Trials

STUDY PROTOCOL

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Vitamin D combined with whole-body vibration training for the treatment of osteo-sarcopenia: study protocol for a randomized controlled trial

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Abstract

Background Osteo-sarcopenia (OS) has become a global public health problem and a frontier research problem, as a combination of sarcopenia (SP) and osteoporosis (OP) diseases. The clinical performances include muscle weakness, systemic bone pain, standing difficulty, even falls and fractures, etc., which seriously affect the patient's life and work. The pathological mechanism of the OS may be the abnormal metabolism which disrupts the equilibrium stability of the musculoskeletal system. Therefore, this study combined vitamin D (Vit. D) and whole-body vibration training (WBVT) to intervene in subjects of OS, aiming to evaluate the effectiveness and safety of the diagnosis and treatment protocol and to explore the efficacy mechanism.

Methods We propose a multicenter, parallel-group clinical trial to evaluate the efficacy and safety of Vit. D combined with WBVT intervention in OS. Subjects who met the inclusion or exclusion criteria and signed the informed consent form would be randomly assigned to the WBVT group, Vit. D group, or WBVT+ Vit. D group. All subjects will be treated for 1 month and followed up after 3 and 6 months. The primary outcomes are lumbar bone mineral density (BMD) and appendicular skeletal muscle mass (ASM) measured by dual-energy X-ray absorptiometry (DXA) and handgrip strength measured by grip strength meter. Secondary outcomes include serum markers of myostatin (MSTN), irisin and bone turnover markers (BTM), SARC-CalF questionnaire, 1-min test question of osteoporosis risk, patient health status (evaluated by the SF-36 health survey), physical performance measurement that includes 5-time chair stand test, 6-m walk, and the short physical performance battery (SPPB).

Discussion If Vit. D combined with WBVT can well relieve OS symptoms without adverse effects, this protocol may be a new treatment strategy for OS. After therapeutic intervention, if the serum marker MSTN/irisin is significant, both have the potential to become sensitive indicators for screening OS effective drugs and treatments, which also indicates that WBVT combined with Vit. D plays a role in improving OS by regulating MSTN/irisin.

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Keywords Osteo-sarcopenia, Whole-body vibration training, Vitamin D, Irisin, Myostatin

Introduction

Background and rationale {6a}

Sarcopenia(SP) and osteoporosis(OP) are the two most common chronic diseases of the musculoskeletal system in the elderly population. Studies have shown that bone mass and muscle fiber numbers in humans peak at age 30 and 35 years, declining slowly with increasing age, so the incidence of SP and OP increases significantly with the aging of the population [1]. In recent years, the epidemiological data on SP in the Chinese population showed that the prevalence of SP in the community elderly is 8.9–38.8%, the prevalence of men is higher than women [2]. The prevalence of OP in people over 50 years old was 20.7% in women, 14.4% in men, and the prevalence increased significantly over 60 years old, especially in women [3]. The musculoskeletal system is a dynamic environment. Muscle and bone are two main components of the musculoskeletal system; both of them are derived from the mesoderm and are adjacent in physiological and anatomical positions, belonging to the motor system [4, 5]. Muscle and bone are two main components of the musculoskeletal system, both of them are derived from the mesoderm and are adjacent in physiological and anatomical positions, belonging to the motor system [4, 5]. Muscles and bones are not only providers and objects of mechanical load, but both are endocrine organs. Muscle and bone have the interaction of myogenic factors and bone factors in cells and molecules, and there is an inseparable close relationship between them in genetics, physiology, and anatomy [6–10]. Muscle and bone are the physiological, pathophysiological basis of SP and OP, and they contain each other to maintain musculoskeletal dynamic balance [11].

Therefore, based on musculoskeletal correlation studies and the co-pathogenesis of SP and OP, Binkley et al. proposed the concept of OS [12]. However, at present, only a small amount of experts have proposed diagnostic criteria for OS, mostly based on the diagnostic criteria that meet both SP and OP [13]. After studying the interrelationship between muscle and bone, providing certain intervention treatments for diseases related to reduced muscle mass and bone mass can effectively reduce the disability and mortality rate of OS and improve the quality of life for the elderly. OS belongs to age proliferative disease, and clinical single treatment of SP or OP is common. Combining bone with muscle's common target to intervene comprehensively is the etiology treatment of OS. Studies show that moderate exercise and drug treatment benefit the remission of OS and improve the prognosis [14]. Vitamin D (Vit. D) is one of the important basic components of healthy bones. Besides Vit. D's established promoting role in calcium and phosphate homeostasis, it can act on osteocytes directly and promote bone mineralization [15]. Vit. D promotes muscle and bone health by the muscle-bone axis, and it can regulate the expression of muscle and bone factors positively and regulate the injury regeneration of muscle and bone resorption bidirectionally [15]. And Vit. D plays an indispensable role in the physiological function of skeletal- and muscle-related diseases [16]. Whole-body vibration training (WBVT) is a rehabilitation training method, which induces neuromuscular reflex through mechanical vibration and external resistance load, promotes muscle contraction, and gives bone repetitive stress stimulation to improve the structure and function of the musculoskeletal system [17]. It is mostly directly used in muscle, bone, nerve, and other aspects.

