

The Favorable Effects of a High-Intensity Resistance Training on Sarcopenia in Older Community-Dwelling Men with Osteosarcopenia: The Randomized Controlled FrOST Study

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Purpose: Sarcopenia, the loss of muscle mass combined with the loss of muscle function, has become a public health issue. There is an urgent need for interventions. The study aimed to determine the effect of high-intensity resistance training (HI-RT), a time- and cost-efficient training modality, on sarcopenia in osteosarcopenic (OS) older men.

Methods: Forty-three community-dwelling men aged ≥ 72 years from Northern Bavaria, Germany, with OS were randomly assigned to either an active HI-RT group (HI-RT) or an inactive control group (CG). Both received dietary protein (up to 1.5 g/kg/day in HI-RT and 1.2 g/kg/day in CG) and Vitamin-D (up to 800 IE/d) supplements. The HI-RT was applied as a consistently supervised single-set training on resistance exercise machines using intensifying strategies, with two training sessions/week, structured into three phases (ranging from 8 to 12 weeks) totaling 28 weeks. The primary study endpoint was the Sarcopenia Z-score; secondary endpoints were changes in the underlying physiological parameters, skeletal muscle mass index (SMI), handgrip-strength and gait velocity.

Results: The results show a significant effect of the exercise intervention on the sarcopenia Z-score in the HI-RT ($p < 0.001$) and a significant worsening of it in the CG ($p = 0.012$) in the intention-to-treat analysis, as well as a significant intergroup change ($p < 0.001$). Analysis upon the underlying parameters showed a significant increase of skeletal muscle mass index (SMI) in the HI-RT group ($p < 0.001$) and a significant intergroup difference of SMI ($p < 0.001$) and handgrip strength ($p < 0.001$). There were no adverse effects related to dietary supplementation or training.

Conclusion: The results clearly confirm the favorable effects of HI-RT on sarcopenia. We conclude that HI-RT is a feasible, highly efficient and safe training modality for combating sarcopenia, also in the elderly.

Keywords: HI-RT, high-intensity resistance training, osteosarcopenia, sarcopenia, SMI, community-dwelling, older people

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Introduction

Sarcopenia – the degeneration of muscle mass combined with loss of muscle function due to aging¹ has become a public health matter.² The multiple adverse health outcomes associated with low muscle mass (fractures and falls,^{3–7} insulin resistance and the risk of prediabetes,^{8,9} cardiovascular diseases,¹⁰ cognitive impairment,¹¹ depression¹² and others¹³), the impact of sarcopenia on the individual's life (loss of independence,¹⁴

reduced quality of life,^{12,15,16} earlier necessary admission to nursing homes^{14,17}) and the resulting socioeconomic burden^{18–20} have made the necessity for interventions clear. Many studies have already proven the positive effects of resistance training (RT) combined with a protein-rich diet on sarcopenia.^{21–26} A standardized treatment approach that can be applied to a wide range of sarcopenic patients and includes a validated training protocol has yet to be defined. The training should be time-efficient, considering reasons for abstaining from recommended exercise doses have been time restriction and little enthusiasm^{27,28} and cost-efficient in the face of the high and growing prevalence of sarcopenia²⁹ and the resulting financial burden for stakeholders.^{18,19,30–32} A training modality meeting these criteria is high-intensity resistance training (HI-RT), a single-set resistance training at an intensity of load at 70–85% of the one-repetition maximum (1RM).³³ To have a maximum effect on muscle strength and mass and also parameters like bone density^{34,35} and hormonal levels,³⁶ relative intensity of 70% RM and up is needed, which falls in the range of HI-RT.

A protocol using a modern high-intensity method has not been applied to the often fragile³⁰ cohort of sarcopenic patients. It is time to challenge the presumptions of HI-RT being too demanding and risky for the elderly and make use of this efficient training modality for sarcopenic patients. This study is the first to assess HI-RT as a favorable therapy option for osteosarcopenic community-dwelling men, with this publication focusing on sarcopenia, while the aspect of osteopenia will be dealt with in another publication.

Our central hypothesis was that HI-RT combined with supplemental protein has a significant effect on Sarcopenia, ie, the Sarcopenia Z-score, compared to the control group (CG), which only received protein supplementation.

Our secondary hypothesis was that skeletal muscle mass index (SMI), as an underlying physiologic parameter of the Sarcopenia Z-score, significantly increases in the HI-RT group compared to the CG.

Methods

Trial Design

The Franconian Osteopenia and Sarcopenia Trial (FrOST) is an 18-month randomized controlled exercise study with a balanced parallel two-group design. The research focusses on a cohort of community-dwelling men 72 years and older with morphological sarcopenia and osteopenia. FrOST predominantly pursues two main aims. (1) To determine the effect of HI-RT on bone parameters related to osteoporosis;

(2) to evaluate the impact of HI-RT on muscular parameters related to Sarcopenia. The present publication reports changes in sarcopenia criteria from within the first 6 months of the intervention (June–December 2018). The Institute of Medical Physics (IMP), University of Erlangen-Nürnberg (FAU), Germany, planned, initiated and realized the project, which was approved by the University Ethics Committee of the FAU (Ethikantrag 67_15b and 4464b). The study complies with the Helsinki Declaration “Ethical Principles for Medical Research Involving Human Subjects.” After receiving detailed information, all study participants gave their written informed consent. The project was registered under ClinicalTrials.gov: NCT03453463.

