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# Biophysical and nutritional combination treatment for myosteatosis in patients with sarcopenia: a study protocol for single-blinded randomised controlled trial

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## ABSTRACT

**Introduction** Sarcopenia is characterised by age-related loss of skeletal muscle and function and is associated with risks of adverse outcomes. The prevalence of sarcopenia increases due to ageing population and effective interventions is in need. Previous studies showed that β-hydroxy β-methylbutyrate (HMB) supplement and vibration treatment (VT) enhanced muscle quality, while the coapplication of the two interventions had further improved muscle mass and function in sarcopenic mice model. This study aims to investigate the efficacy of this combination treatment in combating sarcopenia in older people. The findings of this study will demonstrate the effect of combination treatment as an alternative for managing sarcopenia.

**Methods and analysis** In this single-blinded randomised controlled trial, subjects will be screened based on the Asian Working Group for Sarcopenia (AWGS) 2019 definition. 200 subjects who are aged 65 or above and identified sarcopenic according to the AWGS algorithm will be recruited. They will be randomised to one of the following four groups: (1) Control+ONS; (2) HMB+ONS; (3) VT+ONS and (4) HMB+VT + ONS, where ONS stands for oral nutritional supplement. ONS will be taken in the form of protein formular once/day; HMB supplements will be 3 g/day; VT (35 Hz, 0.3 g, where g=gravitational acceleration) will be received for 20 mins/day and at least 3 days/week. The primary outcome assessments are muscle strength and function. Subjects will be assessed at baseline, 3-month and 6-month post treatment.

**Ethics and dissemination** This study was approved by Joint CUHK-NTEC (The Chinese University of Hong Kong and New Territories East Cluster) Clinical Research Management Office (Ref: CRE-2022.223-T) and conformed to the Declaration of Helsinki. Trial results will be published in peer-reviewed journals and disseminated at academic conferences.

**Trial registration number** NCT05525039.

## STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The study investigates the combined effect of HMB supplementation and vibration treatment on 200 sarcopenia patients.
⇒ Participant selection adheres to the AWGS 2019 criteria for identifying individuals with sarcopenia, ensuring a consistent and reliable sample.
⇒ The clinical application of both HMB supplementation and vibration treatment enhances the potential for practical clinical translation of this combined treatment.
⇒ The study cannot be double-blinded since blinding subjects for the LMHFV treatment is not feasible.
⇒ Placebo controls are challenging in vibration studies due to the tangible nature of the treatment.

## INTRODUCTION

Sarcopenia is a syndrome characterised by the age-related progressive loss of muscle mass and function.[1] It is a risk factor for falls and fractures in aged population.[2–4] The ageing population at 65 years or above is expected to increase from 18.4% to 33.3% in 20 years.[5] The prevalence of sarcopenia in Asia ranged from 7.3% to 12%, where there will be more elderly at risk of falls and resulting adverse outcomes.[6–8] Hence, sarcopenia has become an emerging healthcare concern for socioeconomic burden which needs prospective solutions to resolve the challenges.

Myosteatosis (fat infiltration in skeletal muscle) is one of the major factors that contribute to sarcopenia.[9 10] The muscle-derived stem cells resided in muscles are capable of differentiating into muscle, bone or adipose cells.[11] During ageing, the changes in biochemical and biomechanical microenvironment will lead to an increase in adipogenesis which contributes to intramuscular fat infiltration.[12] A recent study also showed that age-related mitochondrial

dysfunction and reduced lipid oxidation could increase myosteatosis.[13]

Low-magnitude high-frequency vibration (LMHFV) is a non-invasive intervention that provides cyclic and systemic mechanical stimulation. It was recently recommended by the Centres for Disease Control and Prevention Compendium of Effective Fall Interventions showing accreditation to the efficacy of LMHFV in fall prevention.[14] Both clinical and preclinical studies have shown that LMHFV can enhance muscle performance and reduce their intramuscular lipids in aged subjects.[11 15 16] Our published preclinical study in mice showed that lipid content in muscle was reduced by 31.07% after receiving LMHFV for 3 months.[11] Adipogenic differentiation of muscle-derived stem cells was also inhibited in LMHFV treated group. Leung *et al* reported that LMHFV (35 Hz, 0.3 g; 20 mins/day) for 18 months had significantly improved quadriceps muscle strength and balancing ability of community older people, resulting in a remarkable reduction in fall incidents with 0.56 adjusted HR.[15]

