significantly during the course from 1765.4 ± 377.8 g to 1724.8 ± 387.5 g ($P = 0.03$).

**Psychosocial distress was reduced through exercise, especially for sense of fatigue**

Effects of the exercise on psychosocial distress were evaluated by using the POMS questionnaires. Before starting the course, the average scores for anxiety, depression, anger, confusion, and fatigue were 53.4 ± 4.3, 62.6 ± 5.6, 55.6 ± 6.7, 56.2 ± 4.3, and 54.6 ± 7.6 respectively (Table 5). The average score of all negative scales was 56.5 ± 4.7. On the other hand, the positive scale of vigor was revealed to be 51.6 ± 3.4 points. After five months of the course, the score of fatigue was significantly reduced to 49.2 ± 7.5 ($P < 0.001$) accompanied by a tendency for reductions in the scores for all the other negative scales of anxiety, depression, anger, and confusion as 48.4 ± 6.2, 53.4 ± 10.5, 50.6 ± 4.0, and 51.4 ± 4.9, respectively ($P = 0.06$, $P = 0.10$, $P = 0.09$, and $P = 0.06$, respectively). Altogether, the average score of all negative scales tended to drop to 50.6 ± 5.6 ($P = 0.09$). In contrast, the average value of the positive scale was 49.8 ± 9.9 at the end of the course and did not change significantly ($P = 0.31$).

## DISCUSSION

The management of insulin resistance is a critical issue for CLD in terms of both liver function and hepatocarcinogenesis. Alteration of the glucose metabolism affects fat metabolism, resulting in the excess production of lipid peroxide and reactive super oxide,[18,19,20] which in turn damage hepatocytes,[6] followed by the development of hepatocellular carcinoma.[21] In practice, however, it is very difficult to manage insulin resistance associated with CLD because calorie restriction conflicts with treatments for malnutrition due to hepatocellular damage. Although a reduction in body weight by exercise has been reported to be advantageous to CLD with obesity,[22] the effects of exercise without weight loss are unclear. Our study suggests that regular exercise can reduce both fasting sugar and insulin levels in the blood without any alteration of BMI or residual liver function. Only the serum concentration of γ-glutamyltranspeptidase (γ-GTP) was significantly improved among the markers indicating liver or biliary cell damage during the course of exercise. It was reported that an exogenous administration of tumor necrosis factor-α (TNF-α) was followed by a dose-related increase of γ-GTP,[23] and the mRNA level of TNF-α in the liver was correlated with γ-GTP in chronic hepatitis type C.[24] Because TNF-α is a key mediator for both insulin resistance[25] and liver cell damage in various liver diseases,[26,27,28,29,30] if γ-GTP can be a surrogate marker of TNF-α expression in the liver, regular exercise may reduce TNF-α expression in the liver, leading to both improvements in insulin sensitivity and the alleviation of liver cell damage.

Because we were concerned that regular exercise would deteriorate protein-energy malnutrition, which is a common finding in cirrhotic patients,[31] an oral intake of BCAA was coupled with the exercise. Numerous reports indicate that BCAA improves not only energy malnutrition but also encephalopathy[32] and/or even insulin resistance.[33] Thus, there are possibilities that the improvements in insulin sensitivity and psychosocial status in this study were obtained through the action of BCAA. However, the effects of BCAA cannot explain all improvements in our setting because the administration of BCAA had been started one month prior to the evaluation of pre-exercise status in this study. BCAA usually shows effects within several weeks after starting its ingestion. Furthermore, there is no report that an oral intake of BCAA alone can increase physical activities such as muscle strength or endurance of exercise. On the other hand, it has been suggested that BCAA is necessary during exercise,[34] improves training efficiency,[35] and reduces central fatigue due to exercise.[36] Thus, BCAA is expected to play a supporting role for the exercise.

After the course of exercise, bone mineral content was significantly reduced in our cases. Accumulating data suggest that metabolic osteopathy is correlated with severity of liver damage associated with an enhanced resorption process in both cholestatic and non-cholestatic diseases.[37, 38] Bone turnover rate is also accelerated even in normal populations by exercise.[39, 40] Taking these findings together, it is not difficult to assume that the exercise-induced acceleration of bone turnover further enhances the resorption process in CLD. Although the precise mechanisms are not clear, these observations strongly suggest that medications for osteoporosis should be taken into consideration during exercise in CLD. In contrast to bone mineral content, controversial observations were obtained for the other body mass composition in this study. Although serum concentration of Cr increased without any decrease in Ccr, neither indicators for muscular degeneration, such

as serum concentration of creatine phosphokinase and urinary excretion level of 3-methyl-histidine, nor fat-free mass, which was calculated from the data of whole body DEXA, were significantly changed after the exercise. It was reported, however, that an altered distribution of water in various body compositions due to liver diseases hinders the accurate measurement of fat-free mass even using whole body DEXA.[41] Because muscle strength was significantly increased in grasping power and knee extension, it is reasonable to interpret the increment of Cr concentration after the exercise as a result of increased muscle bulk.

