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Effects of beta-hydroxy beta-methyl butyrate calcium combined with exercise therapy in patients with cardiac disease: a study protocol for clinical trial

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ABSTRACT

Introduction The current treatment for heart disease consists of exercise therapy in addition to pharmacotherapy, nutritional support and lifestyle guidance. In general, nutritional support focuses on protein, salt and energy restrictions, with no active protein or amino acid intake in cases involving moderate or higher renal failure. From this perspective, patients with cardiac disease are at high risk of frailty.

Beta-hydroxy beta-methyl butyrate (HMB) is a metabolite of leucine. HMB is widely used for muscle strengthening and can be safely ingested even by patients with renal failure. The proposed study protocol will investigate the effects of HMB-calcium (HMB-Ca) administered in combination with comprehensive cardiac rehabilitation for muscle strength, muscle mass and cardiac function in patients with cardiac disease during the convalescent period. The primary outcome will be knee extensor strength. Secondary outcomes will be gross isometric limb strength and skeletal muscle mass.

Methods and analysis This study will be a single-blinded, randomised, controlled trial with parallel comparisons between two groups. The study period will be 60 days from the start of outpatient cardiac rehabilitation. Participants will be randomly divided into two groups: an HMB group consuming HMB-Ca one time per day for 60 days; and a Placebo group consuming reduced maltose once one time per day for 60 days. Exercise therapy will be performed by both groups.

Ethics and dissemination The study protocol will be published in a peer-reviewed journal. Ethics approval was provided by the Showa University Clinical Research Review Board.

Trial registration number jRCTs031220139; Japan Registry of Clinical Trails.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Unlike previous comprehensive cardiac rehabilitation, beta-hydroxy beta-methyl butyrate (HMB), a metabolite of leucine, will be used in nutritional approach.
⇒ HMB can be ingested even in the presence of coexisting renal failure and may be widely indicated in patients with cardiac disease.
⇒ This study examines the effects of combining HMB and cardiac rehabilitation, and, therefore, cannot detect the effects of HMB alone in patients with cardiac disease.
⇒ There will be selection bias as follows: (1) participants may be more motivated to rehabilitate compared with those who did not participate in the study and (2) patients with negative opinions about nutritional supplementation may have been excluded.
⇒ It will be a study limitation that compliance with nutritional interventions will be assessed using self-report sheets rather than HMB-calcium concentrations in serum.

INTRODUCTION

The prevalence of heart disease increases with age, and mortality rates for heart disease continue to increase worldwide,[1] making this pathology the second leading cause of death in the Japanese population.[2] Patients with heart disease show decreased exercise tolerance due to deficits in cardiac and skeletal muscle function, resulting in dyspnoea during daily life. Exercise tolerance is well known to affect the prognosis of heart disease[3] and is also strongly associated with skeletal muscle strength and muscle mass.[4] Since hospitalisation results in reduced exercise tolerance and physical function deficits in most older patients, maintaining and improving physical and muscular functions even after discharge are important. Current treatments for heart disease comprise exercise therapy in addition to pharmacotherapy, nutritional support and lifestyle guidance. In Japan, comprehensive cardiac rehabilitation is performed nationwide for the purpose of improving healthy life expectancy, life prognosis and quality of life (QOL). Although safe for patients with cardiac disease, low-load

exercise has the problem of low efficacy compared with high-load exercise.[4]

Previous studies[5–7] have suggested that combining supplementation with branched chain amino acids (BCAAs) and exercise therapy offers an effective method for bridging this gap. However, patients with cardiac disease often have reduced renal function and are, thus, unable to benefit from this approach. In general, nutritional support focuses on protein, salt and energy restriction, with no active protein or amino acid intake in cases of moderate or higher renal failure.[8] From this perspective, patients with cardiac disease are at high risk of frailty and show a prevalence 2.7–4.1 times higher.[9] Sarcopenia in patients with chronic heart failure (CHF) is generally complicated by conditions such as metabolic disorders and decreased vascular function.[10] As described above, physical fitness and muscle strength are known to affect the life prognosis of patients with cardiac disease, and these factors, thus, represent a very important index.[11 12]