At present, our understanding of OS pathophysiology and diagnosis and treatment is still insufficient, and more high-quality clinical research is needed [18]. In this study, a multicenter, parallel-group clinical trial was used to verify the efficacy of Vit. D combined with WBVT to improve OS. The results of this study will provide some evidence support for the clinical use of WBVT and Vit. D intervention in OS, and enrich the clinical treatment of OS.

Objectives {7}

This study is a multicenter, parallel-group clinical trial to evaluate the efficacy and safety of Vit. D supplements combined with WBVT on OS.

Trial design {8}

The trial design is a prospective, multicenter, parallel-group randomized trial. The study is a three-armed superiority interventional study comparing the therapeutic effects of Vit. D supplements combined with WBVT on OS. Eligible participants would be randomized 1:1:1 to one of three parallel groups (Vit.D, WBVT, WBVT+Vit.D), and they could withdraw at any stage. The group receives Vit. D active drug calcitriol 0.25 μg, WBVT, or calcitriol combined with WBVT for 1 month. After randomization, the Clinical Study Coordinator (CRC) will schedule treatment sessions. All recruitment procedures would be documented in the log file. This trial protocol uses the Standard Protocol Items:

Recommendations for Interventional Trials (SPIRIT) reporting guidance [19]. Figure 1 for the study flowchart.

Methods: participants, interventions, and outcomes

Study setting {9}

Patients will be collected at four university-affiliated hospitals in Shaanxi Province, China: (1) Affiliated Hospital of Shaanxi University of Chinese Medicine, (2) Xi'an Honghui Hospital, (3) Xi'an Hospital of Traditional Chinese Medicine, and (4) Baoji Hospital of Traditional Chinese Medicine. The clinical trial will be conducted in these four hospitals because they have complete examination and treatment facilities. Enrolled patients will receive follow-up, clinical examination, and fill out questionnaires at the orthopedic clinics of these four hospitals.

Eligibility criteria {10}

Diagnostic criteria

SP diagnostic criteria based on the "Chinese expert consensus on diagnosis and treatment for elderly with sarcopenia (2021) [2]." DXA was used to detect the appendicular skeletal muscle mass (ASM) of the limbs, grip strength instrument to detect the muscle strength of the limbs, 5-time chair stand test, 6-m walk, and SPPB to diagnose physical performance. The consensus cutoffs for low muscle strength, low muscle mass, and low physical performance in sarcopenia diagnosis are as follows: handgrip < 28.0 kg for men and < 18.0 kg for women, muscle mass < 7.0 kg/m^2 in men and < 5.4 kg/m^2 in women, 5-time chair stand test ≥ 12 s, 56-m walk < 1.0 m/s and SPPB ≤ 9 [2]. OP diagnostic criteria based on the "Guidelines for the diagnosis and management of primary osteoporosis(2022) [3]." The guideline indicates that the BTM level can assess the efficacy of anti-OP drugs, and the inhibition of bone turnover reflects that anti-bone resorption therapy is effective. OP can be diagnosed by high bone turnover type, bone mineral density (BMD) *T*-value ≤ − 2.5, and 1-min test question of osteoporosis risk [3]. Subjects who meet the diagnostic criteria for both SP and OP can be diagnosed with OS and enrolled in the trial.