Productivity of rapid turnover proteins and platelet counts are commonly used as indicators for functional liver reserve. A significant decrease in serum concentrations of cholinesterase, prealbumin, and platelet counts after the exercise seems to indicate that the exercise depleted the functional liver reserve in our study. However, other indicators for protein production, such as serum concentrations of albumin, transferrin, and prothrombin activity, were not significantly changed or even tended to be increased after the exercise. Furthermore, the mechanism of thrombocytopenia associated with liver dysfunction is still in debate. Although platelet counts can decrease due to their accumulation and destruction in the enlarged spleen associated with portal hypertension, no gastrointestinal fiber or CT revealed any aggravation of esophageal varices or farther enlargement of spleen after the exercise in this study, respectively (data not shown). On the other hand, it has been reported that expressions of thrombopoietin and its receptor can be reduced without significant liver cell damage leading to abnormal thrombopoiesis.[42,43,44] Taken together with the stable detoxification capability of the liver after the exercise indicated by serum concentration of total bilirubin and $NH_3$, these facts imply that the functional liver reserve should be judged as conserved. Regardless of the mechanisms, the reduction in platelet counts increases the risk of bleeding. Close observation should be paid to prevent hemorrhagic events during exercise in CLD.

In the past 15 years there has been increasing consensus regarding the centrality of patients' subjective perception for the assessment of health status. HRQOL is probably more relevant than length of life because patients are frequently more concerned about quality and disability than about longevity.[8] This is especially true in cases with chronic diseases, in which survival is not at risk for a long time. Although only a few reports are available on HRQOL in CLD, it is suggested that a poor perceived health status, especially fatigue[45,46] and depression,[9] results in impaired HRQOL. Consistently, the average score of depression was the highest of 62.6 ± 5.6 among the negative scales in our cases. Moreover, it is noteworthy that the score of fatigue was significantly decreased after the exercise with a tendency for reduction in all other negative scales. Because fatigue is a symptom resulting from a set of various factors without quantitative objectivity, there is no specific treatments. Although there is no evidence in this study whether fatigability improved on the basis of physical or psychosocial factors or both, regular exercise have the potential to improve HRQOL in CLD.

Although the limited number of patients enrolled in this study diminishes the implication of the results, it is suggested that regular aerobic and resistance exercise coupled with an oral intake of BCAA can be a promising alternative to treat patients with reduced functional liver reserve. Possible adverse effects; reductions in bone mineral content, and platelet counts, demand adequate medications and close evaluation of osteoporosis and portal hypertension. As it is quite difficult to manage insulin resistance, physical activity and psychosocial problems accompanied with CLD, the significance and mechanisms of regular exercise on these issues should be further evaluated for a larger population.

**Acknowledgments.** This study was supported by a grant-in-aid from Otsuka Pharmaceutical Co., Ltd..

## REFERENCES

1) Parkin DM, Bray F, Ferlay J, Pisani P: Global cancer statistics, 2002. *CA Cancer J Clin* **55**: 74-108, 2005.
2) Sherman M: Hepatocellular carcinoma: epidemiology, risk factors, and screening. *Semin Liver Dis* **25**: 143-154, 2005.
3) Yu MC, Yuan J-M: Environmental factors and risk for hepatocellular carcinoma. *Gastroenterology* **127**(5 **Suppl 1**): S72-S78, 2004.
4) Marchesini G, Forlani G, Bugianesi E: Is liver disease a threat to patients with metabolic disorders? *Ann Med* **37**: 333-346, 2005.
5) Lonardo A, Adinolfi LE, Loria P, Carulli N, Ruggiero G, Day CP: Steatosis and hepatitis C virus: mechanisms and significance for hepatic and extrahepatic disease. *Gastroenterology* **126**: 586-597, 2004.
6) Valgimigli M, Valgimigli L, Trere D, Gaiani S, Pedulli GF, Gramantieri L, Bolondi L: Oxidative stress EPR measurement in human liver by radical-probe technique. Correlation with etiology, histology and cell proliferation. *Free Radic Res* **36**: 939-948, 2002.
7) Muller MJ, Pirlich M, Balks HJ, Selberg O: Glucose intolerance in liver cirrhosis: role of hepatic and non-hepatic influences. *Eur J Clin Chem Clin Biochem* **32**: 749-758, 1994.
8) McNeil BJ, Weichselbaum R, Pauker SG: Speech