Participants

Participant recruitment of the FrOST was a multi-stage process. We based FrOST on the Franconian Sarcopenic Obesity (FranSO) study,³⁷ an epidemiologic study with 965 community-dwelling men 70 years+, conducted in 2016. Precisely 24 months later, in January/February 2018, participants from the lowest quartile for SMI (n=242) were invited for a 2-year follow-up (2-year FU) assessment. Out of them, 177 men 72 + were willing to participate and remained after applying the following inclusion criteria: a) Community-dwelling status; b) no amputations of limbs or cardiac pacemaker implants during the last 2 years; c) no (new) implementation of glucocorticoid therapy >7.5 mg/d during the previous 2 years; d) no cognitive impairment that could confound the assessments³⁸ and e) no alcohol abuse of more than 60 g/d ethanol. These 177 remaining men then got reevaluated (2-year FU): only participants with an SMI <7.50 kg/m² (n=103) as determined by direct-segmental, multi-frequency Bio-Impedance-Analysis (DSM-BIA) were further invited for body composition and bone mineral density analysis using Dual-Energy X-ray Absorptiometry (DXA). Subjects were finally included in FrOST when

a) SMI, as assessed by DXA, was below 7.26 kg/m² (≤ -2 standard deviations (SD) T-Score, ie, sarcopenia^{1,39}),

b) bone mineral density at the region of interest (ROI), ie, either the lumbar spine or the proximal femur (total hip or femoral neck) was ≤ -1 SD T-Score (ie, osteopenia⁴⁰),

c) there was no secondary osteoporosis or history of hip fracture and subjects would be able to visit our lab or the gym. Finally, 43 men were eligible and willing to participate in the study. Correspondingly, these 43 subjects were randomly assigned either to a HI-RT (n=21) or an inactive CG (n=22). Figure 1 shows the participants' flow through the study.

Randomization Procedures

Stratified for SMI (3 strata), the 43 study participants were randomly and equally assigned to two study arms, a) HI-RT (n=21) or b) CG (n=22). By drawing lots, participants allocated themselves to the study group. Lots were placed in opaque plastic shells (“kinder egg,” Ferrero, Italy) and drawn from a bowl. Neither participants nor researchers knew the allocation

beforehand. Subsequently, the primary investigator Wolfgang Kemmler (WK) enrolled participants and instructed them in detail about their status, including corresponding dos and don’ts.

Blinding

We conducted a blinded approach that focused on outcome assessors and test assistants only. Outcome assessors were

