CLINICAL TRIAL

JBMR®

Effects of High-Intensity Resistance Training on Osteopenia and Sarcopenia Parameters in Older Men with Osteosarcopenia—One-Year Results of the Randomized Controlled Franconian Osteopenia and Sarcopenia Trial (FrOST)

Wolfgang Kemmler,[1] Matthias Kohl,[2] Michael Fröhlich,[3] Franz Jakob,[4] Klaus Engelke,[1,5] Simon von Stengel,[1] and Daniel Schoene[1]

[1]Institute of Medical Physics, Friedrich-Alexander University of Erlangen-Nürnberg, Erlangen, Germany
[2]Faculty Medical and Life Sciences, University of Furtwangen, Villingen-Schwenningen, Germany
[3]Department of Sports Science, University of Kaiserslautern, Kaiserslautern, Germany
[4]Bernhard-Heine-Center for Locomotion Research, Würzburg, Germany
[5]Department of Medicine III, Friedrich-Alexander University of Erlangen-Nürnberg, University Hospital Erlangen, Erlangen, Germany

ABSTRACT

Dynamic resistance exercise (DRT) might be the most promising agent for fighting sarcopenia in older people. However, the positive effect of DRT on osteopenia/osteoporosis in men has still to be confirmed. To evaluate the effect of low-volume/high-intensity (HIT)-DRT on bone mineral density (BMD) and skeletal muscle mass index (SMI) in men with osteosarcopenia, we initiated the Franconian Osteopenia and Sarcopenia Trial (FrOST). Forty-three sedentary community-dwelling older men (aged 73 to 91 years) with osteopenia/osteoporosis and SMI-based sarcopenia were randomly assigned to a HIT-RT exercise group (EG; $n = 21$) or a control group (CG; $n = 22$). HIT-RT provided a progressive, periodized single-set DRT on machines with high intensity, effort, and velocity twice a week, while CG maintained their lifestyle. Both groups were adequately supplemented with whey protein, vitamin D, and calcium. Primary study endpoint was integral lumbar spine (LS) BMD as determined by quantitative computed tomography. Core secondary study endpoint was SMI as determined by dual-energy X-ray absorptiometry. Additional study endpoints were BMD at the total hip and maximum isokinetic hip−/leg-extensor strength (leg press). After 12 months of exercise, LS-BMD was maintained in the EG and decreased significantly in the CG, resulting in significant between-group differences ($p < 0.001$; standardized mean difference [SMD] = 0.90). In parallel, SMI increased significantly in the EG and decreased significantly in the CG ($p < 0.001$; SMD = 1.95). Total hip BMD changes did not differ significantly between the groups ($p = 0.064$; SMD = 0.65), whereas changes in maximum hip−/leg-extensor strength were much more prominent ($p < 0.001$; SMD = 1.92) in the EG. Considering dropout ($n = 2$), attendance rate (95%), and unintended side effects/injuries ($n = 0$), we believe our HIT-RT protocol to be feasible, attractive, and safe. In summary, we conclude that our combined low-threshold HIT-RT/protein/vitamin D/calcium intervention was feasible, safe, and effective for tackling sarcopenia and osteopenia/osteoporosis in older men with osteosarcopenia. © 2020 The Authors. *Journal of Bone and Mineral Research* published by American Society for Bone and Mineral Research.

KEY WORDS: EXERCISE; OSTEOPOROSIS; SARCOPENIA; AGING; BONE QCT

Introduction

Physiologically, muscles and bones are regarded as "neighbors with close relationships"[1] or even "Siamese twins."[2] In fact, the development and maintenance of bone and muscle are largely parallel.[2] The term "sarco-osteopenia," or more commonly "osteosarcopenia,"[3] designates the simultaneous presence of sarcopenia and osteopenia.[4]

The most effective sarcopenia therapy might be (dynamic) resistance exercise (DRT).[5] In parallel, there is considerable evidence

Received in original form January 9, 2020; revised form March 19, 2020; accepted March 31, 2020. Accepted manuscript online April 9, 2020.
Address correspondence to: Wolfgang Kemmler, PhD, Institute of Medical Physics, Friedrich-Alexander University (FAU) of Erlangen-Nürnberg, Henkestrasse 91, 91052 Erlangen, Germany. E-mail: wolfgang.kemmler@imp.uni-erlangen.de
The peer review history for this article is available at https://publons.com/publon/10.1002/jbmr.4027.

Journal of Bone and Mineral Research, Vol. 35, No. 9, September 2020, pp 1634–1644.
DOI: 10.1002/jbmr.4027

for a positive effect of dedicated exercise on bone mineral density (BMD)[6] and fragility fractures,[7,8] albeit only for postmenopausal women. In contrast, few exercise studies have focused on male cohorts, with about half of them applying DRT protocols (reviewed in Kemmler and colleagues[9]). Summing up their osteogenic findings,[9] the evidence for a relevant effect on BMD was low to negligible, particularly for isolated DRT protocols. However, reviewing these exercise trials, frequent limitations of the study and/or DRT protocols (eg, short study duration, low exercise intensity, low training frequency/low attendance rate, no progression/variation/periodization of the DRT, no supervision, and inadequate BMD assessments) might have diluted the true effect of DRT-type exercise on bone. Apart from the lack of studies in men and the application of state-of-the-art DRT protocols, another rationale for the present study was that no previous study has focused on the vulnerable cohort of people with osteosarcopenia.

Thus, the aim of this study was to validate the effect of a state-of-the-art DRT on recognized parameters of sarcopenia and osteoporosis in older men with osteosarcopenia.

Our primary hypothesis was that, based on adequate supplementation of protein, calcium, and vitamin D, isolated resistance exercise training has a significantly positive effect on BMD at the lumbar spine (LS) as determined by quantitative computed tomography (QCT) in older, community-dwelling (cdw) men with osteosarcopenia compared with a non-exercising control group.

Our core secondary hypothesis was that isolated DRT has a significantly positive effect on skeletal muscle mass index (SMI) as determined by dual-energy X-ray absorptiometry (DXA) in older, cdw men with osteosarcopenia compared with a non-training control group.

Other secondary hypotheses were that isolated DRT has a significantly positive effect on (i) BMD at the total hip region of interest (ROI) as determined by DXA and (ii) maximum dynamic hip- and leg-extensor strength as determined by an isokinetic leg press in older, cdw men with osteosarcopenia compared with a control group.

Materials and Methods

FrOST study

The FrOST (Franconian Osteopenia and Sarcopenia Trial) is an ongoing 18-month clinical exercise study with a randomized and balanced parallel group design. The project focuses on the effect of DRT on parameters characterizing osteopenia and sarcopenia in cdw men aged 72 years and older with osteosarcopenia. The Institute of Medical Physics (IMP), University of Erlangen-Nürnberg (FAU), Germany, initiated the project that was approved by the FAU ethics committee (number 67_15b and 4464b) and the federal bureau of radiation protection (BfS, number Z 5–2246212 - 2017-002). The project fully complies with the Helsinki Declaration.[10] All study participants gave their written informed consent after receiving detailed information. Project registration was conducted under ClinicalTrials.gov: NCT03453463. The present publication reports the main study outcomes on training-induced changes of recognized osteopenia and sarcopenia parameters during the first year (54 weeks) of the intervention (June 2018 to July 2019).