The combination of BCAAs and exercise therapy has been shown to be more useful in achieving muscle strengthening than either BCAA intake or exercise therapy alone.[5–7] Significantly greater increases in muscle strength and mass have been reported with a combined approach compared with the increases seen in older people receiving BCAAs alone. Beta-hydroxy beta-methyl butyrate (HMB) is a metabolite of leucine, a kind of BCAA.[13] HMB has been shown to prevent muscle proteolysis and regulate muscle metabolism.[14–17] Wu *et al* conducted a systematic review and meta-analysis[18] of the effects of HMB supplementation on muscle loss, strength and performance in older adults, finding that HMB supplementation contributed to the preservation of muscle mass. These previous studies[14–18] have shown that HMB contributes to improved muscle mass regardless of age group. HMB-calcium (HMB-Ca) administration has been reported to have no significant effects on renal function.[19 20] Furthermore, similar findings have been reported for patients on maintenance haemodialysis.[21] HMB-Ca, a metabolite of leucine, is widely used for muscle strengthening and can be safely ingested even by patients with renal failure.

Objectives

This proposed protocol is for a study to investigate the effects of HMB-Ca in combination with comprehensive cardiac rehabilitation on muscle strength, muscle mass and cardiac function in patients with cardiac disease during the convalescent period.

METHODS AND ANALYSIS

Study methods

This study will be single-blinded, randomised, controlled trial with parallel comparisons between two groups. An outline of this study is presented in figure 1. The participants will be 52 patients with cardiac disease. Recruitment will be conducted at Showa University Fujigaka Rehabilitation Hospital, the anticipated date for the start of recruitment is scheduled on 16 January 2023 and, the end is scheduled on 31 March 2024. This study was approved by the Showa University Clinical Research Review Board (Reference ID: S12). Explanation of the study will be provided and consent will be obtained by the same cardiologist (YI) during the consultation at the start of outpatient cardiac rehabilitation (OCR).

The study period will be 60 days from the start of OCR. Participants will be randomly allocated to one of two groups: the HMB group (n=26), consuming HMB-Ca one time per day for 60 days; and the placebo group (n=26), consuming reduced maltose one time per day for 60 days. In addition, exercise therapy will be performed by

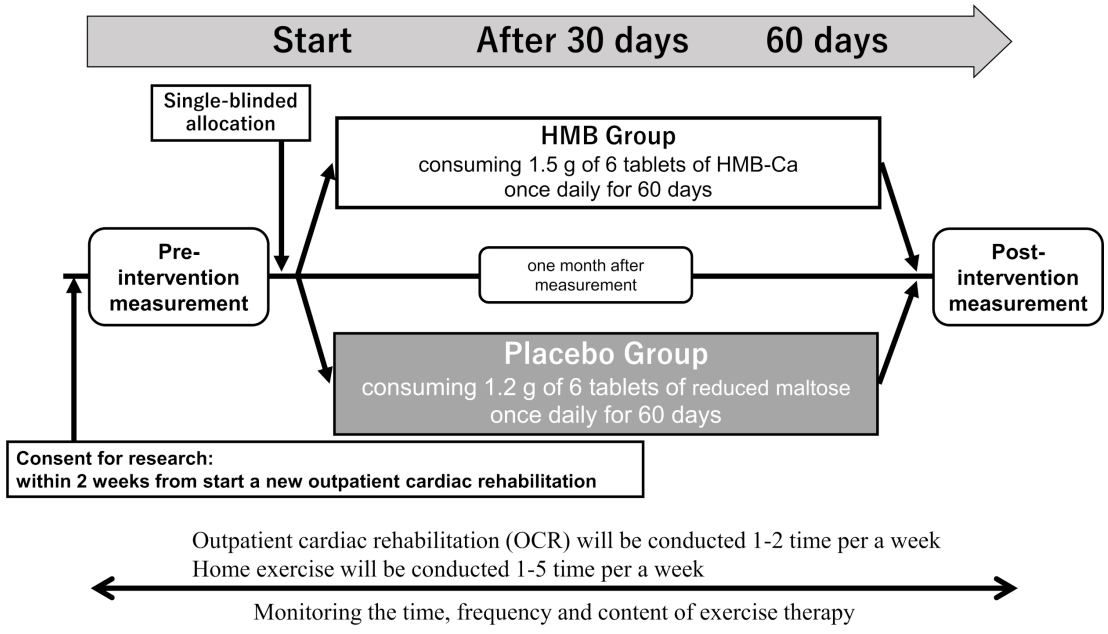

Figure 1 Schematic of the study design. HMB, beta-hydroxy beta-methyl butyrate.

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participants in both groups, as a combination of supervised and unsupervised activities at least three times a week. Supervised exercise therapy will be performed 1–2 times/week, while unsupervised exercise therapy will be performed 1–5 times/week. No prohibitions will be placed on food intake during the trial period.