β-hydroxy β-methylbutyrate (HMB) is a metabolite of leucine which is commonly used as dietary supplement for trained athletes to improve body composition. Previous studies showed that HMB supplement could maintain total lean mass and appendicular lean mass in bedrest elderly.[17] Wang *et al* also reported an increase in grip strength and reduced intramyocellular fat infiltration after HMB supplementation to sarcopenic mice in a preclinical study.[11]

Oral nutritional supplement (ONS) is a type of protein supplement in the form of milk formula. A similar clinical study was published recently on interventions for patients with sarcopenia employing exercise programme with or without ONS.[18] The study suggested that protein intake plays an important role in muscle anabolism for older adults. Also, the anabolic response will reduce with advancing age and there will be a higher need for dietary protein.[19 20]

In view of the above relevant studies, the application of HMB supplementation and vibration treatment (VT) could be promising interventions for sarcopenia. Our animal study demonstrated that the combination of HMB and VT had improved muscle strength and reduced fat mass and fat infiltration after 3 months compared with either treatment alone.[11] Also, for HMB supplementation to work effectively, there should be readily available protein source for muscle protein synthesis and ONS can ensure a minimal sufficient protein intake for patients with sarcopenia.[18 19 21]

In this study, combination of VT and HMB supplementation was proposed to combat sarcopenia by improving muscle strength and physical performance in older people. The aim of this study is to evaluate the efficacy of combination treatment in alleviating sarcopenia, as compared with VT or HMB supplementation alone.

## METHODS AND ANALYSIS

### Study design and grouping

This is a single-blinded randomised controlled trial to investigate the efficacy of combination treatment on sarcopenia. Subjects will be screened for sarcopenia based on the Asian Working Group for Sarcopenia (AWGS) 2019 definition and recruited according to the eligibility criteria. Flow chart in figure 1 summarises the study design. Participants will be randomised to one of the four groups: (1) Control+ONS; (2) HMB+ONS; (3) VT+ONS and (4) HMB+VT + ONS. The treatment will last for 6 months with assessments at baseline, 3 and 6 months. Muscle strength, muscle mass, balancing ability, physical performance and quality of life will be evaluated.

### Sample size determination

The sample size is estimated based on our preclinical animal data[11] and a recent similar study with combination treatment to treat sarcopenia.[18] The maximum grip strength in patients with sarcopenia with or without exercise were 16.21±5.01 kg and 19.37±7.11 kg, respectively, from which the calculated effect size is 0.248. A sample size of 41 per group will have 80% power to detect a significant difference using two-way repeated-measures analysis of variance (ANOVA) with 0.05 significance level (PASS, NCSS, USA). Assuming dropout rate of 15%, n=48 per group is required for the study. By rounding to n=50 per group, a total sample size of n=200 is finalised.

### Recruitment strategy

Subjects will be recruited to this study through regular educational talks in our collaborating community centres, promotional materials in community centres or on social media and also referral from our collaborators. Participants will be screened by bioelectrical impedance analysis, handgrip and gait speed according to AWGS 2019 definition. Participants who meet the frailty criteria will be invited to join our research study in Prince of Wales Hospital, Shatin, Hong Kong. All participants will be informed of the potential benefits and risks before they sign the written informed consent. They can withdraw from the study anytime without any condition.

### Inclusion and exclusion criteria

Adults aged ≥65 years who are classified as sarcopenic after the screening (defined by AWGS 2019 criteria) will be included to the study. Exclusion criteria are the subjects with pathological bone diseases, chronic inflammatory conditions such as rheumatoid arthritis, neurological problems affecting gait speed, receiving regular guided exercises more than three times per week, chair-bound or bed-bound and not able to stand on vibration platform, with cardiovascular concern such as with pacemaker in situ or malignancy and with acute fractures or severe osteoarthritis.