Participants

The recruitment procedure has been described in detail elsewhere.[11] In brief, individuals of the lowest SMI quartile (n = 242) from the Franconian Sarcopenic Obesity (FranSO) study (n = 965)[12,13] who participated in the 24-month follow-up (FU) were contacted. A total of 180 men willing to participate responded and were checked for eligibility for FrOST. Inclusion criteria were (i) community-dwelling men, aged 72 years and older; (ii) SMI, as determined by DXA, ≤7.26 kg/m^2 (< −2 SD T-score, ie, morphometric sarcopenia[14,15]; and (iii) BMD at the LS or total hip (tHip) ROI < −1 SD T-score, ie, osteopenia or osteoporosis).[16] The exclusion criteria were (i) secondary osteoporosis, (ii) a history of hip fracture; (iii) (osteo)anabolic and antiresorptive pharmaceutical therapy; (iv) glucocorticoid therapy >7.5 mg/d during the previous 2 years; (v) diseases and health problems (inclusive cognitive impairment) that prevent dynamic resistance exercise on machines; (vi) participation in regular resistance exercise (>60 min/week) during the last 5 years; (vii) alcohol consumption of more than 60 g/d ethanol; (viii) problems with attending the gym; and (ix) absence of >2 weeks during the intervention period. Finally, 50 participants were eligible, albeit only 43 men agreed to be randomly allocated to the exercise group (EG; n = 21) or control group (CG; n = 22). Five of the seven withdrawals stated unwillingness to exercise, and two men gave time constraints if allocated to the EG as the reason for withdrawing. Fig. 1 shows the participant flow through the study.

Randomization procedures

Stratified for SMI (three strata: <6.70 kg/m^2 versus 6.70–7.00 kg/m^2 versus >7.00 kg/m^2), participants were assigned randomly and balanced to the two study arms. To increase participant compliance with the randomization procedure, the men allocated themselves to the exercise or control group by drawing lots. Lots were placed in small opaque capsules ("kinder egg," Ferrero, Italy) and drawn from a bowl. A person not involved in the present project prepared the lots, thus neither researchers nor participants knew the allocation beforehand. After the randomization procedure, the primary investigator (WK) enrolled participants and instructed them in detail about their study status and corresponding do's and don'ts.

Blinding

Participants were blinded for the dose of protein supplementation (EG 1.5–1.6 versus CG 1.2–1.3 g/kg body-mass/d; we communicated that all participants were supplied with the same amount of protein based on the results of the nutritional analysis) but not for exercise status. However, outcome assessors and test assistants were kept unaware of the participant's group status (EG or CG) and were not allowed to ask, either.

Study procedure

We focused on the effects of exercise on BMD and lean body mass in men. However, we provided a supplementation of protein,[17] cholecalciferol, and calcium[18] (details given below) according to recent recommendations for all participants. Therefore, participants were requested to maintain their dietary habits during the study and they were all asked not to change their physical activity and exercise routines outside the present study intervention.

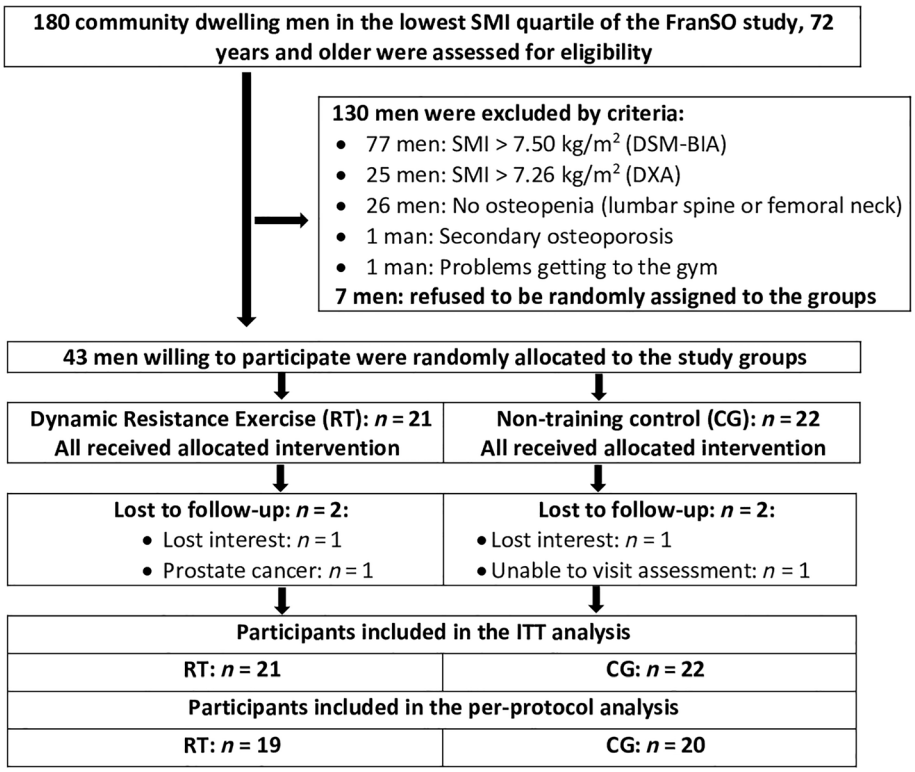

Fig. 1. Participant flow through the study.

Interventions

Resistance training

The exercise intervention focused exclusively on resistance exercise on machines. The consistently supervised sessions were provided in a well-equipped, centrally located gym (Kieser Training, Erlangen, Germany) on Monday, Wednesday, and Friday mornings. Participants were requested to exercise regularly two times/week; however, in intended or unintended cases of temporary inability (holidays, illness), participants were allowed to visit a third session in the week before and/or after. In summary, we applied a periodized high-intensity DRT protocol defined as single-set exercise training with high intensity and effort.[19] With few exceptions, all the major and minor muscle groups were addressed by the various exercises (see below). Detailed training logs prescribed exercises, number of sets, number of repetitions (reps), movement velocity, and absolute exercise intensity (or effort). Intensity of the exercise was consistently scheduled by prescribing a range of reps (ie, 5–7 or 8–10 reps) and the corresponding degree of work to failure ("effort") (eg, maximum effort minus 1–3 reps; defined as non-repetition maximum [nRM[20]]: Set endpoint when trainees complete a predetermined number of repetitions despite the fact that further repetitions could be completed).[21,22] We used the approach of Steele and colleagues,[20] which classified set endpoints in nRM, (self-determined) repetition maximum (RM), or (not applied during year 1) complete momentary muscular failure.

We structured the intervention into periods of 8 to 12 weeks with different aims and training protocols. To increase participant compliance, the aims and procedure of the following training period were explained and discussed in joint briefing meetings.

Phase 1. Four weeks of familiarization and learning of proper lifting technique were followed by 8 weeks of conditioning with a focus on education and experience to select the adequate load to the prescribed varying repetitions. We introduced 14 exercises (leg press, extension, curls, adduction, abduction, latissimus front pulleys, rowing, back extension, inverse fly, bench press, military press, lateral raises, butterfly with extended arms, crunches) conducted on resistance devices (MedX, Ocala, FL, USA); however, only 12 exercises were applied during any one session. One (8 exercises) to two (4 exercises) sets of 8–15 reps, using nearly the full range of motion were prescribed. Total time under tension/rep averaged 5 seconds, structured in a 2-second concentric, 1-second isometric and 2-second eccentric (2-second–1-second–2-second) phase. In phase 1, we scheduled incomplete work to failure.[20] Ninety- to 120-second breaks/rest pauses were specified between the sets or exercises.

Phase 2. We introduced the single-set approach (ie, one set per exercise) structured into two (intensity-based) linearly periodized 4-week phases, with each fourth week as a recovery week with low exercise intensity and effort. Four new exercises were added (calf raises, hip extension, pull-overs, lateral crunches). Per session, 14 of 18 exercises with 90 seconds of rest between the exercises were prescribed. Participants were requested to choose a load that ensured a repetition maximum −1 rep (5–10 reps) or −2 reps (10–18 reps) (repetition in reserve [RIR] approach suggested by Zourdos and colleagues[23]). We did not prescribe a target repetition number (ie, 10 reps) but a repetition range (ie, 5–7 or 8–10 reps). Movement velocity varied

between the sessions from very slow (4 seconds–1 second–4 seconds per rep) to fast (1 second–1 second–2 seconds per rep).