Inclusion criteria

In this study, those patients who match all the inclusion criteria will be selected. The inclusion criteria are as follows: (1) patients who start a new OCR at Showa University Fujigaoka Rehabilitation Hospital, (2) patients with cardiac disease (myocardial infarction or angina, post-open-heart surgery or CHF) as the primary reason for requiring rehabilitation and (3) age >40 years. It has been pointed out that young people with heart disease have preserved physical functions other than cardiac function, whereas the risk of having frailty increases with age in mature and older people.[22 23] In this regard, the target age group was set at 40 years and over.

Exclusion criteria

The exclusion criteria are as follows: (1) patients with severe renal dysfunction (estimated glomerular filtration rate <30%) or receiving dialysis, (2) patients who cannot perform exercise therapy for ≥20 min for reasons other than cardiac disease, (3) patients with depression, schizophrenia or dementia, (4) patients with dysphagia, (5) patients with restricted energy and protein intake due to diabetes or renal dysfunction and (6) patients who the principal investigator or coinvestigator deem as unsuitable for this study. No patients meeting any of the exclusion criteria will be included.

Allocation, concealment and blinding

Participants will be allocated to the HMB or placebo group, and this study will be conducted as a single-blinded study in which the participant will not be told whether they are taking HMB-Ca or reduced maltose. Allocation will be accomplished using the envelope method. For this purpose, the data management officer (AI) will prepare an allocation list in advance using computer-generated random numbers. The allocation list will be enclosed in envelopes and the envelopes containing the allocation list will be properly managed. As soon as consent has been obtained from the subject, the subject will be allocated to the study treatment. The data management officer will inform the chief investigator (TI) of the identification code for the subject and will provide an envelope containing an allocation list.

The HMB-Ca and placebo used in this study will be divided by the administration staff at the hospital pharmacy. The hospital pharmacy is located on a different floor from the centre for rehabilitation and the cardiac rehabilitation unit, so the contents of hospital pharmacy are not visible from the outside. The supplements will be packaged in one 60-day supply bag and sealed individually for each patient in a medicine bag with the same outer packaging and invisible contents. These will then be further placed in bags with a number on the exterior, then stored in the warehouse.

Interventions

HMB-Ca supplementation

A nutritional intervention will be conducted after 60 days for participants in the HMB and placebo groups. The HMB group will be consuming 1.5 g (six tablets) of HMB-Ca (Kobayashi HMB-Ca; Kobayashi Perfumery, Tokyo, Japan: a round shape, uncoated white tablet; diameter 9 mm; thickness 4.9 mm; taste with slightly bitterness) one time per day. The used doses of HMB-Ca varied from 1.5 g to 3 g in previous study.[14–18] If 3 g of HMB-Ca will be applied in this study, 12 tablets of the supplement will need to be taken at a time, and the high number of tablets can affect medication adherence.[24] Therefore, 1.5 g of HMB-Ca will be applied in this study, which will be an unsupervised nutritional intervention. The placebo group will be consuming 1.2 g (six tablets) of reduced maltose (a round shape, uncoated white tablet; diameter 8 mm; thickness 4 mm; taste with slightly sweetness) one time per day. HMB-Ca and placebo look similar but taste slightly different. Supplementation in both groups will be provided in the morning, to be taken with water. Participants will complete the self-report sheet for supplementation for 60 days. These self-report sheets will be collected after finishing the 60 days of the intervention. Compliance rates with supplementation will be calculated.

Exercise therapy

Exercise therapy will be undertaken including supervised exercise as OCR along with unsupervised home exercise. OCR will be conducted 1–2 times/week. Participants will perform 60 min of OCR per session, comprising a warm-up, approximately 30 min of aerobic exercise, 15 min of resistance exercise and cool-down exercise. The resistance exercise (rowing) will be performed using a muscle training machine (Wel-tonic L series; Minato Medical Science, Osaka, Japan). The intensity of resistance exercise will be set at 50% of maximum voluntary contraction. Aerobic exercise will be set based on the results of a cardiopulmonary exercise test (CPET) and exercise will be prescribed according to cardiac rehabilitation guidelines[25] using the anaerobic metabolic threshold (AT) heart rate and Borg scale scores of 11–13 as indicators.