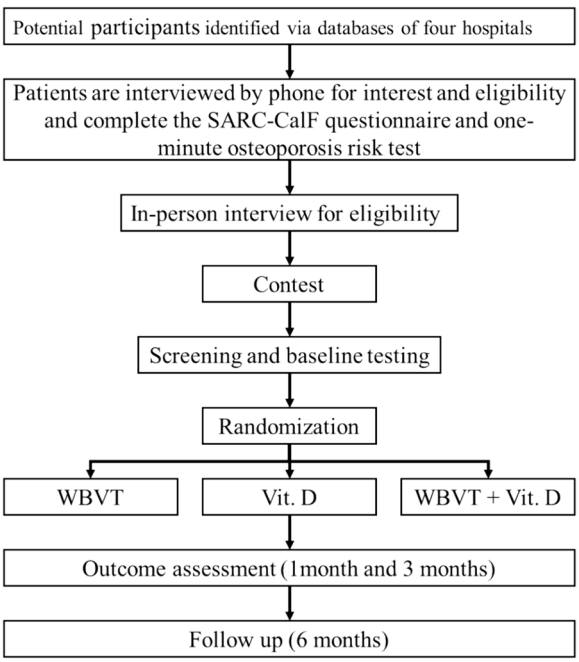

Fig. 1 Flow diagram of the recruitment process, group allocation, and participation in the three interventions. All participants who completed a follow-up were included in the corresponding analysis

Inclusion criteria

Based on the age of 55–85 years, the subjects were required to meet the diagnostic criteria of both SP and OP and sign the informed consent to complete this clinical study.

Exclusion criteria

Subjects with severe chronic diseases such as hypertension and tumors; serious involvement of heart, liver, kidney, and other organs; or endocrine and hematologic diseases are not suitable to be enrolled. Subjects with a history of lumbar or hip surgery, fracture, or other secondary osteoporosis are not eligible for enrollment. Individuals who cannot complete the specified inspection test, such as DXA, are not suitable for enrollment. Subjects who have taken Vit. D or anti-osteoporosis drugs for the last 3 months are not eligible for enrollment. Subjects who also participate in other clinical trials and other unsuitable situations judged by the investigator will not participate in this study.

Who will take informed consent? {26a}

Trained research assistants from four hospitals will first explain the purpose and requirements of our program in detail to eligible participants. The assistant will also obtain written informed consent from all participants prior to their participation in the study.

Additional consent provisions for collection and use of participant data and biological specimens {26b}

The informed consent has included participants' permission for the use of collected data. Further analysis of biological specimens does not apply to this study.

Interventions

Explanation for the choice of comparators {6b}

The studies have found that both Vit. D supplementation and whole body vibration training seem to have an effect on OS, so whether Vit. D supplementation and WBVT are more effective in OS, or whether they are more effective when used together. Moreover, What is the mechanism of action of Vit. D and WBVT on OS? Therefore, Vit. D and WBVT were selected as comparators for the intervention in OS in this trial.

Intervention description {11a}

Eligible participants will be randomly assigned to three parallel groups. WBVT group: 3 times a week, 10~20 min per time, the first intensity is 5 Hz, vibration for 1 min, rest for 1 min, and increase the frequency by 1Hz every week. Vit. D group: take the Vit. D active drug calcitriol, oral 0.25 μg, 1 time per day. Vit. D+WBVT group: WBVT combined with calcitriol, in the same method as before. All subjects will be treated for 1 month and followed up after 3 and 6 months at four hospitals.

Criteria for discontinuing or modifying allocated interventions {11b}

① If the subjects request to withdraw from the clinical investigator and request the doctor to suspend the clinical study, the clinical study of the case can be suspended. ② Poor compliance or huge differences and deviations in the test process, resulting in incomplete data collection. ③ Subjects with serious complications that may continue to worsen after the trial should be judged by the physician before deciding whether to continue the study. ④ During the trial, subjects developed fragility fractures and could be withdrawn from the study after a physician's judgment.

Strategies to improve adherence to interventions {11c}

To improve adherence to the intervention protocol, the staff members of the four hospitals are informed about the study, through oral resentations and WeChat moments at their departments. Subjects participating in this trial will receive free physical examination, bone mineral density test, and related blood index test from clinicians.

Relevant concomitant care permitted or prohibited during the trial {11d}

Participants remain on their standard treatment and medication procedures throughout the study period, and clinicians are advised to manage participants in the usual manner subject to the caveats outlined above.

Provisions for post-trial care {30}

n/a. Not applicable, since ancillary and post-trial care is provided within the standard care.

Outcomes {12}

Primary outcome

Lumbar spine BMD testing The diagnosis of OP is mainly based on the levels of the lumbar spine, hip, and forearm BMD and/or fragility fractures. For postmenopausal women and men over 50 years old, the WHO diagnostic criteria of lumbar spine BMD are recommended and based on DXA measurements (Table 1). The diagnostic criteria for OP based on DXA measurement of lumbar BMD is *T*-value ≤ 2.5 [3].