Phase 3. Starting with phase 3, about one-third of the sets were conducted with an explosive movement in the concentric phase (not for back extension). Additionally, we introduced the repetition maximum approach[20] (set endpoint when trainees properly complete the final repetition possible but if the next repetition were attempted, they would definitely achieve momentary failure;[20] however, according to the definition, sets conducted with high velocity were terminated when explosive velocity was no longer possible). However, this approach was used only for sets ≤10 reps. Breaks between the sets averaged 90 seconds (after nRM) to 120 seconds (after RM).

Phase 4. We additionally introduced the superset approach, a characteristic of HIT-RT. Supersets addressed the same or related muscle groups (eg, knee extension and leg press) or agonist and antagonist (eg, leg press and leg curls). Two or three exercises were included in a superset sequence (altogether 10 exercises). Rest pauses averaged 30 to 45 seconds within a superset block and 2 minutes after a superset.

Phase 5. In phase 5, we further introduced drop sets; ie, after work to RM (≤10 reps) or RM–1 rep, load was immediately decreased by 10% to 20% to complete more reps also conducted up to RM or RM–1 rep. Load was decreased only once. Drop sets referred to seven exercises included in the supersets. Rest pauses averaged 1 minute within and 2 minutes between the supersets.

Protein supplementation

All participants were provided with whey protein powder (Active PRO80, inkospor, Roth, Germany). The chemical score of this product is 159, and 100 g/d represented a caloric value of 1526 kJ (360 kcal) and contained 80 g of whey protein with a high L-Leucine (9 g) and essential amino acid (57 g) component. Further, the supplement contains 2.8% of fat and 6.4% of carbohydrates. Participants were asked to take the protein powder with low-fat milk. Doses of more than 40 g had to be split; however, we did not focus on an intake at a specific time of the day. All participants were instructed in detail how to apply the protein supplementation; participants were also regularly interviewed about and encouraged to maintain their protein intake habits during the WB-EMS sessions. The EG was supplied with up to 1.5–1.6 g/kg body-mass/d, while the CG received 1.2–1.3 g/kg body-mass/d.[17] Dietary protein intake was calculated based on 4-day dietary protocols (see below) conducted by the participants at baseline and after 28 and 54 weeks.

Vitamin D and calcium supplementation

Based on 25 OH vitamin-D 3 (25-OH D3) levels sampled at baseline (see below), participants of the EG or CG with serum concentrations below 75 nmol/L (n = 37) were asked to ingest four cholecalciferol units (MYVITAMINS, Manchester, UK) of 2500 IE/d a week (ie, 10,000 IE/wk). Participants 76–≤ 100 nmol/L were requested to take two capsules of 2500 IE/d a week (ie, 5000 IE/wk).

As per German guidelines,[18] we aimed to ensure a calcium intake of 1000 mg/d in all the participants. The amount of dairy dietary calcium was evaluated based on dietary calcium questionnaires (Rheumaliga, Switzerland). Considering the amount of calcium provided by the protein powder, the required additional daily calcium was provided by calcium capsules (Sankt Bernhard, Bad Dietzenbach, Germany).

Compliance with the intervention

The gym's chip card system allowed accurate assessment of participant attendance rate and exercise duration. Nevertheless, the participants' training logs were checked for attendance after each of the 8- to 12-week meso-cycles. Additionally, the certified instructors who consistently supervised the exercise sessions noted participant attendance. In parallel, instructors determined participant compliance with the prescribed exercise protocol by monitoring the load/repetition proportion listed by the participants.

Adherence to the prescribed supplementation of protein, vitamin D, and calcium was monitored by (i) checking the corresponding distribution logs; (ii) biweekly phone calls of the nutritionist; and (iii) personal interviews at 28-, 36-, and 52-week follow-up assessments.

Study outcomes

Primary study outcome:

- Integral BMD at the lumbar spine as determined by QCT at baseline and after 54 weeks.

Secondary study outcomes:

- SMI as determined by DXA at baseline and after 54 weeks.
- BMD at the total hip ROI as determined by DXA at baseline and after 54 weeks.
- Maximum dynamic hip- and leg-extensor strength as determined by an isokinetic leg press at baseline and after 54 weeks.

Changes of trial outcomes after trial commencement

No changes of trial outcomes were made after trial commencement.

Assessments

The 54-week assessments were conducted during a regeneration week. Participants were asked to maintain their physical activities and diet but not to exercise 48 hours before the tests. We placed great emphasis on the standardization of the assessments. All the tests/measures were consistently conducted and analyzed by the same research assistant at about the same time of the day (±2 hours), with the same calibrated devices and in identical order at the same location.

Body height was assessed by a Holtain stadiometer (Crymych Dyfed, UK); direct-segmental, multi-frequency Bio-Impedance-Analysis (DSM-BIA; InBody 770, Seoul, Korea) was used to determine body mass and body composition (in parallel to DXA, we also measured body composition by BIA; however, data reported here refer to the DXA assessment.) BMD at the lumbar spine, proximal femur ROIs, and total body as well as body composition was evaluated by DXA (QDR 4500a, Discovery upgrade, Hologic Inc., Bedford, MA, USA). Based on the total body scan (excluding the skull), subtotal lean body mass (LBM) was assessed using the "compare mode" at follow-up, so that area and placement of the baseline assessment could be reproduced exactly. Using the LBM results of the upper and lower limbs according to the standard analysis of the DXA device, we calculated the appendicular

skeletal muscle mass (ASMM). According to Baumgartner,[14] SMI was defined as ASMM/body height (kg/m^2). We applied weekly spine phantom measurements using the specifications provided by the manufacturer. Long-term coefficient of variation for BMD at the LS from study start to 12-month assessment was 0.5% as determined by the weekly spine phantom measurements.

CT scans of the lumbar spine were obtained on a Somatom Force scanner (Siemens, Erlangen, Germany). Participants were scanned on top of a Siemens Osteo phantom, which was used for simultaneous BMD calibration. Scans covered mid T_{12} to mid L_3 and were acquired with 120 kV, 100 mA as reference current-time product, CAREDose 3D, pitch 1 and with a collimation of 38.4 mm. Filtered back-projection was used for reconstruction. Slice thickness and reconstruction increment were set to 1 mm, each with a BR40s kernel and a field of view of 20 cm, which fully included the vertebral body and the BDC phantom. Table height was constant for all CT scans. Scans were analyzed with MIAF-Spine version 5.0.0R (MIAF: Medical Image Analysis Framework, University of Erlangen-Nürnberg, Germany). For the purpose of this study, integral BMD averaged over L_1 and L_2 vertebrae was obtained. The same CT scanner was used for all subject scans of this study. The same acquisition and reconstruction protocol was used for all scans. Hounsfield units of the CT scanner were regularly calibrated according to the manufacturer recommendations. The stability of the calibration of the HU values to BMD was monitored using the in-scan calibration phantoms. Specifically the parameters of the resulting calibration equation obtained for each scan were controlled for drifts and breakpoints, but no corrections had to be applied.[24]

Maximum isokinetic leg−/hip-extensor strength was tested using an isokinetic leg press (CON-TREX LP, Physiomed, Laipersdorf, Germany) at baseline and after 28 weeks, 36 weeks, and 1 year. Maximum bilateral hip/leg extension strength was conducted in a sitting, slightly supine (15°) position, fixed by hip and chest straps. The ankle was positioned on a flexible sliding footplate. The range of motion during leg extension was 30° to 90° within the knee angle, using the standard velocity of 0.5 m/s. After briefing and familiarization with the testing procedure, participants were requested to perform five repetitions with maximum voluntary effort (specification: "push as strongly as possible"). Two trials intermitted by 2 minutes of rest were conducted; the higher value for maximum hip/leg extension strength was included in the data analysis.

