

# Effect of physical exercise on sarcopaenia in patients with overt hepatic encephalopathy: a study protocol for a randomised controlled trial

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## ABSTRACT

**Introduction** Limited data are currently available for patients with overt hepatic encephalopathy (OHE) receiving physical exercise (PE). The aim of the current study is to prospectively examine the effect of PE on sarcopaenia in patients with OHE.

**Methods and analysis** At the time of patient recruitment, a precise assessment for nutritional status and daily physical activities will be performed in each subject. Study participants will be randomly assigned into two groups: (1) the PE group and (2) the control group. In the PE group, we will conduct guidance to study participants once a month at the outpatient nutrition guidance room. We will also instruct them to do exercise with >3 metabolic equivalents (mets; energy consumption in physical activities/resting metabolic rate) for 60 min per day and to do exercise >23 mets per week. Improvement of sarcopaenia as defined by muscle mass and muscle strength at 3 months after the randomisation will be the primary endpoint. Sarcopaenia will be defined based on the current Japanese guidelines. We prospectively compared the improvement of sarcopaenia in the two groups.

**Ethics and dissemination** This study has received approval from the Institutional Review Board at Hyogo college of medicine (approval no. 2768). Final data will be publicly disseminated irrespective of the study results. A report releasing study results will be submitted for publication in an appropriate journal after completion of data collection.

**Trial registration number** UMIN000029248; Pre-results. No patient is registered at the submission of our manuscript.

## INTRODUCTION

Hepatic encephalopathy (HE) is defined as 'brain disorder caused by liver failure and/or portosystemic shunts manifesting as a wide spectrum of neurological or

## Strengths and limitations of this study

- ▶ To the best of our knowledge, the current study is the first prospective interventional study (randomised trial) to examine the effect of physical exercise in patients with overt hepatic encephalopathy on sarcopaenia.
- ▶ This study limitation is that our study results will be limited to a Japanese population and validation studies on other ethnic backgrounds will be needed.

psychiatric abnormalities ranging from subclinical symptoms to hepatic coma'.<sup>1</sup> HE can be either overt meaning evident and readily diagnosed, or covert requiring psychometric screening for the definite diagnosis.<sup>1</sup>

Regular physical activity favourably impacts the risk for disease onset and progression of several chronic diseases.<sup>2,3</sup> However, investigations with regard to the effects of exercise on chronic liver diseases (CLDs) are relatively recent.<sup>2,3</sup> In patients with compensated liver cirrhosis (LC), physical exercise (PE) has been proved to be safe and probably beneficial in the longer term although PE may acutely increase portal vein pressure.<sup>4,5</sup> While in patients with decompensated LC having potential risk for developing HE, it is well recognised that further loss of muscle mass can play a significant role in the worsening of HE. Several investigators therefore presumed that PE and branched-chain amino acid

(BCAA) therapy could ameliorate muscle mass loss and prevent HE.<sup>6</sup>

The decreased muscle mass and muscle strength which is related to ageing is termed primary sarcopaenia.<sup>7,8</sup> Secondary sarcopaenia is defined as the decreased muscle mass and muscle strength that accompanies underlying diseases, such as chronic kidney disease, CLDs, inflammatory diseases, malignancies and malnutrition (insufficient protein or caloric intake).<sup>7,8</sup> Considering the critical role for the metabolism of the liver, secondary sarcopaenia due to nutritional disorders or other relevant factors can frequently occur in CLDs. Sarcopaenia in patients with LC is of clinical importance as it can affect the quality of life such patients.<sup>9–12</sup> Skeletal muscle mass is central for ammonia clearance, and in turn, Hyperammonemia impairs skeletal muscle synthesis, resulting in deterioration of sarcopaenia.<sup>13</sup>

As described earlier, PE conveys multiple health benefits both in healthy persons and several chronic diseases.<sup>14</sup> Despite these benefits, scarce data are currently available for patients with overt hepatic encephalopathy (OHE) receiving PE. The aim of the current study is to prospectively examine the effect of PE on sarcopaenia in patients with OHE.