Skeletal muscle mass DXA is a noninvasive muscle mass measurement instrument, and the muscle mass measurement standard is based on height-adjusted muscle mass to determine the best way to measure muscle mass [limb muscle mass (kg)/height^2 (m^2)]. The consensus cutoffs for low muscle mass in sarcopenia diagnosis are as follows: < 7.0 kg/m^2 in men and < 5.4 kg/m^2 in women by DXA [2].

Muscle strength Upper limb grip strength is the evaluation index of handgrip strength. A grip strength device is the most commonly used tool, in order to avoid manual reading errors, we will use a digital display electronic grip strength device to guarantee the accuracy of the data. For the test, the subject uses the dominant hand to grip with maximum strength, and the test is performed at least 2 times, the maximum value is selected. The consensus recommends low muscle strength diagnostic cutoffs of handgrip < 28.0 kg for men and < 18.0 kg for women [2].

Secondary outcome

SARC-CalF questionnaire SARC-CalF is a modified version of SARC-F, the screening tool of choice

Table 1 BMD classification criteria based on DXA measurement

T-value	Classification
≥ − 1.0	Normal
− 2. 5~− 1.0	Low bone mass
≤ − 2.5	Osteoporosis
≤ − 2.5 + fragility fractures	Severe osteoporosis

for SP, and includes muscle strength (S), assistance in walking(A), rise from a chair(R), climb stairs(C), number of falls (F), and calf circumference. It was shown that the SARC-CalF has a new additional item: calf circumference compared to the previous version, which significantly improves the sensitivity and diagnostic accuracy of screening for SP in the elderly. A calf circumference of < 34 cm in men and < 33 cm in women is considered positive. A total of SARC-CalF scores ≥ 11 is considered positive for SP [20, 21].

One-minute test question of osteoporosis risk One-minute test question of osteoporosis risk are used to initially screen subjects who may be at risk for OP based on a brief patient history, but cannot be used for OP diagnosis [22].

Assessment of patient health status The SF-36 is a universal scale developed by the American Medical Research Group to measure quality of life and is a comprehensive indicator of individual health status, which is widely accepted and used internationally. The SF-36 has been shown to have good reliability and validity in the elderly population [23]. The SF-36 consists of 36 items, 35 of which are used in the calculation of eight separate scale scores. The physical functioning scale (10 items) is the longest scale. The general health and mental health scales have five items each and the vitality and role physical scales have four items each. The role emotional scale has three items and the bodily pain and social functioning scales have two items each. The remaining item of the SF-36 is a health transition question that asks about changes in general health over the past 12 months [14]. This questionnaire will be completed at all the measurement points (baseline, 1 month after the treatment, 3 and 6 months of follow-up) [24].

Physical performance There are several methods currently used to test physical performance, including 5-time chair stand test, 6-m walk, and SPPB.

Five-time chair stand test The 5-time chair stand test [25] can be used as a simple alternative method to measure lower limb strength, focusing on the determination of quadriceps group strength. A seat with a height of about 46 cm was used for the measurement, and the time required for the subject to complete five consecutive up-sit movements at the fastest speed without using the arms was recorded, and the experiment was repeated three times to take the average of the calculated times [2].

Six-meter walk Walking speed is the simplest, fastest, and safest method of assessing physical performance. It is measured by instructing the subject to pass through a certain test area at a regular walking speed without accelerating or decelerating midway, and measuring it at least twice and calculating its average value. Six-meter walking speed experiment ≤ 1.0 m/s indicates a decrease in physical performance [2].

The short physical performance battery The SPPB is a comprehensive physical performance test that includes an assessment of gait speed, a balance test, and a chair stand test. The individual test scores were 4 points and the total score was 12 points. A score of SPPB ≤ 9 points indicates poor physical performance [2].

Detection of serum markers of irisin, MSTN, Vit. D, and bone turnover markers BTM reflect the rate of bone resorption and formation, which will be measured with Vit. D by the Laboratory Department of the Affiliated Hospital of Shaanxi University of Chinese Medicine (ISO15189 certified). Serum irisin and MSTN levels will be measured by this researcher with ELISA kits.

Participant timeline {13}

The study flowchart is illustrated in Fig. 1.

Sample size {14}

BMD will be employed as the primary outcome for sample size estimation. Based on the result of relevant studies [26], the difference in BMD between the two groups is 0.88. It is estimated that a sample size of 24 in each group will have 90% power to detect a significant difference using variance analysis with a 0.05 significance level. To account for an anticipated dropout of 20%, we further increase the sample size to $n = 30$ for each arm (total $n = 90$).