### Randomisation and blinding

After obtaining written consent, recruited participants will be randomised by drawing sealed envelope with random numbers representing different groups. Except the independent research staff responsible for grouping randomisation and the participants, investigators, outcome assessors and statistician will be blinded from the grouping randomisation, while the allocation list will

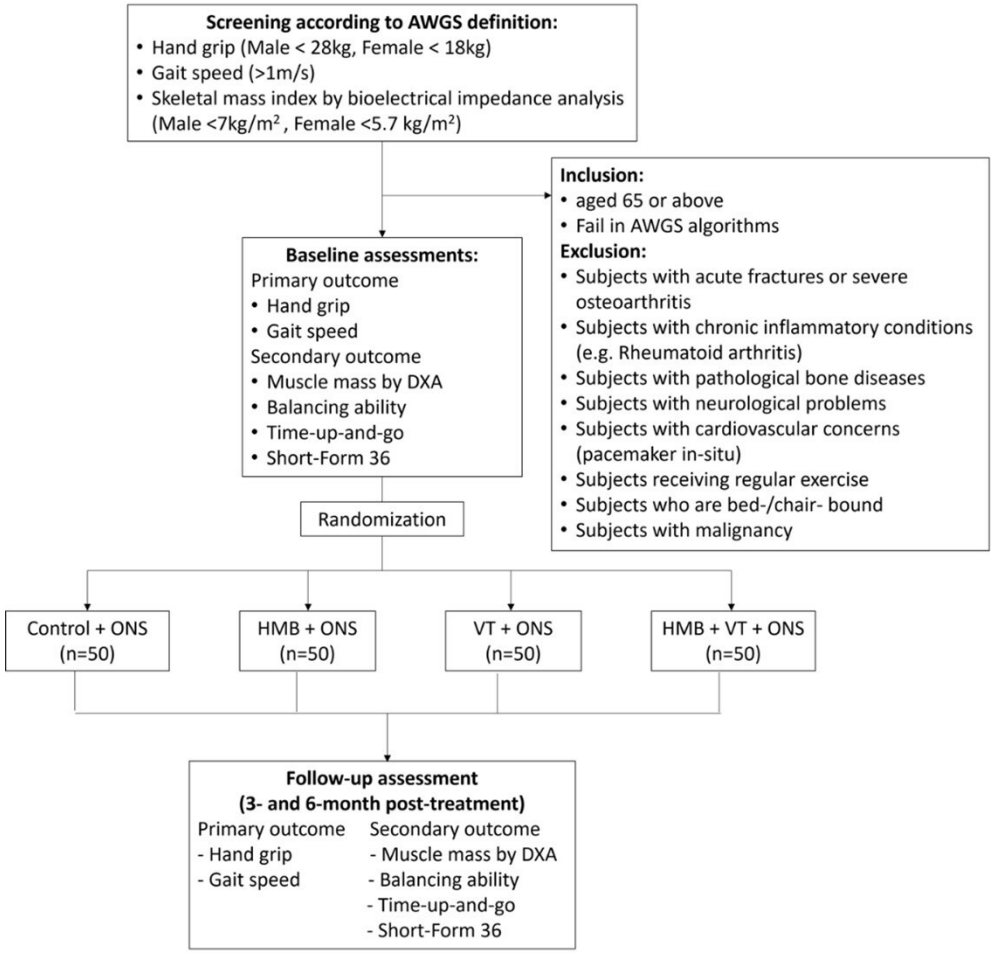


**Figure 1** Flow chart showing the study design for this clinical trial. AWGS, Asian Working Group for Sarcopenia; HMB, β-hydroxy β-methylbutyrate; ONS, oral nutritional supplement; VT, vibration treatment.

be kept confidential. Blinding of the participants is not feasible, as LMHFV can be easily felt and they will have to record their compliance of supplement intake and vibration therapy.

## Interventions

### Oral nutritional supplements

Protein supplement will be distributed to participants at baseline and 3-month follow-up. The ONS sachets (Ensure Gold, Abbott, Hong Kong) will be taken at breakfast with 1 sachet per day for 6 months.[18] Participants will be reminded to record the intake of ONS for compliance evaluation and regular phone reminders will be arranged.