To quantify the relative intensity (% 1RM) of our approach of prescribing a range of reps and the corresponding "effort,"[20] we frequently conducted 1RM-maximum tests for leg and bench press according to the approach of Kraemer.[25]

Participants completed a standardized questionnaire[26] at baseline that asked for (i) demographic parameters; (ii) diseases, pharmacologic therapy/dietary supplements, and operations; (iii) physical limitations; (iv) falls and injurious falls; (v) injuries and low-trauma fractures within the last year; and (f) lifestyle, including physical activity and exercise.[27] After 28 weeks, 36 weeks, and 1 year, participants conducted a follow-up questionnaire that focused on changes during the study period that might affect our study endpoints. Apart from changes of exercise habits and physical activity that were monitored by a specific questionnaire,[27] high emphasis was placed on changes of medication and emerging or worsening of existing complaints/diseases. Therefore, participants were required to carefully list their medications, supplements, and diseases at home before visiting the test center. Finally, questionnaires were carefully checked for consistency, completeness, and accuracy in close interaction between the primary investigator and participants.

Four-day diet records were conducted by all the participants at baseline and after 54 weeks. Participants were provided with diet records (Freiburger Nutrition Record, nutri-science, Hausach, Germany) and were carefully instructed on how to keep the records. The Freiburger Nutrition Record is based on a tally list of how often specified food products were consumed. The same research assistant consistently analyzed the diet records. Participants had to record the protocol three weekdays and one weekend day typical for their nutritional habits. Results of the diet records were carefully checked and discussed with the participants. In cases of unrealistic results (eg, energy intake <1000 kcal/d or >3500 kcal/d), the participant was asked to complete another diet record based on more representative days.

Sample size

The sample size calculation for the FrOST project was based on integral BMD at the LS as determined by QCT. Assuming an effect (Δ-EG versus Δ-CG) on BMD-LS of 4.0 ± 3.5%[26] and applying a *t* test-based sample size calculation, 16 participants per group were required to detect a type-I error of alpha = 0.05 with 90% power (1-β). However, to adjust for dropouts and missing values relevant for the additional per protocol analysis, we opted to include more participants.

Statistical analysis

Intention to treat (ITT) analyses included all participants randomly assigned to the study arms (EG versus CG) regardless of their loss to follow-up or compliance. Multiple imputation (ITT) was calculated using R statistics software (R Development Core Team, Vienna, Austria) in combination with Amelia II.[28] The full data set was used for multiple imputations, with imputation being repeated 100 times. Imputation worked well in all cases as confirmed by over-imputation diagnostic plots ("observed versus imputed values") provided by Amelia II. Per protocol analyses that included all participants with complete data sets (baseline and 1 year) were also applied for primary and secondary outcomes. Normal distribution of the data was checked by statistical (Shapiro-Wilks) and graphical (qq-plots) tests. All the primary and secondary outcomes addressed here were analyzed by dependent *t* tests. To identify differences between EG and CG, *t* test comparisons with pooled SD were applied. All tests were 2-tailed, and significance was accepted at $p < 0.05$. We further calculated standardized mean difference (SMD) according to Cohen,[29] to indicate the size of the effect for primary and core secondary endpoint variables.

Results

Participant and exercise characteristics

Table 1 displays participants' baseline characteristics. With one exception, no significant differences were observed between the exercise and control group. Average dietary protein intake was very high in the CG, however, and differed significantly from the EG (Table 1).

Two participants of the EG and 2 participants of the CG were lost to 1-year FU (Fig. 1). Participants in the EG exercised on average 102.1 of 108 scheduled sessions per week (95 ± 4%). Fourteen EG men completed all the prescribed sessions. Average net time to complete the session was 47 ± 4 minutes. In general,

Table 1. Baseline Characteristics of the Participants of the Exercise Group (EG) and Control Group (CG)

Variable	EG (n = 21)	CG (n = 22)	*p* Value
Age (years)	77.8 ± 3.6	79.2 ± 4.7	0.262
Body mass index (kg/m^2)	25.0 ± 3.0	24.5 ± 1.9	0.515
Total Body Fat (DXA) [%]	34.5 ± 6.1	33.6 ± 4.0	0.563
Physical activity (index)[1]	4.45 ± 1.32	4.15 ± 1.53	0.490
Exercise per week (min)	59 ± 56	46 ± 52	0.780
Three or more diseases (*n*)[2]	10	12	0.826
Hip and knee arthritis (*n*)[2]	2	2	0.959
Low back pain (*n*)	3	4	0.527
Diabetes mellitus type II (*n*)	1	1	0.960
Handgrip-strength (kg)	30.7 ± 5.1	30.0 ± 4.3	0.675
Habitual gait velocity (m/s)	1.25 ± 0.17	1.26 ± 0.15	0.703
LLFDI (index)[3]	1.51 ± 0.74	1.44 ± 0.53	0.727
25 (OH)D (nmol/L)[4]	43.8 ± 17.5	54.0 ± 21.1	0.126
Energy intake (MJ/d)[5]	8.84 ± 1.71	9.39 ± 2.42	0.407
Protein intake (g/kg/d)[5]	1.10 ± 0.25	1.29 ± 0.34	0.043
Calcium intake (mg/d)[6]	802 ± 226	833 ± 282	0.636
Smokers (*n*)	3	4	0.959

[1] Scale from (1) "very low" to (7) "very high."[27]
[2] Using the ICD-10-based disease cluster of Schäfer et al.[30]
[3] Late Life Function Disability Instrument[31] scale from (1) "no problem" to (5) "impossible."
[4] Roche Diagnostics, Mannheim, Germany.
[5] As determined by a 4-day dietary record.
[6] As determined by a Calcium Questionnaire provided by Rheumaliga, Switzerland.

compliance with the exercise protocol was high. However, compliance with the set endpoint-based prescription of intensity was less positive. Although participants said in their training logs that they worked to repetition maximum, it was apparent that the individual proportion of load and repetitions did not always agree with the study defaults. Analyzing the completed training logs of the participants retrospectively, we estimate that one-fourth to one-third of the sets were conducted with inadequate low effort. However, of importance, we did not observe any unintended side effects during the exercise session or negative effects apart from delayed onset muscle soreness (DOMS) reported by the EG participants.

Compliance with the whey protein, calcium, and vitamin D supplementation according to the supply logs, biweekly phone calls, and personal interviews at 28-week, 36-week, and 1-year follow-up assessments was high (see also below). Based on our logs and the 54-week FU dietary analysis, total protein intake of the EG and CG averaged 1.59 ± 0.15 and 1.23 ± 0.12 g/kg BM/d, respectively.

Study endpoints

Primary study outcome

Table 2 displays the results of the LS-BMD assessments by QCT. LS-BMD decreased significantly in the CG (−2.5 ± 4.7%; $p = 0.029$) and increased non-significantly in the EG (1.6 ± 4.3%; $p = 0.090$). In summary, integral BMD as the primary study outcome demonstrated a significant effect ($p = 0.006$; SMD = 0.90) after 1 year of intervention. (Table 2). Data calculated by per protocol analyses confirmed the results of the ITT analyses.

Secondary study outcomes

SMI increased significantly in the EG (3.6 ± 3.0%; $p < 0.001$) and decreased significantly (−1.2 ± 1.9%; $p = 0.03$) in the CG (Table 3). Changes between groups were significant ($p < 0.001$) and of high effect size (SMD = 1.95). Again, per protocol analyses confirmed the findings of the ITT analyses.

Areal BMD at the total hip ROI decreased significantly in the CG (−1.2 ± 1.8%; $p = 0.004$) and was maintained in the EG (0 ± 1.9%; $p = 0.857$). Only borderline non-significant differences between changes of the EG and CG were observed ($p = 0.064$) by the ITT analysis (Table 4); however, the adjuvant per-protocol analysis indicated significant differences ($p = 0.039$) between the groups (SMD = 0.65).