Recruitment {15}

Subjects were required to complete the SARC-CalF questionnaire to determine whether they had possible SP, while completing the International Osteoporosis Foundation (IOF) 1-min test question of osteoporosis risk to determine whether they had possible OP. Subjects would be further tested for positive results on both the SARC-CalF questionnaire and 1-min test question of osteoporosis risk.

Assignment of interventions: allocation

Sequence generation {16a}

A total of 90 patients will be enrolled. Participants will be randomized into 1:1:1 allocation, blocked randomization with 30 participants in the vitamin D group, 30 participants in the WBVT group, and 30 participants in the Vit.

D + WBVT group. The randomization will be done using a computer randomization program before the intervention. This will be overseen by a biostatistician who is not involved in the recruitment of patients and data analysis. Hence, the patients and research personnel are blinded until the start of treatment.

Concealment mechanism {16b}

Allocation concealment will be ensured as the computer randomization program will not release the randomization code until the patient has been recruited into the trial. Because patients are treated differently, it is not possible to blind subjects and researchers, but data collection and analysis are done by dedicated statisticians. Subjects and researchers are blind to data, and statisticians are blind to study grouping.

Implementation {16c}

The principal investigator will enroll participants. The computer randomization program will generate the allocation sequence at a 1:1:1 ratio. An independent research staff will assign participants to interventions.

Assignment of interventions: blinding

Who will be blinded {17a}

Due to the characteristics and design of interventional studies, participants and researchers were not blinded to interventions; data analysts, however, will be blinded to the assignment of interventions. Outcome evaluation and statistical analysis will be performed by independent investigators who are blinded to patient allocation.

Procedure for unblinding if needed {17b}

Blinding is not applicable to this trial.

Data collection and management

Plans for assessment and collection of outcomes {18a}

The primary outcomes are lumbar BMD and ASM measured by DXA and handgrip strength measured by grip strength meter. Secondary outcomes include serum markers of myostatin (MSTN), Irisin and BTM, SARC-CalF questionnaire, 1-min test question of Osteoporosis risk, patient health status (evaluated by the SF-36 health survey), physical performance measurement (measured by 5-time chair stand test, 6-m walk, and SPPB) and adverse events (AEs) as reported in the trial. All indicators were measured at baseline and after 6 months of follow-up, and some measures were measured after 1 month of treatment and 3 months of follow-up, as shown in Table 2.

Table 2 Schedule for date collection: outcome measures per visits

Measures	Screening	Visit 1 (1st month)	Visit 2 (3rd month)	Visit 3 (6th month)
SARC-CalF	○			
One-minute test question of osteoporosis risk	○			
SF-36	○	○	○	○
BMD	○		○	○
ASM	○		○	○
Handgrip strength	○	○	○	○
Physical performance	○	○	○	○
Serum MSTN, Irisin, Vit. D, and bone turnover markers	○	○	○	○
Adverse experiences		○	○	○

Physical performance includes a 5-time chair stand test, 6-m walk, and SPPB

Bone turnover markers include procollagen type 1 N-peptide (P1NP) and C-terminal telopeptide of type 1 collagen (S-CTX)

Plans to promote participant retention and complete follow-up {18b}

To promote participant retention, the participant will be assigned to one investigator who is in contact with the participant during the whole study and who will perform the measurements. Patients will be contacted weekly for their intake of the intervention and 1 week before the assessment to enhance the attendance rate. Special assessment sessions on the weekend or in the evening will be arranged under special circumstances to enhance subject compliance. Patients who default a scheduled appointment will be contacted by the investigators to rearrange another appointment within 1 week.

Data management {19}

Clinical data will be collected and recorded by trained research assistants in our research center. Clinical examination data will be entered on case report forms and then entered electronically. Consistency checks by another technician will be performed to ensure data entry accuracy. All data will be stored in password-protected computers. The study will be conducted in compliance with Good Clinical Practices to ensure the rights and well-being of the participants and that the data collected are complete and verifiable from source documents. Patients are free to withdraw from the study at any time without

giving any reasons, and their medical care or legal rights will not be affected. Patient files will be maintained in storage for a period of 3 years after completion of the study.

Confidentiality {27}

All records containing personal information will be stored separately in the database and will only be shared within the study for research purposes. Only healthcare professionals and investigators have access to the information necessary for conducting the intervention.

Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}

Blood will be collected at the clinical sites for evaluation. After arrival at the local research laboratory at each site, the samples will be collected, transported, stored, and prepared according to local protocols. Blood will be stored at 2–8 °C before handling within the required time. All samples collected during the trial will be labeled with the patients' identification code and will not contain any identifiable data. Patients have the option of consenting to their samples being stored for future research uses. Samples will be stored anonymously at a central location for a minimum of 5 years and a maximum of 10 years after completion of the study, after which these specimens will be destroyed by incineration according to local guidelines and protocols. The potential usage of the stored samples is included in the informed consent form. Nevertheless, further usage of the samples will need to be approved by the institutional ethical committee.

Statistical methods

Statistical methods for primary and secondary outcomes {20a}

We will collect and analyze the data according to the intention-to-treat principle, and when the baseline characteristics of the three data groups are not comparable, secondary analyses will be conducted to adjust for differences. Analysis of variance with repeated measures was used to compare data results between groups, and all data were statistically analyzed using SPSS 23. 0 version statistical software with mean ± standard deviation for measures and using *t*-test for analyses, and chi-square test for comparison, with $P < 0.05$ indicating statistically significant differences.

Interim analyses {21b}

The duration of this trial was 6 months and no interim analysis is planned.

Methods for additional analyses (e.g., subgroup analyses) {20b}

Before and after the intervention, a subgroup analysis of simple muscle or bone changes will be performed to determine the effect of Vit. D and WBVT on muscle and bone, respectively.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}

Both intention-to-treat (ITT) analysis and per-protocol (PP) analysis will be conducted. Specifically, the interpretation of the intervention effect would be more likely to consider ITT as the gold standard approach. However, both ITT and PP analyses will be reported alongside each other for comparison. To conduct ITT analysis with incomplete data, missing data will be imputed using multiple imputation techniques.

Plans to give access to the full protocol, participant-level data, and statistical code {31c}

The dataset analyzed during the current study and the statistical code are available from the corresponding author upon reasonable request. There are no additives to the protocol available as reported in this manuscript. This article incorporates the full study protocol.

Oversight and monitoring

Composition of the coordinating center and trial steering committee {5d}

The composition of the trial steering committee is composed of four members of the sponsor, including the principal investigator and the coordinating investigator. The coordinating investigator receives day-to-day support for the trial from the investigators. The trial steering committee will be monthly informed about how the study is running.

Composition of the data monitoring committee, its role and reporting structure {21a}

The data monitoring committee (DMC) comprises data scientists and statisticians from the Shaanxi University of Chinese Medicine. Their primary responsibility is to ensure the data quality of the study by conducting audits of the trial every 2 months. The DMC operates independently of the sponsor with no competing interests. The committee charter is subject to further review upon request from the corresponding author.

Adverse event reporting and harms {22}

Adverse events in this trial include deaths, emergency room visits, onset of cognitive impairment, onset of physical dysfunction, and hospitalization lasting longer

than 24 h. The investigators will collect and record the adverse events at the end of the study and then examine the association between their incidence and the health conditions of elderly individuals.

Frequency and plans for auditing trial conduct {23}

The trial conduct will be audited by DMC every 3 months. The auditing process will be conducted independently of both the investigators and the sponsor.

Plans for communicating important protocol amendments to relevant parties (e.g., trial participants, ethical committees) {25}

There are no plans to amend the agreement. However, any changes to the protocol will be submitted by the principal investigator to be approved by the research grant committee of the Direct Grant and the ethical committee before implementation. In addition, trial participants will be notified.

Dissemination plans {31a}

The research findings will be published in peer-reviewed journals and disseminated to healthcare professionals, the public, and other relevant groups as soon as the results are available. The funder has no role or restriction in the decision of publication.

Discussion

SP is a progressive, systemic skeletal muscle disease associated with aging, characterized by a decrease in overall muscle mass, muscle strength, and/or physical performance. SP is closely related to activity disorders, falls, low BMD, and metabolic disorders, and is one of the important reasons and manifestations of the gradual decline of physiological function in the elderly [27, 28]. OP is the most common bone disease, which is a metabolic bone disease characterized by reduced bone mass and bone microstructure damage of bone tissue, increased bone fragility, and susceptibility to fracture [29]. The combination of the pathological characteristics of OP and OS makes OS's prevalence have a progressive increase with the onset of global aging [30]. The results of a two-way Mendelian randomization study [31] showed that there is a direct causal relationship between the BMD of femoral neck, lumbar spine, forearm, and ASM, with a stronger correlation between ASM and lumbar spine BMD. Clinical studies have shown [32] that SP is not only a loss of ASM but also muscle strength and function, and that grip strength is the most important test for SP and is significantly associated with OP. OS increases the risk of homeostatic imbalance in the musculoskeletal system [33]. To better prevent and treat OS, this study will enrich the clinical treatment of OS by using a multicenter, parallel-group clinical trial to verify the efficacy of pharmacological interventions combined with exercise therapy to improve OS.