### HMB supplementation

HMB supplement will be distributed to participants at baseline and 3-month follow-up. The capsules will be taken at meal with 1 g dosage, three times a day (total 3 g/day) for 6 months.[17] Participants will be instructed to follow the prescribed dosage and keep the unused supplement for compliance record check during follow-up visits. Regular phone calls will be made and booklets will be distributed for monitoring of compliance.

### Vibration treatment

Participants will be assigned to a collaborating community centre in their neighbourhood which has equipped with vibration platform (V-Health Ltd, Hong Kong). The regime for VT is to stand on the platform and receive vibration at 35 Hz, 0.3 g (g=gravitational acceleration) for 20 mins/day, at least 3 days /week for 6 months.[15] Safety precautions and operating procedures will be instructed to both participants and staff in collaborating community centres. Participants will be reminded to record their compliance in the booklet provided. The usage of LMHFV will be counterchecked by built-in SD data card in the vibration platform. Follow-up phone calls will be arranged regularly before visits for the second and last timepoints.

## Outcome measures

### Primary outcomes

Muscle strength and muscle performance are the primary outcomes of this study.[22 23] Handgrip strength will be measured using a dynamometer (5030JI, JAMAR, IL, USA) on each hand of the participants. They will be instructed to hold the device with the arm at 90° and elbow to the side of body. According to AWGS 2019 definition,

men with handgrip strength less than 28 kg and women less than 18 kg are defined as sarcopenic. Gait speed will be assessed by a 6-m-walk test. 1 m/s is the cut-off value defined by AWGS 2019 for diagnosing sarcopenia.

### Secondary outcomes

Height-adjusted skeletal muscle mass will be assessed by whole body scan with DXA (Dual-energy X-ray absorptiometry) (Horizon, Hologic, Massachusetts, USA).[22] Total appendicular muscle mass will be calculated by summation of muscle mass of four limbs. The cut-off value is defined as less than 7 kg for male and less than 5.4 kg for female.

Balancing ability will be evaluated with Biodex Balance System SD (Biodex Medical Systems, New York, USA).[15 23 24] The posture stability will be assessed when the participants are required to maintain centre of gravity on the balancing platform. Limits of stability will also be assessed, according to participants' directional control and reaction time for movements on the platform.[24]

Time-up-and-go test will be performed.[22 24] Time will be recorded for participants to rise from a chair, walk 3 m, turn around and walk back to the chair then sit down.

The 36-item Short-Form Health Survey (SF-36) on health-related quality of life will be assessed by validated Chinese version of the SF-36.[15 22–24] Participants' physical and mental components will be evaluated and the total score will be analysed. Higher scores indicate a better quality of life.

### Statistical analysis

Data in this study will be analysed according to the intention-to-treat principle. Normality test will be performed to determine normal distribution of data. Two-way repeated measure ANOVA will be used to compare measured outcomes with post-hoc Bonferroni tests. Statistical significance is set at $p \leq 0.05$ (SPSS V.20.0, IBM, USA).

### Data management

All personal information of the participants will be kept in locked cupboard and saved on password-protected computers. All data collection will be performed with strict adherence to professional standard of confidentiality. Data monitoring committee consist of only principal investigator, authorised research personnel and ethical committee members can access the personal data of participants. Important documents will be retained for 3 years after the completion of study.

### Data statement

The protocol and datasets used or analysed in this study will be available from the corresponding author on reasonable request. Researchers who provide a methodologically sound proposal may access data to achieve aims in the approved proposal.

## Patient and public involvement

Patients and the public were not involved in the design or planning of the study. Members of the public are involved in recruitment or conduct of the study. Test results will be reported to participants after their end-point assessments. Research results will be available to the public and patients in the form of educational talks and booklets.

## Ethics and dissemination

This study was approved by Joint CUHK-NTEC Clinical Research Management Office (CRE-2022.223-T) and conformed to the Declaration of Helsinki. Trial results will be published in peer-reviewed journals and disseminated at academic conferences.