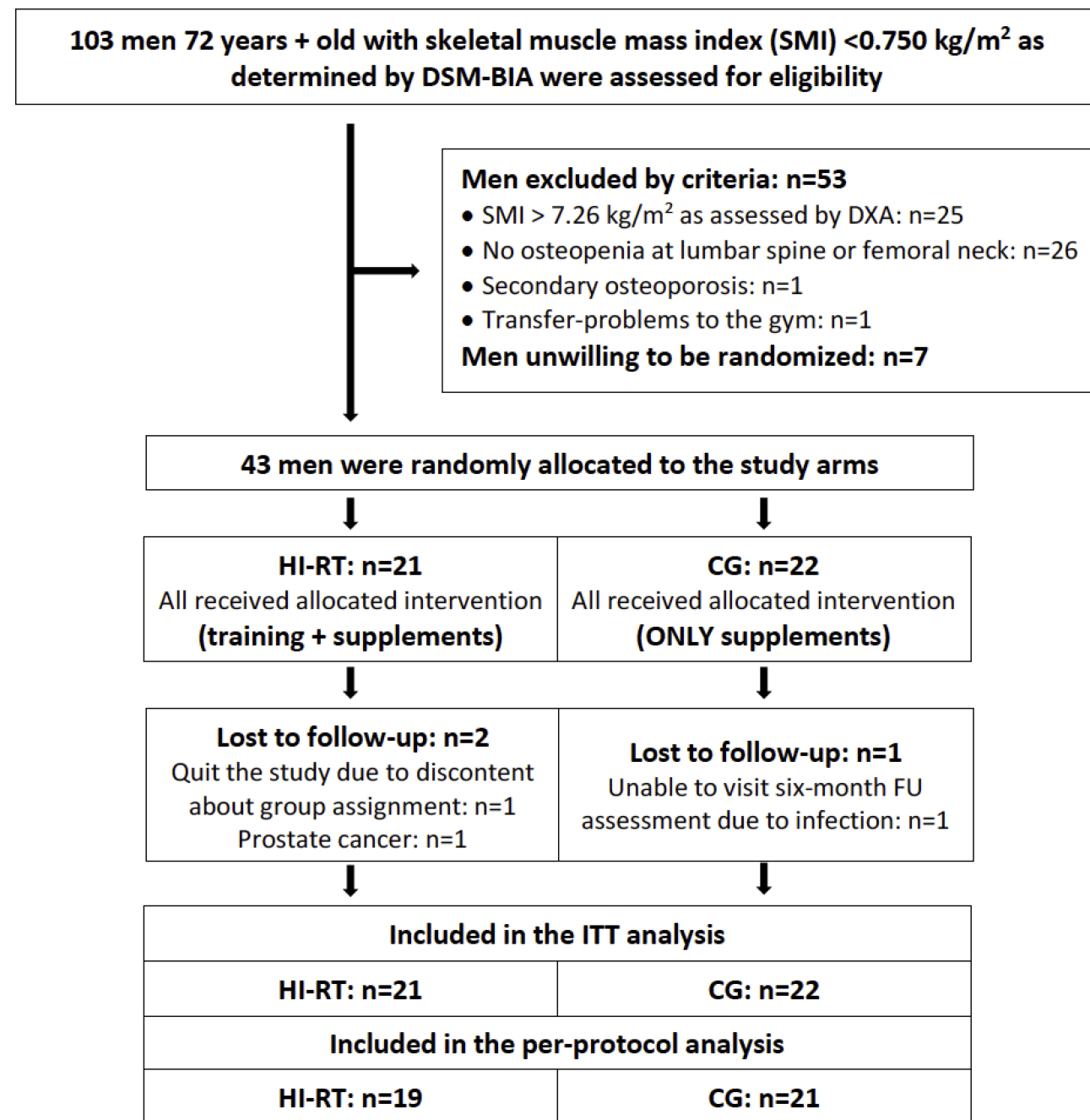


Figure 1 Participants' flow through the study.

Abbreviations: DSM-BIA, direct-segmental multi-frequency bioimpedance analysis; DXA, dual-energy X-ray absorptiometry; HI-RT, high-intensity resistance training; CG, control group; FU, follow-up; ITT, intention to treat.

unaware of the participant's group status (HI-RT or CG) and were not allowed to ask correspondingly.

Study Procedure and Intervention

Subjects have been intensively informed about dos and don'ts by the principal study investigator (WK). Maintaining and not changing physical activity and exercise outside the study intervention as well as maintaining dietary habits has been requested of them. Furthermore, all participants have been asked to restrain from intense physical activity and exercise 48 h pre-assessment.

Exercise Protocol

The consistently supervised resistance exercise training started in June 2018 and has been performed in a well-equipped gym (Kieser-Training, Erlangen, Germany), which is centrally located and can be easily reached via public transportation.

Participants of the HI-RT group have been provided with training logs, which prescribe exercises, number of sets (first phase only), number of repetitions (reps), movement velocity and the required exercise intensity (non-repetition maximum (nRM), repetition maximum (RM) or work to failure (MF))⁴¹ in the given training phase.

The following example is intended to help the reader better understand the concept of intensity in resistance training and how modification of repetition maximum and load regulate intensity.

An athlete who can lift 100 kg in the bench press in the correct form once has a 1RM of 100 kg for that specific exercise, thus lifting 75–80 kg would fall into the range of 75–80%RM, defined as the intensity of load.⁴² Work to failure refers to the intensity of effort and means respective athlete can lift x repetitions until muscle failure (MF), ie, the “set endpoint when trainees complete the final repetition possible whereby if the next repetition was attempted they would definitely achieve MF” as defined by Giessing et al.⁴³ In practice, the work to failure approach is usually achieved with a self-determined repetition maximum (sdRM), meaning the “set endpoint when the trainee determines they could not complete the next repetition if it were attempted (ie, they predict MF on the following repetition) as Steele et al⁴¹ have extended the four definitions by Giessing et al.⁴³

We did not prescribe a precise number of reps or a given load as deduced by 1RM assessments or 1RM calculated by xRM-tests (eg, Ref. 44). Instead, we prescribed the range of reps and the corresponding level of effort (nRM, RM) to regulate exercise intensity.

Consequently, the participants had to choose a weight for themselves with which they could perform an exercise x - y times (= prescribed range of reps) in order to reach the predefined intensity of effort (= prescribed level of effort)

During the first 28 weeks of the intervention, the resistance training (RT) was structured into three phases with 2 training sessions/week. (Either on Monday or/and Wednesday or/and Friday morning.) During phase 1, we started with 4 weeks of briefing and familiarization, and a further 8 weeks of conditioning. Strong emphasis was put on bringing the importance of the proper relationship between repetitions and corresponding load across to the patients under the premise of the prescribed repetition maximum.⁴¹ Per session, 12 out of 14 exercises (latissimus front pulleys, rowing, back extension, inverse fly, bench press, shoulder press, lateral raises, butterfly with extended arms, crunches, leg press, leg extension, leg curls, leg adduction and abduction) were conducted over the full range of motion on resistance-devices (MedX, Ocala, FL, USA). The protocol prescribed 1–2 sets of 8–15 reps, time under tension of 2s concentric, 1s isometric and 2s eccentric (2s-1s-2s) per rep and a non-repetition maximum (nRM: maximum effort minus 1–3 reps).⁴¹ Breaks between sets or exercises were consistently 90–120 s. Applying these criteria to the example earlier, the bodybuilder would first have to determine which weight he can lift on the bench press 15 times with correct form before MF and then deduct 1–3 reps, thus lifting this determined weight for 12–14 reps in order to reach the non-repetition maximum.⁴¹

During phase 2, the single-set approach, characteristic for HI-RT, was implemented. Up from this phase, we applied 8-week phases, each consisting of 2 linearly periodized four 4-week phases, with each fourth week as a recovery week with low exercise intensity. Fourteen to fifteen exercises out of a pool of 18 (additionally to the above-listed exercises, calf raises, hip extension, pullovers, lateral crunches) were applied. Apart from the 10 core exercises consistently used, weekly sessions slightly differed for the exercises prescribed. Apart from the recovery weeks with no prescription of nRM, the protocol prescribed 7–18 reps/set, selecting a load that ensured maximum effort (RM) –1 rep (up to 10 reps) to –2 reps (more than 10 reps). Of importance, we did not prescribe a target repetition (eg, 7 reps). Instead, we specified a repetition sector (7–10 reps) that should be realized by the participants keeping in mind the level of effort (nRM, RM). Breaks between the exercises were consistently 90 s. We generated periodization by decreasing the number of reps from 15–18 reps/set/session to 7–10 reps/set/session during the 3-week cycle of linear

periodization. We placed strong emphasis during phase 2 on movement velocity that varied between 4s-1s-4s to 1s-1s-2s per rep. However, we did still not focus on an explosive movement during the concentric phase during phase 2. Coming back to the exemplary bodybuilder, during phase 2, he would start with a weight in the bench press, which he would be able to perform 20 reps with and then deduct 2 reps from it to determine the nRM. Over 3 weeks, he would decrease the number of repetitions down to 7–10 reps still ensuring to reach the nRM by choosing correspondingly higher loads.