Vit. D promotes intestinal absorption of calcium and phosphorus and plays an important regulatory role in calcium homeostasis and bone health. The results of a randomized controlled trial showed that active Vit. D significantly improved physical performance and lumbar spine BMD and reduced the risk of falls in subjects, compared to stable Vit. D [34]. Bischoff-Ferrari HA and partners concluded that Vit. D may improve musculoskeletal function by affecting factors directly related to ASM, in addition to enhancing BMD [35]. Vit. D indirectly affects muscle function and reduces the incidence of SP by regulating the proliferation and differentiation, the balance of calcium and phosphorus metabolism, and the energy metabolism of myocytes. Vit. D also plays an important regulatory role in cardiovascular diseases, diabetes, autoimmune diseases, and so on, providing a strong guarantee for the health of the elderly, especially for the prevention and treatment of OS in the elderly [36, 37].

In this study, Vit. D combined with WBVT was chosen to intervene in OS. Exercise is one of the effective means to modulate aging diseases, a large body of research evidence shows [38] that WBVT is effective in improving BMD and preventing further bone loss in patients with OP, thus limiting the risk of fracture. The acute effect of exercise induces the ability to mediate the interaction of muscle, bone, and endocrine systems to enhance ASM and bone strength by generating physical forces through exercise, external devices, and so on, which in turn stimulate the secretion of growth and biochemical factors [39].

The result of metabolic exercise is an increase in muscle mass and bone strength, which are both influenced by changes in external mechanical load and each other. Muscles release a variety of endocrine factors that promote bone formation and stimulate the increase of bone strength and bone density through muscle contraction [38]. The WBVT selected in this study can stimulate osteoprogenitor-osteoblast activity [40, 41] and increase the levels of various sex hormones and cytokines. It is often used clinically to act directly on nerve, muscle, and skeletal structures, helping to enhance muscle endurance, BMD, and improve balance function. The WBVT is mostly used in the rehabilitation of elderly populations, which is particularly effective in musculoskeletal degenerative diseases such as OS.

Modern medical research has revealed that the core pathological mechanism of OS is the synergistic degeneration of skeletal muscle and bone, and its musculoskeletal relationship is closely linked to several aspects such as biomechanical, endocrine, and signaling

pathways [42]. MSTN [43] is an actin secreted by skeletal muscle, and its elevated plasma levels increase skeletal muscle fibrosis and cause muscle atrophy. MSTN can lead to the decline of skeletal muscle mass by regulating the division cycle of myoblasts, the expression of myogenic regulators, and so on, finally inducing SP. MSTN can also affect bone metabolism by regulating the differentiation of osteoblast (OB), osteoclast (OC), and bone mesenchymal stem cells (BMSCs), and is an important factor in the regulation between muscle and bone [44, 45]. Peng et al [46] found that skeletal muscle mass decreased gradually with age, but serum MSTN expression level increased with age, which shows serum MSTN is negatively correlated with skeletal muscle mass. MSTN downregulates the Wnt pathway to inhibit OB differentiation and formation, regulates the Smad2 pathway to promote OC formation, inhibits bone metabolism, and reduces BMD [47, 48]. Torres-Costoso et al [49] concluded that skeletal muscle mass is an important influence factor on BMD. Therefore, MSTN can affect BMD by reducing skeletal muscle mass and thus can be used as a detection index for OS.

Counterbalancing MSTN is irisin, which can reduce the negative effects of MSTN on musculoskeletal metabolism, and the two intermodulate to balance skeletal muscle mass and osteogenesis levels [50, 51]. Irisin can improve bone metabolism by acting directly on bone cells or regulating bone gene expression [52]. Several studies have shown [53–55] that irisin can directly target OB, upregulate the expression levels of key OB transcription factors activating transcription factor 4 (ATF4) and runt-related transcription factor 2 (Runx2), and increase alkaline phosphatase (ALP) activity and calcium deposition, thus promoting OB differentiation. Irisin can inhibit OC formation by decreasing receptor activators for nuclear factor-κ B ligand (RANKL) expression. Irisin promotes the proliferation of BMSCs and OB differentiation through the Wnt/β-catenin signaling pathway [56], which is related positively to BMD [57]. Irisin positively acts on the musculoskeletal system and has the potential to be a sensitive indicator for screening effective drugs and treatments for OS [58].