# DISCUSSION

To our knowledge, this is the first randomised controlled trial to investigate the combination treatment of LMHFV and HMB supplementation on sarcopenia. With the current ageing population worldwide, the prevalence of sarcopenia is increasing. Patients with sarcopenia have low muscle strength and declined physical performance which will lead to falls and even fragility fractures. With LMHFV and HMB interventions, the pathogenesis factors of sarcopenia like fat infiltration can be tackled. Moreover, the addition of ONS in this randomised controlled trial provides minimum protein intake to ensure effective function of HMB supplements in facilitating muscle protein synthesis and ONS can also act as a placebo control in the study.

Sarcopenia is a degenerative condition that muscle mass and function will progressively deteriorate with increasing age. Currently, there is no approved medications for sarcopenia, while recommendations are usually made to patients to have regular exercises and increase protein intake. Patients with sarcopenia are often frail and have reduced mobility which can lead to further deterioration of muscles.[25] LMHFV provides passive loading to the musculoskeletal system which can maintain the muscles and bone metabolism by simply standing on a vibrating platform, providing stimulation even for less active or physically unfit patients with sarcopenia. Bone quality is generally maintained through mechanical loading from daily activities such as walking, while skeletal muscles require regular contractions to preserve their functions.[26–28] Maintaining posture and balance on a vibrating platform can help train muscle coordination and contraction. Numerous studies have demonstrated that muscle strength, muscle function, balancing ability and bone mineral density can be improved after LMHFV treatment, whereas fall rate can be decreased after 18-month LMHFV treatment.[15 16 29] Regarding nutritional intervention for patients with sarcopenia, protein supplements, essential amino acid supplements and HMB supplements are commonly recommended to ensure sufficient protein building blocks for muscle maintenance. HMB supplementation is extensively reported to facilitate muscle growth, improve body composition and slow protein degradation.[30 31] Additionally, ONS in liquid form can enhance protein availability in patients with

sarcopenia with chewing difficulties or gastrointestinal disorders, ensuring a consistent protein supply for muscle growth. Given these factors, there is great potential for using HMB supplementation and LMHFV in sarcopenia treatment, as supported by previous studies. However, the efficacy of this combination treatment in humans remains to be demonstrated. The aim of this randomised controlled trial is to investigate the efficacy of combined LMHFV and HMB treatment in combating sarcopenia in older people.

The strength of this clinical trial is the use of validated interventions in managing age-related muscle deterioration. All interventions adopted in this trial are well recognised for enhancing muscle strength.[15 18 30] Our preclinical study had demonstrated promising results in combating sarcopenia with the combination of LMHFV and HMB supplements, which a positive effect is expected in the clinical trial. Most importantly, the intervention programmes are simple to follow by participants. There are LMHFV platforms available at their nearest community centres and they can access the facilities easily. HMB supplements and ONS are also simple to administer with recommended dosage. The simplicity of interventions implies a higher chance of acquiring good compliance.

There are some limitations in this study. Given that the vibration signals of LMHFV intervention are perceptible to patients, conducting a double-blinded clinical trial is challenging. We will only keep the investigators, assessors and statistician blind to the groupings. Also, this study greatly relies on self-reported compliance, which can be subject to bias. Compliance record booklets will be distributed to participants who will be instructed to record daily on completion of their respective interventions. SD data card in vibration platform will be used to verify compliance and regular reminder phone calls will also be made. Moreover, participants in VT groups are required to visit community centres at least three times weekly, whereas other participants only need consume supplementations. This lifestyle change may introduce adherence and completion bias. All participants are encouraged to engage in a 30-min daily walk in their respective neighbourhoods, aiming to balance the level of outdoor activities between VT groups visiting community centres and other groups potentially staying home.

This study offers valuable insights to the novel combination interventions for sarcopenia management. If these interventions prove positive, they have the potential to enhance clinical sarcopenia management strategies. This trial will provide important clinical data, assisting in evaluating and delineating the efficacy and underlying mechanisms of this combination treatment for sarcopenia.

## Trial status

The trial was commenced on 7 November 2022 and is currently recruiting participants. The first subject was recruited on 12 January 2023. The anticipated date of study completion is 30 April 2025.

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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.

**Patient consent for publication** Not applicable.

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