Using a comparable training schedule described for phase 2; however, with a slightly lower range of repetitions (12–15 decreasing to 6–8 reps), the repetition maximum approach⁴¹ characteristic for HI-RT was introduced during phase 3. We carefully increased the number of (core) exercises that should be executed almost to muscular failure (here: defined as 1RM⁴¹) from four during week 1 to eight in week 7 (week 8 was a recovery week). [Figure 2](#) visualizes the exercise protocol.

Protein Supplementation

Protein supplementation has been based on 4-day dietary protocols (see below). We have intended a total protein intake of 1.5 g/kg body mass/d in the HI-RT and a corresponding intake of 1.2 g/kg body mass/d²⁵ in the CG. Participants with a dietary protein intake <1.5 g/kg/d (HI-RT) or <1.2 g/kg/d (CG) have been provided with protein supplements. The protein powder used in FrOST (Active PRO80, inkospor, Roth, Germany) consists of whey protein with a chemical score of 156. One hundred grams contain 80 g of protein (10.4 g of Leucine), 5 g of carbohydrates and 1.8 g of fat resulting in

a calorific value of 362 kcal/100 g protein powder. Furthermore, 300 mg of calcium has been enclosed with a 25 g/portion of the protein powder. Participants have been requested to ingest the prescribed dose accurately on a daily base and to split doses higher than 30 g/d. We have suggested to mix the protein powder with low-fat milk when applicable (or possible) in order to increase the participants' dietary calcium intake. Compliance with prescribed protein powder intake has been queried regularly during the exercise sessions.

Vit-D/Calcium Supplementation

Based on blood concentrations of 25 OH Vitamin-D 3 (25-OH D3), participants with levels below 30 ng/mL (n=37) have been asked to supplement 10.000 IE/week (2x2500 IE/d, twice a week; MYVITAMINS, Manchester, UK). Participants between 30 and 40 ng/mL (n=4) have been requested to take 5.000 IE/week (2x2500 IE/d, once a week).

We have intended to realize a calcium intake of about 1000 mg/d in all participants.⁴⁵ Based on a dietary calcium questionnaire (Rheumaleague Suisse), we calculated the amount of daily dietary calcium intake. After also considering the calcium provided by the protein powder, we prescribed the additionally required daily calcium to be ingested by calcium capsules (Sankt Bernhard, Bad Dietzenbach, Germany). Each capsule contains 625 mg of calcium-carbonate with 250 mg of pure calcium.

Study Outcomes

Primary Outcome

Changes in Sarcopenia Z-score applying the European Working Group of Sarcopenia in Older People (EWGSOP I) approach¹ from baseline to six-month FU.

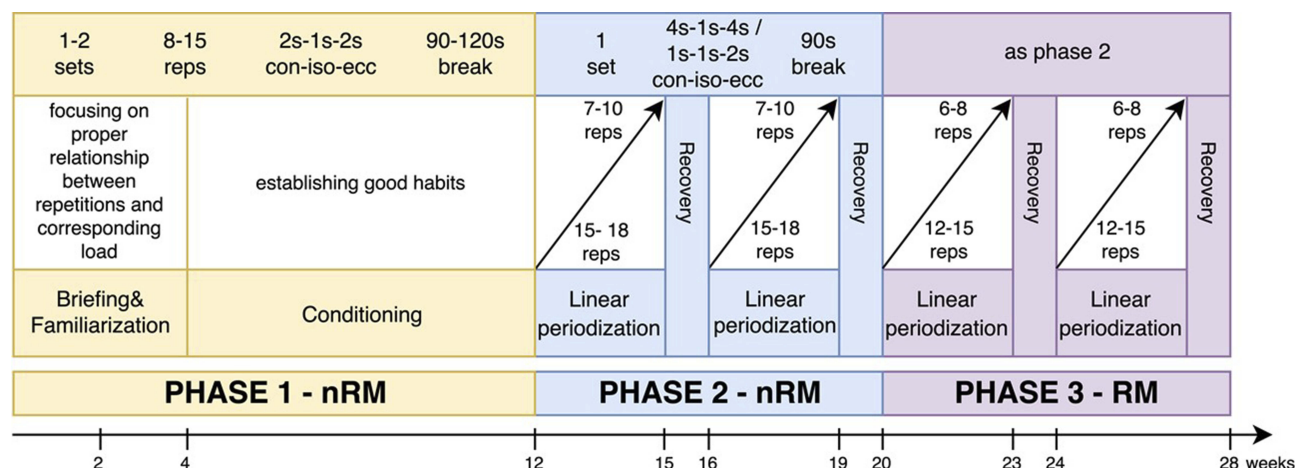


Figure 2 Exercise protocol.