The results of clinical studies have shown that serum biochemical indicators such as P1NP, S-CTX, and Vit. D are important indicators reflecting the condition of elderly patients with OP combined with SP [59]. And BTM levels are the best detectors of clinical response to the rate of bone resorption and formation, so in this study, serum levels of BTM series, irisin, MSTN, and Vit. D were measured to investigate their effects on musculoskeletal production by affecting the energy conversion of the body and to analyze their significant correlation with the development of OS.

SP and OP are two diseases closely related to aging, with similar risk factors such as mechanical, genetic, and endocrine, and often occur together, which are clinically referred to as OS. In this study, a multicenter, parallel-group clinical trial design was selected, and eligible subjects were randomly assigned to the WBVT group, Vit. D group, and WBVT + Vit. D group, refer to the "Chinese expert consensus on diagnosis and treatment for elderly with sarcopenia (2021)" and "Guidelines for the diagnosis and management of primary osteoporosis(2022)." From this research trial, we may conclude that (1) WBVT combined with Vit. D can promote the healthy development of the musculoskeletal system, and both combinations are significantly more effective and safer than monotherapy in the treatment of OS. (2) Muscle-derived factors irisin and MSTN are antagonistic factors that play opposite regulatory roles in the diagnosis and treatment of SP and OP and can be used as a diagnostic index of OS. (3) WBVT combined with Vit. D plays a role in improving OS by regulating irisin/MSTN. Currently, there is a lack of drugs or means to the common targets of SP and OP in clinical practice. This study can enrich OS's diagnosis and treatment targets, improve the diagnosis and treatment rate, and improve the elderly life quality. At the same time, it provides a scientific basis for the clinical use of comprehensive therapies to prevent and treat OS and has an important role in promoting the progress of medical and health technology in China.

Trial status

Ethical approval of the primary review committee (Affiliated Hospital of Shaanxi University of Traditional Chinese Medicine) was received on May 10, 2023 (SZFYIEC-PJ-No. 41 of 2023). The PRIME trial was published in the Chinese Clinical Trial Registry on 03/26/2024 (ChiCTR2400082269). Approval was obtained for protocol version 3.1, dated 03/10/2024. The first participant was included on April 1, 2024. The anticipated recruitment completion date is expected on April 30, 2025.

Abbreviations

AEs	Adverse events
ALP	Alkaline phosphatase
ASM	Appendicular skeletal muscle mass
ATF4	Activating transcription factor 4
BMD	Bone mineral density
BMSCs	Bone mesenchymal stem cells
BTM	Bone turnover markers
CRC	Clinical study coordinator
DMC	Data monitoring committee
DXA	Dual-energy x-ray absorptiometry
IOF	International Osteoporosis Foundation
ITT	Intention-to-treat
MSTN	Myostatin
OB	Osteoblast
OC	Osteoclast

OP	Osteoporosis
OS	Osteo-sarcopenia
P1NP	Procollagen type 1 n-peptide
PP	Per-protocol
RANKL	Receptor activator for nuclear factor-κ B ligand
Runx2	Runt-related transcription factor 2
SARC-CalF	Muscle strength (S), assistance in walking (A), rise from a chair (R), climb stairs (C), number of falls (F), and calf circumference
S-CTX	C-terminal telopeptide of type 1 collagen
SP	Sarcopenia
SPPB	Short physical performance battery
Vit. D	Vitamin D
WBVT	Whole-body vibration training

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Not applicable.

Authors' contributions {31b}
FY, KZ, and WL contributed to the design of the study. WL, LT, and JL contributed to writing the manuscript, and FC and MC contributed to complete the inclusion and follow-up of patients in the clinical trial protocol. YL, YZ, and LY contributed to the management and analysis of clinical trial data. All authors read and approved the final manuscript.

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Availability of data and materials {29}
The data generated in this study are available from the corresponding author upon request.

Declarations

Ethics approval and consent to participate {24}
This study was reviewed and approved by the Affiliated Hospital of Shaanxi University of Traditional Chinese Medicine Clinical Research Ethics Committee (Reference number: SZFYIEC-PJ-Number [40] of 2023). Written informed consent will be obtained from all individual participants included in the study.

Consent for publication {32}
Not applicable - no identifying images or other personal or clinical details of participants are presented here or will be presented in reports of the trial results. The participant information materials and informed consent form are available from the corresponding author on request.

Competing interests {28}
The authors declare that there is no competing interest regarding the publication of this paper.

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