Finally, maximum hip and leg extensor strength increased significantly ($p < 0.001$) by 27 ± 15% in the EG and was maintained (−1.4 ± 8.9%) in the CG ($p = 0.599$). The between-group difference was statistically significant ($p < 0.001$) and supported by

Table 2. Baseline Data and Changes of the Primary Study Endpoint Integral Bone Mineral Density as Assessed by QCT in the Exercise and Control Groups

	CG MV (95% CI)	EG MV (95% CI)	Difference MV (95% CI)	*p* Value
QCT: integral BMD lumbar spine (mg/cm^3)				
Baseline	166.7 (154 to 179)	176.3 (171 to 182)	9.6 (−2.6 to 21.9)	0.121
Changes	−4.1 (−0.7 to −7.3)	2.9 (−0.5 to 6.0)	7.0 (2.2 to 11.8)	0.006

QCT = quantitative computed tomography; CG = control group; MV = mean value; CI = confidence interval; EG = exercise group; BMD = bone mineral density.

Table 3. Baseline Data and Changes of SMI in the Exercise and Control Groups

	CG MV ± SD	EG MV ± SD	Difference MV (95% CI)	*p* value
Skeletal muscle mass index (SMI) (kg/m^2)				
Baseline	6.89 (6.74 to 7.02)	7.01 (6.85 to 7.16)	—	0.671
Changes	−0.08 (−0.01 to −0.15)	0.25 (0.18 to 0.33)	0.32 (0.22 to 0.43)	<0.001

CG = control group; MV = mean value; CI = confidence interval; EG = exercise group.

the high effect size (SMD = 1.92) (Table 5). Per protocol analysis fully confirmed the ITT data.

Confounding parameters

Apart from the supplementation, no relevant changes (all *p* values >0.701) of selected dietary intake parameters (eg, energy, macro-nutrition, calcium) were observed. 25OHD increased significantly (<0.001) in both groups; however the levels (EG 63 ± 14 versus CG 67 ± 19 nmol/L) still averaged below the lower range of corresponding recommendations (ie, 75 nmol/L[18]). Physical activity and exercise outside the exercise intervention as determined by dedicated questionnaires[27] were also maintained in both groups. However, two men of the EG and one man of the CG reported longer periods (3–5 weeks) of inactivity due to diseases (herpes zoster, respiratory tract infection) or hospitalization (prostate OP).

Discussion

The present randomized controlled trial (RCT) is the first study to address recognized parameters of osteoporosis (BMD) and sarcopenia (SMI) by exercise in the vulnerable cohort of older people with osteosarcopenia. Apart from this unique feature, the present exercise study offers other novel aspects: (i) The consequent application of a promising, time-effective HIT-RT exercise protocol, ie, a single-set DRT protocol applied with high strain magnitude, rate, and high effort normally applied to younger people only. (ii) No other study that focuses on bone included similarly old male participants. (iii) No other exercise study in men opted to apply QCT to determine LS volumetric BMD and thus derive results largely independent of spinal degeneration and aortic calcification that are frequently observed in older people.[32] (iv) Apart from the HIT-RT approach, the present study is one of the few exercise RCTs in older people that consequently consider exercise principles (eg, progression, individualization, variation, periodization), which originate from competitive sports.

Our results clearly indicate the favorable effect of a time-efficient, high-velocity/high-intensity/high-effort DRT on lumbar spine and (less pronounced) proximal femur BMD as well as lean body mass and muscle strength in this cohort of independent-living men 73 to 91 years old. This result could not necessarily be expected. As mentioned, the favorable effect of exercise on BMD is not clearly evidenced in male cohorts.[9] (Kulkuljan and colleagues were the one group[33] to report significant favorable effects of exercise [weight-bearing and DRT] on BMD, albeit for the femoral neck ROI only.) Correspondingly, in contrast to postmenopausal women,[34] the favorable impact of isolated DRT on BMD in older men is also vague. On the other hand, the positive effect of RT-type exercise on muscle strength[35–37] and, to a lower degree, on muscular morphology[37–40] in older men (and women) has been clearly demonstrated. However, reported hypertrophic effects in older people are usually not very pronounced.[41–43] Hence, our 0.32 kg/m^2 effect on SMI (corresponding to a 1.41 kg effect on LBM) (Table 3) fell within the very upper range of DRT studies conducted so far[44,45] be it with or without supplements (eg, protein, vitamin D, creatine).[37,39,46–49] Because of its dedication to BMD,[50] our intervention was without a doubt longer than most other protocols. Exercise volume (2× 45–50 min/wk) was much lower, however, compared with the three sessions of multiple-set exercise protocol predominately applied in the area of "muscle" or "bone" (see reviews[6,39,51]). Our rationale for this approach was that many older people are unwilling or unable to exercise frequently.[52] Thus, time efficiency realized by low exercise volume might be a key feature for the implementation of exercise protocols for preventing or treating osteosarcopenia. We further focused on a periodized, high-intensity/high-effort/high-velocity HIT-RT protocol. Translated to bone physiology, we applied a high-strain magnitude[53]/high-strain rate[54] strategy with low cycle number/area,[55] varying strain duration (eg, the explosive 4-second concentric part of the repetition) and frequency (0.1 to 0.5 Hz).[56] We further respect aspects of short- and long-term bone desensitization[57] through varying strain magnitude and rate as well as unloading periods. Apart from joint reaction forces, we applied axial loading of the LS and/or hip ROI by selected exercises (ie, semi-supine leg press, calf raises, military press). Additional, endogenous exercise-induced responses of (osteo)-anabolic agents (eg, hGH, IGF-1, testosterone), often reported for high-intensity RT protocols (see review[58]), were expected to additionally increase the sensitivity of bone cells to mechanical loading[59–61] and to muscle protein synthesis.[58] Taking up the latter aspect and summarizing promising strategies to affect muscle mass and strength, most key aspects should have been captured by our exercise protocol.[62,63] Applying frequent exercise intensity peaks of 85% 1RM (based on our 1RM tests, 4 reps to RM [2 seconds–1 second-2 seconds] as applied

Table 4. Baseline Data and Changes of BMD at the Total Hip as Determined by DXA in the Exercise and Control Groups

	CG MV (95% CI)	EG MV (95% CI)	Difference MV (95% CI)	*p* Value
DXA: areal BMD total hip (mg/cm^2)				
Baseline	0.869 (0.826 to 0.911)	0.894 (0.856 to 0.932)	—	0.364
Changes	−0.010 (−0.004 to −0.016)	−0.000 (−0.006 to 0.005)	0.010 (0.001 to −0.020)	0.064

BMD = bone mineral density; DXA = dual-energy X-ray absorptiometry; CG = control group; MV = mean value; CI = confidence interval; EG = exercise group.

Table 5. Baseline Data and Changes of Maximum Dynamic Strength of the Hip and Leg Extensors in the Exercise and Control Groups

	CG MV (95% CI)	EG MV (95% CI)	Difference MV (95% CI)	*p* Value
Maximum hip/leg extensor strength (leg press) (N)				
Baseline	1746 (1570 to 1924)	1620 (1391 to 1832)	–––––––	0.368
Changes	−26 (−126 to 73)	481 (377 to 586)	506 (359 to 656)	<0.001

CG = control group; MV = mean value; CI = confidence interval; EG = exercise group.

by the protocol corresponded to ≈85% 1RM; 18 reps [RM-2 reps] prescribed with longer time under tension [4-1-4] corresponded to ≈55% 1RM), partly with high velocity and a repetition-to-maximum approach with intensifying strategies,[19] muscular tension, muscle damage, and metabolic stress, ie, determinants considered to be primarily responsible for initiating the hypertrophic response to resistance exercise,[62] were addressed.