Abbreviations: reps, repetitions; con, concentric; iso, isometric; ecc, eccentric; nRM, non-repetition maximum; RM, one-repetition maximum.

Secondary Outcomes

Changes in Sarcopenia criteria constituting the Sarcopenia Z-score from baseline to six-month FU, ie,

- Changes in SMI
- Changes in habitual gait velocity
- Changes in handgrip strength

Changes to Trial Outcomes After Trial Commencement

No changes to trial outcomes were conducted after trial commencement.

Assessments

Baseline and FU assessments were performed using the identical calibrated devices, in precisely the same setting and at the same time of the day (± 90 mins). However, research assistants who guided and supervised the tests were not consistently identical between baseline and 6-month FU.

The Sarcopenia Z-score, according to the EWGSOP-I approach, included SMI, gait velocity and handgrip strength. Cut-off values applied were 0.8 m/s for gait velocity and 30 kg for handgrip strength. However, divergent from the cut-off value for skeletal muscle mass index (SMI) suggested by the EWGSOP-I for BIA assessments,^{46–48} we applied the “Weissenfels Score” (7.177 kg/m^2),^b (T-Score-based approach of SMI ($\text{ASMM}/\text{height}^2$) based on 2 SD below the mean value of a young reference cohort of 1189 healthy Caucasian men 18–35 years old.) specifically designed for this northern Bavarian cohort of CD men 70 years+.⁴⁹ Based on the cut-offs and individual data, we calculated the Sarcopenia Z-score:

$$\text{Z-Score} = ((30 - \text{individual handgrip strength})/\text{SD handgrip strength}) + ((0.8 - \text{individual gait velocity})/\text{SD gait velocity}) + ((7.177 - \text{individual SMI})/\text{SD SMI}).$$

Height was measured using a stadiometer (Holtain, Crymych Dyfed., Great Britain), body mass and composition were determined via direct-segmental multi-frequency bioimpedance analysis (DSM-BIA; InBody 770, Seoul, Korea) and by DXA (QDR 4500a, Discovery-upgrade, Hologic Inc., Bedford, USA). In both cases, we applied standard protocols suggested by the manufacturer. Since we opt to focus on BIA assessment of muscle mass during the 6-month FU assessment, we would like to report methods of DXA evaluation of bone mineral density and body composition in a future publication.

Soft lean body mass was defined as bone and fat-free body mass. Body fat (%) refers to the amount of fat in the

whole body. Comparable to the calculation of the BMI (ie, $\text{body mass}/\text{height}^2$; kg/m^2) and following the approach suggested by Baumgartner et al,⁵⁰ skeletal muscle mass index (SMI) was calculated as fat-free mass of the upper and lower extremities (=appendicular skeletal muscle mass) divided by squared body height (kg/m^2). In order to standardize the BIA assessment, we consistently used the same BIA test protocol, which includes minor physical activity for 8 hrs and 15 mins of rest in a supine position immediately before the BIA assessment. Furthermore, all participants were provided with written specifications about dos and don'ts, including essential nutritional guidance 24 before testing.

A standardized assessment of habitual gait speed⁵¹ was performed using the 10 m protocol recommended for research.⁵² Participants started walking in an upright position 3 m before the first photosensor (HL 2–31, TagHeuer, La Chaux-de-Fonds, Suisse) and stopped 2 m after the second photosensor. Tests were performed wearing regular shoes without any specific walking aids. Standardized instructions to the participants were consistently “walk at a speed just as if you were walking along the street to go to the shops.”

Handgrip strength was tested three times each for the dominant and the non-dominant hand using a calibrated Jamar handgrip dynamometer (Sammons Preston Inc., Bollington, USA). Handgrip width was adjusted individually to participant hand size. Tests were performed while standing upright, arms down by the side⁵³ with 30 s rest between the trials. The standardized instruction to the participants was consistently “squeeze as strongly as possible.” We included the highest result of the three trials for the dominant hand in the analysis.

General characteristics (eg, family and educational status, professional career), medication, diseases and lifestyle (including physical activity and exercise⁵⁴), falls, injurious falls, fractures and self-rated degree of independence were determined using a standardized questionnaire completed by the participants while visiting our lab. Before the tests, we asked participants to list their medications and diseases in order to generate completeness and accuracy of the questionnaire. This summary was checked by the principal investigator (WK) in cooperation with the participants before the tests were conducted. During this interaction, the degree of independence and autonomy, family status, social network and use of ambulatory nursing services was inquired more specifically. The 6-month FU questionnaire predominately focused on changes in confounding variables concerning lifestyle, including physical activity and

exercise, diseases, medication and dietary intake. Further, we asked for falls and self-rated degree of independence.

Sample Size

Sample size analysis of FrOST was based on quantitative computed tomography (QCT) of the lumbar spine. However, since this or other bone parameters were not determined at 6-month FU, we would like to report the statistical power of our sample size (HI-RT: $n=21$ vs CG: $n=22$) with the focus on the Sarcopenia Z-score. Applying a *t*-test based sample size calculation to the effect (exercise vs CG) on Sarcopenia Z-score (0.46 ± 0.51) reported by a comparable trial with older men,³⁷ the sample size of 21 participants/group corresponds to a 86% power ($1-\beta$) at a type-I-error of $\alpha=0.05$.