### Patient eligibility criteria

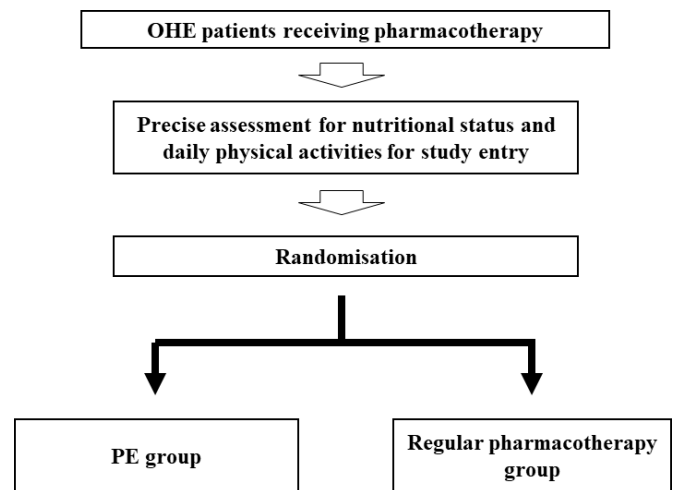
From a view point of clinical practice, it should be emphasised that PE under insufficient nutrients and protein intake could be dangerous in OHE patients, given that it could accelerate further protein catabolism and muscle mass loss.<sup>15</sup> At the time of patient recruitment, a precise assessment for nutritional status and daily physical activities will be thus performed in each subject.

### Inclusion criteria

1. Gender is not limited.
2. Patients with OHE aged  $\geq 20$  years receiving pharmacotherapy (hospitalised or ambulatory patients). OHE will be defined using medical interview and number connection test (NCT).<sup>16</sup> Aetiologies for OHE are liver diseases related. Aetiologies for liver diseases are not limited.

### Exclusion criteria

1. Patients with acute liver failure and patients with overt HE will be excluded.
2. Patients with severe depression or psychiatric disorder.
3. Patients with severe OHE who are expected to be difficult to participate in this study.
4. Patients with severe underlying diseases such as advanced malignancies, severe infection, severe chronic heart failure and respiratory disorders.
5. Pregnant or lactating female patients.
6. Patients who will be concerned about falling.
7. Patients who were judged to be inappropriate for the study subjects from the view point of ability to participate in PE.



➤ Primary endpoint :

Improvement of sarcopaenia (muscle mass and muscle strength)

**Figure 1** Study design. OHE, overt hepatic encephalopathy; PE, physical exercise.

## STUDY PROTOCOL

### Study design: non-double blind randomised controlled trial

Our study participants are patients with OHE receiving pharmacotherapy. Pharmacotherapy will include lactulose, rifaximin, neomycin and BCAA therapy. Study participants will be randomly assigned into two groups: (1) the PE group and (2) the control group (regular observation group) (figure 1).

### OHE and NCT

Patients with subjective clinical symptoms will be defined as patients with OHE (based on West Haven criteria). Patients without subjective clinical symptoms will be categorised into normal patients and patients with covert HE: (1) patients with no objective symptoms and  $< 120$ s in the NCT will be defined as normal; (2) other remaining patients will be defined as patients with covert HE<sup>17–19</sup> (table 1).

**Table 1** Definition of HE

	Positive subjective symptoms	Positive objective symptoms	$\geq 120$ s in NCT
Normal	No	No	No
Overt HE	Yes	Yes	No
	Yes	No	No
	Yes	Yes	Yes
	Yes	No	Yes
Covert HE	No	No	Yes
	No	Yes	No
	No	Yes	Yes

HE, hepatic encephalopathy; NCT, number connection test.

## Physical exercise

In the PE group, we will conduct guidance to study participants once a month at the outpatient nutrition guidance room. We will also instruct them to do exercise with >3 metabolic equivalents (mets; energy consumption in physical activities/resting metabolic rate) for 60 min per day and to do exercise >23 mets per week.<sup>20–25</sup> In the PE group, physical activities equal to or higher than walking for 60 min per day should be strongly recommended for each study participant. In both groups, pharmacotherapy in each underlying liver disease will be continued and we will ask all patients for self-declare of daily amount of exercise. Direct monitoring for exercise will not be performed.

## Primary endpoints

### Improvement of sarcopaenia

Sarcopaenia will be defined based on the current Japanese guidelines.<sup>26</sup> Muscle mass using bioimpedance analysis (BIA) and muscle strength (hand grip) for the assessment of sarcopaenia will be calculated once a month. Improvement of sarcopaenia at 3 months after the randomisation will be the primary endpoint. We prospectively compared the improvement of sarcopaenia in the two groups.