On days the patient does not attend the hospital, home exercise will be conducted 1–5 times/week, with instructions to walk at the pulse rate within the AT as a guide, and the frequency of home exercise will be checked similarly to supplementation. Participants will complete the self-report sheet for home exercise for 60 days. These self-report sheets will be collected after finishing the 60 days of the intervention. Compliance rates with home exercise will be calculated. In addition to exercise therapy, OCR will consist of nursing interviews with nurses and nutritional guidance from a dietician.

Table 1 Measurement protocol

Item	Before starting intervention	One month after supplementation	Post intervention
Period	Within 2 weeks OCR starting	28–32 days after	60–67 days after
Patient content	●	–	–
Demographics	●	–	–
Knee extensor muscle strength	●	●	●
Grip strength	●	●	●
Leg press strength	●	●	●
Skeletal muscle mass (RF muscle)	●	●	●
Skeletal muscle mass (whole body: BIA)	●	–	●
Physical functions (SPPB・ 10 m timed gait test)	●	●	●
QOL assessment (SF-12)	●	–	●
CPET	●	–	●
Biochemical examination microRNA	●	●	●
BDNF	●	–	●
Nutritional assessment	●	–	●
Adverse events	Constant monitoring during outpatient cardiac rehabilitation		
Vital signs	Constant monitoring during outpatient cardiac rehabilitation		

BDNF, brain-derived neurotrophic factor; BIA, bioelectrical impedance; CPET, cardiopulmonary exercise test; OCR, outpatient cardiac rehabilitation; QOL, quality of life; RF, rectus femoris; SPPB, short physical performance battery.

Outcome measures

Measurements will be conducted before starting the intervention, at 1 month after the end of the supplementation period (28–32 days after starting the intervention), and in the postintervention period (60–67 days after starting the intervention). OCR is available Monday to Saturday during the week, with no OCR on Sunday. Measurements will be conducted when the OCR will be seen. It is difficult to assess everyone at around 60 days postintervention and also 30-day period. Measurements will, therefore, be conducted within the designated scheduled measurement days. The measurement protocol is presented in table 1.

The primary outcome will be knee extensor muscle strength. Secondary outcomes will be gross isometric limb strength (leg press strength and grip strength), skeletal muscle mass (whole-body muscle mass and rectus femoris (RF) muscle mass), physical functions (short physical performance battery (SPPB) and 10 m timed gait test), CPET parameters (peak VO_2 and peak-load/AT), biochemical examinations (albumin, total protein, brain natriuretic peptide, creatinine, blood urea nitrogen, estimated glomerular filtration rate, cystatin C), microRNA (miR-181a, miR-181b, miR-181c, miR-484), brain-derived neurotrophic factor (BDNF), QOL assessment (SF-12v2, Japanese edition) and nutritional assessment (brief-type self-administered diet history questionnaire (BDHQ), energy consumption and nutrient composition of urine).

Muscle strength measurements

Knee extensor muscle strength (body weight ratio: kgF/kg) on the dominant side and on the non-dominant side will be measured using a hand-held dynamometer (Mobie Z; SAKAI Medical, Tokyo, Japan). In the sitting position, the hand-held dynamometer will be placed anterior to the fibula, 2.5 cm proximal to the malleolus.

Leg press strength will be measured using a muscle training machine (Weltonic L series; Minato Medical Science, Osaka, Japan). Before measurement, participants will be familiarised with this machine. Measurement will be performed in a position with the knees and hips in 90° of flexion.

Grip strength will be measured using a Smedley-type grip dynamometer (Grip-D; Takei Scientific Instruments, Niigata, Japan). Grip strength testing will be performed two times on the dominant side at maximum effort.

These muscle strength measurements will be conducted in two trials, taking the higher value for analysis.

Skeletal muscle mass

Whole-body skeletal muscle mass

Skeletal muscle mass will be measured by the bioelectrical impedance (BIA) method (InBody S10; InBody Japan, Tokyo, Japan), which uses weak currents and electrical resistance. Individuals with pacemakers or metallic materials in the body therefore will not be assessed. These patients who cannot be measured by BIA still be included. Measurements will be conducted after 2 min resting in a supine position, the participants will not be able to move or speak during it.