and survival: tradeoffs between quality and quantity of life in laryngeal cancer. *N Engl J Med* **305**: 982-987, 1981.
9) Hauser W, Holtmann G, Grandt D: Determinants of health-related quality of life in patients with chronic liver diseases. *Clin Gastroenterol Hepatol* **2**: 157-163, 2004.
10) Rowan PJ, Al-Jurdi R, Tavakoli-Tabasi S, Kunik ME, Satrom SL, El-Serag HB: Physical and psychosocial contributors to quality of life in veterans with hepatitis C not on antiviral therapy. *J Clin Gastroenterol* **39**: 731-736, 2005.
11) Hasbum B, Real JT, Sanchez C, Priego MA, Diaz J, Viguer A, Basanta M, Martínez-Valls J, Marín J, Carmena R, Ascaso JF: Effects of a controlled program of moderate physical exercise on insulin sensitivity in nonobese, nondiabetic subjects. *Clin J Sport Med* **16**: 46-50, 2006.
12) Atlantis E, Chow C-M, Kirby A, Singh MF:An effective exercise-based intervention for improving mental health and quality of life measures: a randomized controlled trial. *Prev Med* **39**: 424-434, 2004.
13) DiLorenzo TM, Bargman EP, Stucky-Ropp R, Brassington GS, Frensch PA, LaFontaine T: Long-term effects of aerobic exercise on psychological outcomes. *Prev Med* **28**: 75-85, 1999.
14) Elavsky S, McAuley E, Motl RW, Konopack JF, Marquez DX, Hu L, Jerome GJ, Diener E: Physical activity enhances long-term quality of life in older adults: efficacy, esteem, and affective influences. *Ann Behav Med* **30**: 138-145, 2005.
15) McNair DM, Lorr M, Droppleman LF: Manual of the profile of the mood states. San Diego, Educational and Industrial Testing Service, 1981.
16) Lunneborg CE: Data analysis by resampling. concepts and applications edition 1. Pacific Grove; Duxbury Press, 1999.
17) Lunneborg CE: Random assignment of available cases: bootstrap standard errors and confidence intervals. *Psychol Methods* **6**: 402-412, 2001.
18) Avramoglu RK, Basciano H, Adeli K: Lipid and lipoprotein dysregulation in insulin resistant states. *Clin Chim Acta* **368**: 1-19, 2006.
19) Furukawa S, Fujita T, Shimabukuro M, Iwaki M, Yamada Y, Nakajima Y, Nakayama O, Makishima M, Matsuda M, Shimomura I: Increased oxidative stress in obesity and its impact on metabolic syndrome. *J Clin Invest* **114**: 1752-1761, 2004.
20) Schrader M, Fahimi HD: Mammalian peroxisomes and reactive oxygen species. *Histochem Cell Biol* **122**: 383-393, 2004.
21) Powell EE, Jonsson JR, Clouston AD: Steatosis: co-factor in other liver diseases. *Hepatology* **42**: 5-13, 2005.
22) Hickman IJ, Jonsson JR, Prins JB, Ash S, Purdie DM, Clouston AD, Powell EE: Modest weight loss and physical activity in overweight patients with chronic liver disease results in sustained improvements in alanine aminotransferase, fasting insulin, and quality of life. *Gut* **53(3)**: 413-419, 2004.
23) Sheron N, Lau JY, Daniels HM, Webster J, Eddleston AL, Alexander GJ, Williams R:Tumour necrosis factor to treat chronic hepatitis B virus infection. *Lancet* **336 (8710)**: 321-322, 1990.
24) Taliani G, Badolato MC, Nigro G, Biasin M, Boddi V, Pasquazzi C, Clerici M: Serum concentration of gammaGT is a surrogate marker of hepatic TNF-alpha mRNA expression in chronic hepatitis C. *Clin Immunol* **105 (3)**: 279-285, 2002.
25) Uysal KT, Wiesbrock SM, Marino MW, Hotamisligil GS: Protection from obesity-induced insulin resistance in mice lacking TNF-alpha function. *Nature* **389 (6651)**: 610-614, 1997.
26) Bird GL, Sheron N, Goka AK, Alexander GJ, Williams RS: Increased plasma tumor necrosis factor in severe alcoholic hepatitis. *Ann Intern Med* **112(12)**: 917-920, 1990.
27) Torre F, Rossol S, Pelli N, Basso M, Delfino A, Picciotto A: Kinetics of soluble tumour necrosis factor (TNF)-alpha receptors and cytokines in the early phase of treatment for chronic hepatitis C: comparison between interferon (IFN)-alpha alone, IFN-alpha plus amantadine or plus ribavirin. *Clin Exp Immunol* **136(3)**: 507-512, 2004.
28) Fang JW, Shen WW, Meager A, Lau JY: Activation of the tumor necrosis factor-alpha system in the liver in chronic hepatitis B virus infection. *Am J Gastroenterol* **91(4)**: 748-753, 1996.
29) Rudiger HA, Clavien P-A: Tumor necrosis factor alpha, but not Fas, mediates hepatocellular apoptosis in the murine ischemic liver. *Gastroenterology* **122(1)**: 202-210, 2002.
30) Streetz K, Leifeld L, Grundmann D, Ramakers J, Eckert K, Spengler U, Brenner D, Manns M, Trautwein C: Tumor necrosis factor alpha in the pathogenesis of human and murine fulminant hepatic failure. *Gastroenterology* **119(2)**: 446-460, 2000.
31) Tajika M, Kato M, Mohri H, Miwa Y, Kato T, Ohnishi H, Moriwaki H: Prognostic value of energy metabolism in patients with viral liver cirrhosis. *Nutrition* **18**: 229-234, 2002.
32) Charlton M: Branched-chain amino Acid enriched supplements as therapy for liver disease. *J Nutr* **136**: 295S-298S, 2006.
33) Tsuchiya M, Sakaida I, Okamoto M, Okita K: The effect of a late evening snack in patients with liver cirrhosis. *Hepatol Res* **31**: 95-103, 2005.
34) Smriga M, Kameishi M, Torii K: Exercise-dependent