## Secondary endpoints (examination for study)

### Brain MRI findings

There is paucity of objectivity in the diagnosis of HE. Additionally, serum ammonia levels do not always correlate the degree of HE.<sup>27–28</sup> On the other hand, neuroimaging, in particular brain MRI, increasingly reveals diffuse abnormalities of brain activity and altered organisation for functional connective networks.<sup>29</sup> In this study, evaluation for HE using brain MRI such as pallidal hyperintensity will be performed every 6 months and changes over time in brain MRI findings will be assessed.<sup>30</sup>

### Changes over time in baseline characteristics

Body weight, platelet count, serum albumin, aspartate aminotransferase, alanine aminotransferase, total cholesterol, triglyceride, low-density lipoprotein, high-density lipoprotein, fasting blood glucose, haemoglobin A1c, homeostasis model assessment of insulin resistance, BCAA, BCAA to tyrosine ratio, serum hyaluronic acid<sup>31</sup> and Wisteria floribunda agglutinin-positive Mac-2-binding protein.<sup>32</sup>

## Follow-up and standard of care

During the study period and after completion of the study, all subjects will be seen in clinic every 4 weeks to address complications from liver disease and other comorbidities. Compliance with pharmacotherapy will be in particular emphasised. Routine laboratory testings (haematology, biochemistry and coagulation) will be mandatory at study entry and at completion of study, and on an as-needed basis.

## Stopping criteria

A major concern with regard to PE is the increase in portal hypertension, and the subsequent higher risk for LC-related complications such as the development of ascites, spontaneous bacterial peritonitis and variceal bleeding.<sup>5 14 33</sup> Thus, when the deterioration of OHE as compared with baseline grade is confirmed during study in the PE group, PE will be stopped to the patient.

## Case registration period

From October 2017 to March 2021.

## Data collection

A research assistant will collect data elements from patient medical records, including:

Baseline data:

- Gender and age
- Height and body weight
- Vital signs
- Drinking history and smoking history
- Cause for underlying liver diseases
- Previous treatments
- Comorbid conditions
- Baseline laboratory tests
- Child-Pugh classification and results for NCT
- Presence or absence of ascites on radiological findings

## Statistical methods

### Descriptive statistics

Data will be entered into JMP V.13 software (SAS Institute, Cary, North Carolina, USA) and all data will be checked to ensure their consistency. Data in each time point will be compared. Quantitative variables will be compared by paired or unpaired *t*-test. Categorical variables will be compared using the Pearson  $\chi^2$  test or Fisher exact test as appropriate.

## Sample size

Based on our previous results of BIA, assuming that  $\alpha$  error (type 1 error) is 0.05, detection power ( $\beta$ ) is 0.8, difference in the two groups to be detected measured using BIA is 10 and SD of outcome is 10, in order to randomly assign one to one, the number of necessary cases in both groups will be 17 cases (total of 34 cases).<sup>26 34</sup> Considering the number of dropped out cases, a total of 40 cases will be required.

## DISCUSSION

No data could exist with regard to the usefulness of PE for patients with OHE on sarcopaenia. To the best of our knowledge, this is the first prospective interventional study assessing objectively the effect of PE on sarcopaenia for patients with OHE.

From a view point of clinical practice, it should be emphasised that PE under insufficient nutrients and protein intake could be dangerous in patients with OHE, given that it could promote further protein catabolism

and thereby muscle mass deletion. An appropriate nutritional assessment will be indicated prior to initiating PE in our subjects. Additionally, caution should be exercised in patients with ascites and marked stimulation of vasoconstrictor systems (renin–aldosterone and sympathetic nervous systems), given that renal dysfunction can develop after PE in our subjects.<sup>15</sup> Regarding this point, we will perform the current randomised controlled trial with full care. Patients with high risk for PE-related complications such as falling will be excluded from our study subjects.

One of major strength of our study is that this study is randomised controlled trial. One study drawback is that the current study will be based on a Japanese population, and additional investigations on different ethnic populations are required to further verify the efficacy of PE on sarcopaenia and extrapolate to other races. However, if the effectiveness of PE on sarcopaenia in subjects with OHE is confirmed in this randomised trial, then useful information will be provided for clinicians.

### Ethics and dissemination

#### Research ethics approval

The study protocol, informed consent form and other submitted documents were reviewed and approved.

#### Confidentiality

On recruitment, the research assistant will provide a unique scrambled identification (ID) number to each study participant. Only the ID number will be used to identify subjects. Data sheets and any printout of electronic files will be saved in a locked filing cabinet in a secure office in the department of Hepatobiliary and Pancreatic disease, Department of Internal Medicine, Hyogo College of Medicine, Hyogo, Japan, with limited access.

#### Dissemination policy

Final data will be publicly disseminated irrespective of the study results. A report releasing study results will be submitted for publication in an appropriate journal after completion of data collection.

**Contributors** KY, HN and HE: analysed data and wrote the article. SN: supervised the randomised trial. Other authors: recruited candidates and collected relevant data.

**Competing interests** None declared.

**Ethics approval** Institutional Review Board at Hyogo College of Medicine (approval no. 2768).

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