RF muscle measurement

Measurements will be conducted by a coinvestigator (KA). RF muscle mass will be measured using an ultrasonic reflectoscope (Portable Ultrasound Probe for Education fST9600; Lequio Power Technology, Okinawa, Japan). Muscle mass and echo intensity of the RF muscle will be measured at a point 10 cm proximal from the top of the patella, with the participant in a supine position. Cross-sectional area of the RF muscle will be calculated using the method described by Berger *et al*.[26]

Statistical considerations

Sample size calculation

Effect size was estimated at 0.5 based on studies of the combined effects of exercise and nutritional intervention using knee extension muscle strength as the primary outcome[6 7 27] and nutritional intervention in cardiac disease.[28] In preliminary studies, the Pearson correlation for knee extensor strength was 0.83 between the preintervention period and 1 month after the intervention[29] and 0.82 between the preintervention period and 3 months after intervention.[7] Since the sample size required for hypothesis testing using a two-sided analysis of covariance model with alpha=0.05 and beta=0.2 will be 48, the number of cases to be enrolled is set at 52 subjects.

Statistical analysis

Analysis of the primary outcome

Efficacy analysis will be conducted using the full analysis set. If the missing data of the outcome occur due to participant who is drop out of the intervention or the follow-up measurement. As a rule, complementation will not be used. Analyses of primary outcomes will be analysed using mixed-effects models. Analysis will be conducted using mixed-effects models for repeated measures with baseline values, group, measurement time point and group/measurement time point interactions as explanatory variables. A heterogeneous variance structure will be used. Estimation and comparisons of group differences will be calculated using this model. The level of significance will be set at 0.05. Analysis will be conducted before starting the intervention, 1 month after starting the supplementation period and in the postintervention period as the period for primary comparison.

Analyses for secondary outcomes

Grip strength, lower limb extensor strength, skeletal muscle mass (RF muscle) and physical functions (SPPB; 10 m timed gait test) will be analysed in the same way as for the primary outcome. Skeletal muscle mass (whole body), QOL assessment (SF-12), CPET parameters, BDNF and nutritional assessment will be compared between the two groups using unpaired t tests before starting the intervention and in the postintervention period. Improvement rates of secondary outcomes from baseline to the postintervention period will be compared between groups using the unpaired t test.

All data will be analysed using JMP software (V.16; SAS Institute Japan, Tokyo, Japan).

Monitoring

Research quality and data management

A director (HI) will undertake monitoring for the purpose of quality control of the study. HI will also designate a monitor to be in charge of monitoring. This monitor will ensure that the study is conducted in compliance with the latest research protocol and regulatory requirements throughout the study period, in accordance with a separate procedure to be developed. In addition, the monitor must not divulge personal patient information obtained during monitoring. Raw data from this study will be managed by the data monitoring committee (Showa University Research Administration Centre) after the study is completed.

Data statement

In accordance with the Japanese 'Clinical Trials Act', the datasets in this study will not be available.

Harms and stopping guideline

The times of onset of diseases and defects, date of onset and outcome, severity, outcome, causal relationship to the study and progress should be recorded in the medical record. Severity will be judged according to the following criteria: mild, disease or defect recovers without requiring treatment; moderate, disease or defect requires additional treatment or treatment after administration of the study medicine; or severe, administration of the study medicine is difficult to continue.

Where adverse events are suspected to have occurred as a result of the conduct of this research, a report will be made to the director of Showa University Fujigaoka Rehabilitation Hospital and the Minister of Health, Labour and Welfare. Adverse events are defined as follows: death, a condition that may lead to death, occurrence of a disability, a condition that may lead to disability, or a condition requiring hospitalisation for treatment. If an adverse event occurs, instructions will be sought from the manager of the implementing medical institution or the Minister of Health, Labour and Welfare regarding the continuation of the research.

Patient and public involvement

Patient experience and feedback on the determination of the size of HMB-Ca tablets have been used as a reference

point. Other than that, patient and public is not involved in the decisions regarding the study design, recruitment and conduct of this study.

Ethics and dissemination

This protocol will be published in a peer-reviewed journal. Ethics approval has been obtained from the Showa University Clinical Research Review Board (ID: S12). The protocol for this study has been registered with the Japan Registry of Clinical Trails (ID: jRCTs031220139; registration date: 16 June 2022; URL: https://jrct.niph.go.jp/en-latest-detail/jRCTs031220139). The results will be presented at a conference and submitted to a peer-reviewed journal, and the final analysis will be submitted for publication.

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Contributors Conception: TI and RM. Design of the work: TI, RM and EI. Statistical analysis: DN. Funding: TI, NT and AI. Conduct of this study: RM, KA, SA and SN. Drafting and revision of the manuscript: TI, RM, EI and YI. Data management: AI, YI and MH. Supervision of the study: HI. All authors read and approved the final manuscript.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

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