Because of the combined intervention, it is difficult to validate the contribution of protein, vitamin D, and calcium on our result on muscle and bone. In contrast to vitamin D and calcium, protein doses differ slightly between the EG and CG (1.2 versus 1.5 g/kg/d), although both groups remained within the recommended range.[17] A review of the beneficial effect of protein intake on LS-BMD failed to show a consensus. Although one meta-analysis did not report positive protein-induced effects,[64] another meta-analysis provided evidence for a significant superior effect (0.5%) of high versus low protein intake[65] on BMD at the LS. Further, although the relevance of adequate vitamin D, Ca, and protein/EAA intake for muscle and/or bone mass is obvious,[18,66,67] the combined effect of exercise and vitamin D or protein/essential amino acids (EAA) is less evident. Antoniak and colleagues[46] did not observe positive effects of vitamin D (400–2000 IU/d) on LBM but on leg strength after RT. In parallel, evidence for an additional effect of protein or EAA to exercise on muscle mass or function for older people[48,49,68,69] or people with sarcopenia[69–71] is reported to be still inconsistent and overall low at best. Thus, we speculate that HIT-RT might contribute most prominently to the present result on BMD and muscle parameters, whereas adequate vitamin D, calcium, and protein supplementation contributed a more "permissive" effect.[60] Nevertheless, in summary, we have to attribute the results on BMD and particularly SMI to the combined intervention of HIT-RT and dietary supplements.

Some features and limitations of this study should be addressed to allow the reader to adequately estimate our results. (i) We applied HIT-RT, an approach that might at first be considered inappropriate for men in their late 70s or even 80s. While high intensity (without RM) or high velocity per se, at least in a controlled movement on strength devices, is not critical for this cohort,[72,73] our high-effort strategy might be potentially related to an increased risk of injury, overstrain, or cardiometabolic complications. However, even during a 1RM test situation (ie, work to momentary failure), increased risk of injuries[74,75] or cardiovascular complications[76] were not reported for older people, at least when properly introduced and supervised. (ii) We based our exercise prescription on a range of reps (eg, 8–10) and a given set endpoint (eg, RM). In contrast, most other RT studies prescribed training load as a percentage of the one-repetition maximum (1RM). However, apart from the considerable amount of work to regularly determine 1 RM for each of the exercises applied and the negative consequences of testing errors or atypical test performance[77] for the subsequent load prescription, two further aspects support our approach. First, fixed loads for given reps do not account for variation in daily performance. Further, the number of reps that can be performed at the same percentage of 1RM varies substantially not only between subjects[78] but also between exercises.[79] Both 1RM and RIR-based strategies were considered to be similarly effective for increasing muscle size and strength,[77] whereas RIR approaches[23] were superior to traditional rating of perceived exertion (RPE) concepts,[80] eg, the Borg scale. (iii) Although we emphasized a clear and comprehensive communication of our loading strategy, we are aware that the participants did not always properly implement our RIR or RM specifications. Reviewing the training logs, we estimate that up to one-third of the sets were still conducted with inadequate low effort. (iv) Osteosarcopenia consists of two components; correspondingly, it might have been more adequate to address both bone and muscle as primary study endpoints. Because of the aspect that exercise-induced changes of SMI have been very pronounced in our earlier studies, in this study we decided to focus on integral LS-BMD and treat SMI as a core secondary endpoint. However, according to recent recommendations[81] we do not adjust for secondary endpoints; thus, one might criticize that we do not adequately account for the multiple test problem inherent when addressing osteosarcopenia. (v) The attendance rate of our physical intervention was very satisfying (95 ± 4%) and indicates the high attractiveness and feasibility of the exercise program. (vi) While current recommendations on 25OHD levels cannot be realized,[18] vitamin D supplementation resulted in a significant increase of 25OHD in both groups. Although not significant ($p = 0.210$), 25OHD increase was more pronounced in the HIT-RT, an aspect that might further contribute to the positive study result on BMD, SMI, and muscle force. (vii) Apart from effectiveness, feasibility, and attractiveness, safety should always be a key aspect of exercise programs in older people. So far, we have not observed any negative exercise effects in our cohort. We attribute this in particular to the constant supervision and interaction, coupled with the careful briefing, familiarization, and conditioning throughout the training process. (viii) It is difficult to decide whether our results can be generalized to the larger cohort of older people. However, considering that sarcopenia and sarcopenic obesity (dependent on the corresponding definition of obesity, 30% to 50% of our cohort feature sarcopenic obesity [SO]) include aspects of inflammation,[82] mitochondrial abnormalities,[83] and oxidative stress,[84] factors potentially decreasing muscle and/or bone response to exercise, it is plausible that changes of BMD and SMI might be even more prominent in healthy older people.

In conclusion, we report here for the first time to our knowledge, that HIT-DRT supported by vitamin D/calcium/protein supplementation applied in older men with osteosarcopenia generates favorable effects on bone, lean body mass, and muscle force compared with a control group, also supplemented with vitamin D, calcium, and whey protein. Of note, although this protocol applies high-velocity/intensity/effort DRT in a time-efficient

manner, it appears to be well accepted and safe. Thus, FrOST might serve as a blueprint for an exercise protocol applicable in older men with sarcopenia and osteoporosis.

Disclosures

None of the authors had any advisory board or financial interests that constitute a conflict of interest for this article.

Acknowledgments

The authors are very grateful for the support of Kieser Training (Erlangen, Germany), which provided the gym facilities and exercise supervision support. The authors further acknowledge the contribution of the Institute of Radiology, FAU, Germany. Authors' roles: WK, SvS, FJ, MF, KE, DS, and MK contributed to the study conception and design. WK, SvS, and KE collected the data. WK and MK analyzed the data. WK, SvS, FJ, MF, KE, MK, and DS interpreted the data. WK wrote the manuscript that was carefully revised by SvS, FJ, MF, KE, MK, and DS. All authors approved of the final version.