Statistical Analysis

The intention to treat (ITT) analysis included all participants who were randomly assigned to the two study arms (HI-RT vs CG) regardless of their compliance or whether they were lost to FU. R statistics software (R Development Core Team Vienna, Austria) was used in combination with multiple imputation by Amelia II.⁵⁵ The full data set was used for multiple imputations, with imputation being repeated 100 times. Overimputation diagnostic plots provided by Amelia II confirmed that the multiple imputation worked well in all cases. Based on a statistically and graphically checked normal distribution, the primary and secondary outcomes that are addressed here were analyzed by dependent *t*-tests for within-group (intra-group) changes. Pairwise *t*-test comparisons (HI-RT vs CG) with pooled SD were applied in order to identify group differences. Mean values (MV), standard deviations (SD) and 95% confidence intervals (95% CI) were used to describe the data. Additionally, we applied a per-protocol analysis (PPA) for the primary study endpoint that included only participants with complete data sets. To identify differences between the groups, we used repeated-measures ANOVA in the PPA. All tests were two-tailed; significance was accepted at $p < 0.05$. We further calculate Standardized Mean Difference (SMD) according to Cohen (d ;⁵⁶) to analyze effect sizes.

Results

One participant of the CG and two participants of the HI-RT group got lost to FU. Concerning the latter group, one man withdrew immediately after randomization (did not agree with the group assignment), another participant was unable to visit the 6-month FU due to therapy of prostate

cancer. One man of the CG was unable to visit the 6-month FU due to influenza infection. Attendance to the HI-RT sessions was high.

In summary, subjects participated in $95 \pm 4\%$ of the 52 sessions. The average exercise time/session after the conditioning period was 50 ± 9 mins. Apart from periods of muscle pain and delayed onset of muscular soreness (DOMS), no further exercise-induced complaints or unintended side effects were reported. Table 1 gives baseline characteristics. Apart from body height, no significant differences between the groups were observed.

Tables 2–4 report changes from baseline to 6-month FU assessment: Tables 2 and 3 in primary and secondary endpoints and Table 4 in potentially confounding parameters. Asterisks indicate the significance levels of intragroup changes. Differences in absolute changes between the groups are reported using mean difference and 95% confidence intervals (95% CI). Finally, in the right row of the table, exact *p*-values are listed for baseline differences and differences in absolute change in the given parameter between the CG and HI-RT. Additional listings in the text complete this data; absolute *p*-values for intragroup changes, SMD for group differences in absolute

Table 1 Baseline Characteristics of the Participants of the CG and HI-RT Group

Variable	CG ($n=22$)	HI-RT ($n=21$)	<i>p</i>
Age [years]	79.2 ± 4.7	77.8 ± 3.6	0.262
Body height [cm]	169.2 ± 5.5	172.8 ± 5.2	0.039
Body mass [kg] ^a	70.2 ± 7.1	74.7 ± 10.1	0.113
Soft lean body mass [kg] ^a	46.9 ± 3.4	48.4 ± 3.3	0.164
Total body fat rate [%]	28.6 ± 5.8	30.5 ± 6.8	0.330
Number of diseases [n] ^b	2.14 ± 0.92	2.00 ± 1.11	0.656
Hip or knee arthrosis [n]	2	2	0.959
Chronic low back pain [n]	4	3	0.731
Physical activity [Index] ^c	4.15 ± 1.53	4.45 ± 1.32	0.490
Exercisers [n]	13	11	0.654
Training volume [min/week]	59 ± 56	46 ± 52	0.780
25 OHD baseline [ng/mL]	21.6 ± 8.4	17.5 ± 7.0	0.126
Energy intake [kcal/d] ^d	2291 ± 590	2155 ± 416	0.407
Protein intake [g/d] ^d	89.3 ± 25.9	81.6 ± 19.9	0.299
Independence grade [Index] ^e	1.68 ± 0.82	1.80 ± 0.80	0.791
Smokers [n]	4	3	0.959

Notes: ^aAs determined by DSM-BIA (InBody 770, Seoul, Korea). ^bUsing the ICD-10-based disease cluster of Schäfer et al.⁵⁷ ^cScale from (1) very low to (7) very high.⁵⁴ ^dAs determined by a 4-day dietary record. ^eRating scale from 1 (no help from others to conduct my daily life at all) to 7 (unable to conduct most challenges of daily life).

Abbreviations: DSM-BIA, direct-segmental multi-frequency bioimpedance analysis; HI-RT, high-intensity resistance training; CG, control group.

Table 2 Baseline Data and Changes in the Sarcopenia Z-Score in the GC and HI-RT and Corresponding Between-Group Differences

	CG MV±SD	HI-RT MV ±SD	Difference MV (95% CI)	p-Value
Sarcopenia Z-score [Index]				
Baseline	-0.11 ± 1.18	-0.09 ± 1.94	–	0.981
Six-month follow-up	0.43 ± 0.74*	-1.01 ± 0.78***	1.44 (0.95 to 1.92)	<0.001

Notes: *P<0.05; ***P<0.001.

Abbreviations: HI-RT, high-intensity resistance training; CG, control group; MV, mean value; SD, standard deviation; CI, confidence interval.