preference for a mixture of branched-chain amino acids and homeostatic control of brain serotonin in exercising rats. *J Nutr* **136**: 548S-552S, 2006.
35) Ohtani M, Sugita M, Maruyama K: Amino acid mixture improves training efficiency in athletes. *J Nutr* **136**: 538S-543S, 2006.
36) Blomstrand E: A role for branched-chain amino acids in reducing central fatigue. *J Nutr* **136**: 544S-547S, 2006.
37) Corazza GR, Trevisani F, Di Stefano M, De Notariis S, Veneto G, Cecchetti L, Minguzzi L, Gasbarrini G, Bernardi M: Early increase of bone resorption in patients with liver cirrhosis secondary to viral hepatitis. *Dig Dis Sci* **45**: 1392-1399, 2000.
38) Uretmen S, Gol M, Cimrin D, Irmak E: Effects of chronic liver disease on bone mineral density and bone metabolism markers in postmenopausal women. *Eur J Obstet Gynecol Reprod Biol* **123**: 67-71, 2005.
39) Maimoun L, Manetta J, Couret I, Dupuy AM, Mariano-Goulart D, Micallef JP, Peruchon E, Rossi M: The intensity level of physical exercise and the bone metabolism response. *Int J Sports Med* **27**: 105-111, 2006.
40) O'Kane JW, Hutchinson E, Atley LM, Eyre DR: Sport-related differences in biomarkers of bone resorption and cartilage degradation in endurance athletes. *Osteoarthritis Cartilage* **14**: 71-76, 2006.
41) Strauss BJ, Gibson PR, Stroud DB, Borovnicar DJ, Xiong DW, Keogh J: Total body dual X-ray absorptiometry is a good measure of both fat mass and fat-free mass in liver cirrhosis compared to "gold-standard" techniques. Melbourne Liver Group. *Ann N Y Acad Sci* **904**: 55-62, 2000.
42) Ishikawa T, Ichida T, Matsuda Y, Sugitani S, Sugiyama M, Kato T, Miyazaki H, Asakura H: Reduced expression of thrombopoietin is involved in thrombocytopenia in human and rat liver cirrhosis. *J Gastroenterol Hepatol* **13**: 907-913, 1998.
43) Ishikawa T, Ichida T, Sugahara S, Yamagiwa S, Matsuda Y, Uehara K, Kato T, Miyazaki H, Asakura H: Thrombopoietin receptor (c-Mpl) is constitutively expressed on platelets of patients with liver cirrhosis, and correlates with its disease progression. *Hepatol Res* **23**: 115-121, 2002.
44) Ishikawa T, Ichida T, Matsuda Y, Sugitani S, Sugiyama M, Kato T, Miyazaki H, Asakura H: Expression of hepatic thrombopoietin mRNA in primary cultured hepatocytes and in rats with acute liver injury or bone marrow suppression with or without cirrhosis. *J Gastroenterol Hepatol* **15**: 647-653, 2000.
45) Obhrai J, Hall Y, Anand BS: Assessment of fatigue and psychologic disturbances in patients with hepatitis C virus infection. *J Clin Gastroenterol* **32**: 413-417, 2001.
46) Jones EA: Fatigue complicating chronic liver disease. *Metab Brain Dis* **19**: 421-429, 2004.