References

1. DiGirolamo DJ, Kiel DP, Esser KA. Bone and skeletal muscle: neighbors with close ties. J Bone Miner Res. 2013;28(7):1509–18.
2. Laurent MR, Dubois V, Claessens F, et al. Muscle-bone interactions: from experimental models to the clinic? A critical update. Mol Cell Endocrinol. 2016;432:14–36.
3. Binkley N, Buehring B. Beyond FRAX: it's time to consider "sarco-osteopenia". J Clin Densitom. 2009;12(4):413–6.
4. Kull M, Kallikorm R, Lember M. Impact of a new sarco-osteopenia definition on health-related quality of life in a population-based cohort in northern Europe. J Clin Densitom. 2012;15(1):32–8.
5. Dent E, Morley JE, Cruz-Jentoft AJ, et al. International clinical practice guidelines for sarcopenia (ICFSR): screening, diagnosis and management. J Nutr Health Aging. 2018;22(10):1148–61.
6. Howe TE, Shea B, Dawson LJ, et al. Exercise for preventing and treating osteoporosis in postmenopausal women. Cochrane Database Syst Rev. 2011;7:CD000333.
7. Kemmler W, Haberle L, von Stengel S. Effects of exercise on fracture reduction in older adults: a systematic review and meta-analysis. Osteoporos Int. 2013;24(7):1937–50.
8. Kemmler W, Bebenek M, Kohl M, Von Stengel S. Exercise and fractures in postmenopausal women. Final results of the controlled Erlangen fitness and osteoporosis prevention study (EFOPS). Osteoporos Int. 2015;26(10):2491–9.
9. Kemmler W, Shojaa M, Kohl M, von Stengel S. Exercise effects on bone mineral density in older men: a systematic review with special emphasis on study interventions. Osteoporos Int. 2018;29(7):1493–504.
10. World Medical Association. World Medical Association declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA. 2013;310(20):2191–4.
11. Lichtenberg T, von Stengel S, Sieber C, Kemmler W. The favorable effects of a high-intensity resistance training on sarcopenia in older community-dwelling men with osteosarcopenia: the randomized controlled FrOST study. Clin Interv Aging. 2019;14:2173–86.
12. Kemmler W, von Stengel S, Schoene D. Longitudinal changes in muscle mass and function in older men at increased risk for sarcopenia – The FrOST-study. J Frailty Aging. 2019;8(2):57–61.
13. Kemmler W, Teschler M, Weissenfels A, Sieber C, Freiberger E, von Stengel S. Prevalence of sarcopenia and sarcopenic obesity in older German men using recognized definitions: high accordance but low overlap. Osteoporos Int. 2017;28(6):1881–91.
14. Baumgartner RN, Koehler KM, Gallagher D, et al. Epidemiology of sarcopenia among the elderly in New Mexico. Am J Epidemiol. 1998;147(8):755–63.
15. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, et al. Sarcopenia: European consensus on definition and diagnosis: report of the European Working Group on Sarcopenia in Older People. Age Ageing. 2010;39(4):412–23.
16. WHO. Assessment of osteoporotic fracture risk and its application to screening for postmenopausal osteoporosis. Technical Report Series no. 843. Geneva: World Health Organization; 1994.
17. Bauer J, Biolo G, Cederholm T, et al. Evidence-based recommendations for optimal dietary protein intake in older people: a position paper from the PROT-AGE study group. J Am Med Dir Assoc. 2013;14(8):542–59.
18. DVO. Prophylaxe, Diagnostik und Therapie der OSTEOPOROSE bei postmenopausalen Frauen und bei Männern Leitlinie_der DVO e.V. Stuttgart: Schattauer; 2017.
19. Gießing J. HIT-Hochintensitätstraining. Arnsberg: Novagenics-Verlag; 2008.
20. Steele J, Fisher J, Giessing J, Gentil P. Clarity in reporting terminology and definitions of set end points in resistance training. Muscle Nerve. 2017;56(3):368–74.
21. Kemmler W, Wittke A, Bebenek M, Fröhlich M, von Stengel S. High intensity resistance training methods with and without protein supplementation to fight cardiometabolic risk in middle-aged males a randomized controlled trial. Biomed Res Int. 2016;2016:9705287.
22. Kemmler W, Teschler M, Weissenfels A, Fröhlich M, Kohl M, von Stengel S. Ganzkörper-Elektromyostimulationst versus HIT-Krafttraining - Effekte auf Körperzusammensetzung und Muskelkraft. Dtsch Z Sportmed. 2015;66(12):321–7.
23. Zourdos MC, Klemp A, Dolan C, et al. Novel resistance training-specific rating of perceived exertion scale measuring repetitions in reserve. J Strength Cond Res. 2016;30(1):267–75.
24. Engelke K, Mastmeyer A, Bousson V, Fuerst T, Laredo JD, Kalender WA. Reanalysis precision of 3D quantitative computed tomography (QCT) of the spine. Bone. 2009;44(4):566–72.
25. Kraemer WJ, Gordon SE, Fleck SJ, et al. Endogenous anabolic hormonal and growth factor responses to heavy resistance exercise in males and females. Int J Sports Med. 1991;12(2):228–35.
26. Kemmler W, Lauber D, Weineck J, Hensen J, Kalender W, Engelke K. Benefits of 2 years of intense exercise on bone density, physical fitness, and blood lipids in early postmenopausal osteopenic women: results of the Erlangen fitness osteoporosis prevention study (EFOPS). Arch Intern Med. 2004;164(10):1084–91.
27. Kemmler W, Weineck J, Kalender WA, Engelke K. The effect of habitual physical activity, non-athletic exercise, muscle strength, and VO2max on bone mineral density is rather low in early postmenopausal osteopenic women. J Musculoskelet Neuronal Interact. 2004;4(3):325–34.
28. Honaker J, King G, Blackwell M. Amelia II: a program for missing data. J Stat Soft. 2011;45(7):1–47.
29. Cohen J. Statistical power analysis for the behavioral sciences. 2nd ed. Hillsdale: NJ: Lawrence Earlbaum Associate; 1988 pp 8–16.
30. Schafer I, von Leitner EC, Schon G, et al. Multimorbidity patterns in the elderly: a new approach of disease clustering identifies complex interrelations between chronic conditions. PLoS One. 2010;5(12):e15941.
31. McAuley E, Konopack JF, Motl RW, Rosengren K, Morris KS. Measuring disability and function in older women: psychometric properties of the late-life function and disability instrument. J Gerontol A Biol Sci Med Sci. 2005;60(7):901–9.
32. Engelke K, Adams JE, Armbrecht G, et al. Clinical use of quantitative computed tomography and peripheral quantitative computed tomography in the management of osteoporosis in adults: the 2007 ISCD official positions. J Clin Densitom. 2008;11(1):123–62.
33. Kukuljan S, Nowson CA, Sanders KM, et al. Independent and combined effects of calcium-vitamin D3 and exercise on bone structure and strength in older men: an 18-month factorial design randomized controlled trial. J Clin Endocrinol Metab. 2011;96(4):955–63.