Table 3 Baseline Data and Changes in the Sarcopenia Criteria in the Control Group (CG) and High-Intensity Resistance Training Group (HI-RT) and Corresponding Between-Group Differences

	CG MV ± SD	HI-RT MV ± SD	Difference MV (95% CI)	p-Value
Skeletal Muscle Mass Index (SMI) [kg/m ²]				
Baseline	7.10 ± 0.30	7.07 ± 0.33	–	0.681
Changes	-0.03 ± 0.21	0.30 ± 0.22***	0.33 (0.19 to 0.46)	<0.001
Habitual gait velocity [m/s]				
Baseline	1.26 ± 0.15	1.25 ± 0.17	–	0.803
Changes	-0.004 ± 0.051	0.016 ± 0.055	0.020 (-0.01 to 0.06)	0.091
Handgrip strength [kg]				
Baseline	30.0 ± 4.3	30.7 ± 5.1	–	0.675
Changes	-2.04 ± 2.13***	0.15 ± 2.26	2.19 (0.78 to 3.06)	<0.001

Notes: ***P<0.001.

Abbreviations: HI-RT, high-intensity resistance training; CG, control group; MV, mean value; SD, standard deviation; CI, confidence interval.

Table 4 Changes in Potentially Confounding Parameters in the CG and HI-RT and Corresponding Between-Group Differences

	CG MV±SD	HI-RT MV±SD	Difference MV (95% CI)	p-Value
Dietary energy uptake [kcal]				
Changes	7.8 ± 135	13±166	5 (-93 to 104)	0.971
Dietary Protein uptake [g/d]				
Changes	-2.1 ± 12.9	3.5 ± 16.4	5.6 (-4.0 to 15.3)	0.251
Physical activity [Index] ^a				
Changes	0.20 ± 0.88	0.22 ± 0.91	0.02 (-0.58 to 0.63)	0.941

Notes: ^aBased on a scale from (1) very low to (7) very high; see Table 1.

Abbreviations: HI-RT, high-intensity resistance training; CG, control group; MV, mean value; SD, standard deviation; CI, confidence interval.

change and percentage changes from baseline to follow-up are mentioned where applicable and meaningful.

Changes in the primary study endpoint are in Table 2. Based on widely identical baseline data, the Sarcopenia Z-score significantly (p<0.001) improved in the HI-RT and significantly worsened in the CG (p=0.012). Differences between the groups concerning Sarcopenia-Z-score changes

are significant (p<0.001; SMD 1.89). The additionally performed per-protocol analysis using repeated measures ANOVA confirms this result with a slightly lower effect size (p<0.001; SMD 1.77).

Addressing the underlying criteria of the Sarcopenia Z-score according to EWGSOP-I,¹ ie, SMI, habitual gait velocity and handgrip strength, we observed significant

increases for SMI in the HI-RT (+4.2%, $p < 0.001$) and slight decreases in the CG (−0.4%, $p = 0.548$). The difference between the groups was significant ($p < 0.001$, SMD: 1.53) (Table 3). Habitual gait velocity did not change in the CG (−0.3%, $p = 0.639$) and slightly increased in the HI-RT (+1.3%, $p = 0.061$). The difference between the groups was not significant ($p = 0.091$, SMD: 0.38) (Table 3). Handgrip strength maintained in the HI-RT (+0.5%, $p = 0.89$) and significantly decreased in CG (−6.8%, $p < 0.001$). Differences between the groups were significant ($p < 0.001$, SMD: 1.00).

Table 4 gives changes in parameters with a potential impact on our results. There were no relevant changes in diet or lifestyle and participants did not report changes in habitual exercise habits. Apart from the participants that were lost to follow-up (prostate cancer), no participant listed relevant changes in medication, diseases, musculoskeletal injuries or cardiometabolic events. Extended periods (≥ 2 weeks) of diseases or inactivity were also not recorded.

Discussion

The presented results clearly confirm our primary hypothesis – HI-RT combined with supplemental protein (HI-RT&P) had a significantly favorable effect on Sarcopenia, ie, the decrease of the Sarcopenia Z-score, compared to the CG, which only received protein supplement.

This result indicates that without exercise stimuli, sarcopenia naturally progresses and worsens and that the amount of supplemented protein in the CG (1.2 g/kg/d²⁵) alone was ineffective in maintaining muscle mass and function. We had at least expected maintenance of muscle strength and muscle mass because of the benefits of protein supplementation reported on in several publications^{25,26} and the positive results of the FranSO study by Kemmler et al,³⁷ which formed the basis of FrOST. FranSO indicated a sole effect of protein supplementation, even when no exercise was performed. Having said that, it has to be taken into account that in respective trial, an amount above the recommended protein intake (1.7 versus 1.2–1.6 g/kg/day^{25,58}) had been prescribed and this amount of 1.7 g/kg/day was furthermore a much higher amount of consumed protein by the non-exercise CG than in FrOST, in which the non-exercise CG only received 1.2 kg/d. Looking at the positive effect of mere supplementation in the FranSO non-exercise CG as opposed to the lack of effect of supplementation in our trial's non-exercise CG raises the question, whether what is considered an adequate protein intake for the elderly, is actually sufficient. We disregard differences in the formula

of the protein powders as a possible reason for this discrepancy because the critical variable Leucine^{26,59–62} was comparably high in both trials. (Levels of Leucine, 9 vs 10.4 g/100 g). Thus, it can be asked whether a protein intake of 1,7-up g/kg/day should be reevaluated with the dosage being the second variable to be considered for explaining this observation. A meta-analysis by Morton et al contradicts additional effects of higher protein consumption than 1,6 g/kg/day,⁶³ and discussions on general effectivity of protein supplementation continue, but there are strong arguments speaking for an increased intake, too.^{58,63–68} Nevertheless, the possible adverse effects of higher protein intake on kidney and colon health cannot be neglected.⁵⁸ Thus, an optimized balance between not too low, but safe enough has to be aimed for. Further investigations are needed to find the maximum dose for certain, specified target groups. However, even with a lower dose of protein than used in the FranSO trial, our training intervention led to a high increase in muscle mass in the HI-RT group, which proves our second hypothesis right – muscle mass significantly increased in the HI-RT&P group, compared to baseline value and the CG.