34. Zehnacker CH, Bemis-Dougherty A. Effect of weighted exercises on bone mineral density in post menopausal women. A systematic review. J Geriatr Phys Ther. 2007;30(2):79–88.
35. Peterson MD, Rhea MR, Sen A, Gordon PM. Resistance exercise for muscular strength in older adults: a meta-analysis. Ageing Res Rev. 2010;9(3):226–37.
36. Steib S, Schoene D, Pfeifer K. Dose-response relationship of resistance training in older adults: a meta-analysis. Med Sci Sports Exerc. 2010;42(5):902–14.
37. Vlietstra L, Hendrickx W, Waters DL. Exercise interventions in healthy older adults with sarcopenia: a systematic review and meta-analysis. Australas J Ageing. 2018;37(3):169–83.
38. Beckwee D, Delaere A, Aelbrecht S, et al. Exercise interventions for the prevention and treatment of sarcopenia. A systematic umbrella review. J Nutr Health Aging. 2019;23(6):494–502.
39. Borde R, Hortobagyi T, Granacher U. Dose-response relationships of resistance training in healthy old adults: a systematic review and meta-analysis. Sports Med. 2015;45(12):1693–720.
40. Stewart VH, Saunders DH, Greig CA. Responsiveness of muscle size and strength to physical training in very elderly people: a systematic review. Scand J Med Sci Sports. 2014;24(1):e1–10.
41. Distefano G, Goodpaster BH. Effects of exercise and aging on skeletal muscle. Cold Spring Harb Perspect Med. 2018;8(3):pii:a029785.
42. Kumar V, Selby A, Rankin D, et al. Age-related differences in the dose-response relationship of muscle protein synthesis to resistance exercise in young and old men. J Physiol. 2009;587(1):211–7.
43. Welle S, Totterman S, Thornton C. Effect of age on muscle hypertrophy induced by resistance training. J Gerontol A Biol Sci Med Sci. 1996;51(6):M270–5.
44. Stec MJ, Thalacker-Mercer A, Mayhew DL, et al. Randomized, four-arm, dose-response clinical trial to optimize resistance exercise training for older adults with age-related muscle atrophy. Exp Gerontol. 2017;99:98–109.
45. Cassilhas RC, Viana VA, Grassmann V, et al. The impact of resistance exercise on the cognitive function of the elderly. Med Sci Sports Exerc. 2007;39(8):1401–7.
46. Antoniak AE, Greig CA. The effect of combined resistance exercise training and vitamin D3 supplementation on musculoskeletal health and function in older adults: a systematic review and meta-analysis. BMJ Open. 2017;7(7):e014619.
47. Csapo R, Alegre LM. Effects of resistance training with moderate vs heavy loads on muscle mass and strength in the elderly: a meta-analysis. Scand J Med Sci Sports. 2016;26(9):995–1006.
48. Finger D, Goltz FR, Umpierre D, Meyer E, Rosa LH, Schneider CD. Effects of protein supplementation in older adults undergoing resistance training: a systematic review and meta-analysis. Sports Med. 2015;45(2):245–55.
49. Liao CD, Tsauo JY, Wu YT, et al. Effects of protein supplementation combined with resistance exercise on body composition and physical function in older adults: a systematic review and meta-analysis. Am J Clin Nutr. 2017;106(4):1078–91.
50. Eriksen EF. Cellular mechanisms of bone remodeling. Rev Endocr Metab Disord. 2010;11(4):219–27.
51. Peterson MD, Sen A, Gordon PM. Influence of resistance exercise on lean body mass in aging adults: a meta-analysis. Med Sci Sports Exerc. 2011;43(2):249–58.
52. Carlson SA, Fulton JE, Schoenborn CA, Loustalot F. Trend and prevalence estimates based on the 2008 physical activity guidelines for Americans. Am J Prev Med. 2010;39(4):305–13.
53. Rubin CT, Lanyon LE. Regulation of bone mass by mechanical strain magnitude. Calcif Tissue Int. 1985;37(4):411–7.
54. Turner CH, Owan I, Takano Y. Mechanotransduction in bone: role of strain rate. Am J Physiol Endocrinol Metab. 1995;269:E438–42.
55. Rubin CT, Lanyon LE. Regulation of bone formation by applied dynamic loads. J Bone Joint Surg Am. 1984;66(3):397–402.
56. Turner CH, Forwood MR, Otter MW. Mechanotransduction in bone: do bone cells act as sensors of fluid flow? FASEB J. 1994;8(11):875–8.
57. Turner CH, Robling AG. Exercise as an anabolic stimulus for bone. Curr Pharm Des. 2004;10(21):2629–41.
58. Schroeder ET, Villanueva M, West DD, Phillips SM. Are acute post-resistance exercise increases in testosterone, growth hormone, and IGF-1 necessary to stimulate skeletal muscle anabolism and hypertrophy? Med Sci Sports Exerc. 2013;45(11):2044–51.
59. Frost HM. The role of changes in mechanical usage set points in the pathogenesis of osteoporosis. J Bone Miner Res. 1992;7(3):253–61.
60. Frost HM. Bone's mechanostat. A 2003 update. Anat Rec. 2003;275A:1081–101.
61. Turner CH. Homeostatic control of bone structure: an application of feedback theory. Bone. 1991;12(3):203–17.
62. Schoenfeld BJ. The mechanisms of muscle hypertrophy and their application to resistance training. J Strength Cond Res. 2010;24(10):2857–72.
63. American College of Sports Medicine. American College of Sports Medicine position stand. Progression models in resistance training for healthy adults. Med Sci Sports Exerc. 2009;41(3):687–708.
64. Groenendijk I, den Boeft L, van Loon LJC, de Groot L. High versus low dietary protein intake and bone health in older adults: a systematic review and meta-analysis. Comput Struct Biotechnol J. 2019;17:1101–12.
65. Shams-White MM, Chung M, Du M, et al. Dietary protein and bone health: a systematic review and meta-analysis from the National Osteoporosis Foundation. Am J Clin Nutr. 2017;105(6):1528–43.
66. Bauer JM, Verlaan S, Bautmans I, et al. Effects of a vitamin D and leucine-enriched whey protein nutritional supplement on measures of sarcopenia in older adults, the PROVIDE study: a randomized, double-blind, placebo-controlled trial. J Am Med Dir Assoc. 2015;16(9):740–7.
67. Komar B, Schwingshackl L, Hoffmann G. Effects of leucine-rich protein supplements on anthropometric parameter and muscle strength in the elderly: a systematic review and meta-analysis. J Nutr Health Aging. 2015;19(4):437–46.
68. Cermak NM, Res PT, de Groot LC, Saris WH, van Loon LJ. Protein supplementation augments the adaptive response of skeletal muscle to resistance-type exercise training: a meta-analysis. Am J Clin Nutr. 2012;96(6):1454–64.
69. Gade J, Pedersen RBAM. Effect of protein or essential amino acid supplementation during prolonged exercise training in older adults on body composition, muscle strength, and physical performance parameters: a systematic review. Rehabil Proc Outcome. 2018;7:1–12.
70. Hita-Contreras F, Bueno-Notivol J, Martinez-Amat A, Cruz-Diaz D, Hernandez AV, Perez-Lopez FR. Effect of exercise alone or combined with dietary supplements on anthropometric and physical performance measures in community-dwelling elderly people with sarcopenic obesity: a meta-analysis of randomized controlled trials. Maturitas. 2018;116:24–35.
71. Hsu KJ, Liao CD, Tsai MW, Chen CN. Effects of exercise and nutritional intervention on body composition, metabolic health, and physical performance in adults with sarcopenic obesity: a meta-analysis. Nutrients. 2019;11(9):2163.
72. Liu CJ, Latham NK. Progressive resistance strength training for improving physical function in older adults. Cochrane Database Syst Rev. 2009;3:CD002759.
73. Mangione KK, Miller AH, Naughton IV. Cochrane review: improving physical function and performance with progressive resistance strength training in older adults. Phys Ther. 2010;90(12):1711–5.
74. Barnard KL, Adams KJ, Swank AM, Mann E, Denny DM. Injuries and muscle soreness during the one repetition maximum assessment in a cardiac rehabilitation population. J Cardiopulm Rehabil. 1999;19(1):52–8.
75. Kemmler W, Lauber D, Von Stengel S, Engelke K. Developing maximum strength in older adults—a series of studies. In Gießing J, Fröhlich M, Preuss P, eds. Current results of strength training research. Göttingen: Cuvillier Verlag; 2005 pp 114–33.
76. Fiatarone MA, Marks EC, Ryan ND, Meredith CN, Lipsitz LA, Evans WJ. High-intensity strength training in nonagenarians. Effects on skeletal muscle. JAMA. 1990;263(22):3029–34.
77. Helms ER, Byrnes RK, Cooke DM, et al. RPE vs. percentage 1RM loading in periodized programs matched for sets and repetitions. Front Physiol. 2018;9:247.
78. Abadie BR, Altorfer GL, Schuler PB. Does a regression equation to predict maximal strength in untrained lifters remain valid when the subjects are technique trained? J Strength Cond Res. 1999;13(3):259–63.

79. Fröhlich M, Schmidtbleicher D, Emrich E. Belastungssteuerung im Muskelaufbautraining. Belastungsnormativ Intensität versus Wiederholungszahl. Dt Ztschr Sportmed. 2002;53(3):79–83.

80. Helms ER, Cronin J, Storey A, Zourdos MC. Application of the repetitions in reserve-based rating of perceived exertion scale for resistance training. Strength Cond J. 2016;38(4):42–9.

81. Li G, Taljaard M, van den Heuvel ER, et al. An introduction to multiplicity issues in clinical trials: the what, why, when and how. Int J Epidemiol. 2017;46(2):746–55.

82. Kob R, Bollheimer LC, Bertsch T, et al. Sarcopenic obesity: molecular clues to a better understanding of its pathogenesis? Biogerontology. 2015;16(1):15–29.

83. Calvani R, Joseph AM, Adhihetty PJ, et al. Mitochondrial pathways in sarcopenia of aging and disuse muscle atrophy. Biol Chem. 2013;394 (3):393–414.

84. Sullivan-Gunn MJ, Lewandowski PA. Elevated hydrogen peroxide and decreased catalase and glutathione peroxidase protection are associated with aging sarcopenia. BMC Geriatr. 2013;13:104.