The change from baseline to FU showed a gain in skeletal body mass of 4.2% at a significance level of < 0.001 , and although we had aimed at such positive results, we did not anticipate this increase because of the blunted hypertrophic potential of skeletal muscles at older age.⁶⁹ Looking at the hypertrophic effect found in our HI-RT group, we speculate that the higher training stimuli outperformed the blunted anabolic system of this older, sarcopenic cohort. This assumption is in line with a recent umbrella review by Beckwée et al stating that more significant improvements in outcomes correlate with higher training intensities.²² The data by Giessing et al²³ about higher muscular performance and mass gain from HI-RT in comparison to traditional high-volume resistance training (HV-RT, ie, high number of repetitions and/or sets and/or frequency^{23,70,71} at low-moderate intensity³³) support our findings as well. Not only exist those advantages of HI-RT but also are there several disadvantages of HV-RT, eg, the longer time of recovery⁷² along with an increased risk of overtraining and a greater inflammatory response⁷² which itself is considered one factor in the genesis of sarcopenia.^{73,74} Additionally, high levels of heart rate and systolic blood pressure have been observed in HV-RT sets,⁷⁵ another factor that plays a role for sarcopenic patients, which often demonstrate cardiovascular comorbidities.⁷⁶ To the best of our knowledge, our study is the first to evaluate the effects of HI-RT in combination with dietary supplementation on sarcopenic community-dwelling

men of such advanced age. Altogether, it was difficult to make valid comparisons to other studies due to heterogeneity in intervention duration, the modality of resistance training, dietary supplements, cohort size, gender, age, definitions applied and missing training protocol. WB-EMS-training interventions^{37,77} with comparable cohorts have also found significant effects on sarcopenia parameters, including the Sarcopenia Z-score. However, the 4.24% increase in SMI was unique to FrOST and outstanding, FranSO achieved an increase in SMI of 2.54%. As listed in the introduction, many adverse health outcomes are correlated with a decrease in muscle mass.^{3–13} On the contrary, positive health outcomes come along with growth of muscle mass. The gain of such is associated with a higher basal metabolic rate^{78,79} helping combat sarcopenic obesity⁸⁰, and an increase in capillary density⁸¹ and Vo2 peak⁸², both improving cardiovascular economy. Furthermore, in recent years, Sarcolipin (SLN) has gained attention, and contrary to previous findings, it has been found to be the leading player in thermogenesis.⁸³ Of importance, this micropeptide is mainly expressed in striated muscle.⁸⁴ SLN ultimately increases ATP hydrolysis and consequently leads to heat production the muscle,⁸⁵ which demands a high level of energy. Thus, next to playing a vital role in non-shivering thermogenesis⁸⁶, it is a determinant of basal metabolic rate.⁸⁷ This is yet another example of the functions of muscle tissue emphasizing on the importance of maintaining and regaining muscle mass.

Apart from muscle mass as one underlying parameter of the Z-score, we also found a significant intergroup effect for handgrip strength, which was maintained in HI-RT, but significantly decreased in GC. Handgrip strength is easy and inexpensive to measure in clinical practice^{88,89} and thus has been put into focus for early detection⁸⁹ and diagnosis of sarcopenia.⁹⁰ More importantly, low handgrip strength has been discovered as a predictive marker for future falls^{91–93} and has also been related to incident cardiovascular disease^{88,94} and cardiovascular mortality⁸⁸ conditions, which are amongst the top 20 causes for disability-adjusted life years (DALYs).⁹⁵ It can be said that it is crucial to maintain muscle strength to combat frailty and mortality, and our intervention sufficed to ensure this. Addressing habitual gait velocity as the last parameter underlying the Z-score, we did not find a significant outcome. Even though gait speed is considered to be a measurand for lower extremity muscle function,⁹⁶ reciprocally, lower extremity muscle function is not the only factor impacting gait speed. Age-related motor neuron degradation,⁹⁷ range of motion in joints of the lower extremities⁹⁸ and non-muscular factors (eg, cognitive

status^{99,100} and depression¹⁰¹) impact gait speed, while muscle mass plays a minor role.⁹⁷ Thus, we do not find it alarming that gait velocity did not increase significantly.

Apart from the strengths of our study, we want to address some limitations in order to help the reader assess our results and the generalizability of our findings: First of all, the time from baseline to FU was 28 weeks with only 8 weeks of a purebred HI-RT (ie, RM⁴¹ in phase 3). During phases 1 and 2, our participants exercised mostly within the suggested range (training intensity between 75% and 80% RM¹⁰²) for novice to moderately trained individuals, as our subjects can be classified. However, work to momentary muscle failure (MF) being the second criterion that defines HI-RT^{23,33} was not introduced during the first three training periods. In our case, trainees chose an intensity of load at 75–85% of their 1RM, which within a defined repetition range, ensured an intensity of effort (sdRM) that almost led to MF. Hence, not all of our protocol followed a high-intensity approach per se. However, we found it absolutely necessary to build good exercise habits first and then prepare the subjects for the demanding phase 3. By applying this strategy, we have successfully managed to avoid injuries. Furthermore, by getting the group slowly used to this unfamiliar training method, we have avoided drop-outs and established a high level of compliance. Although we only applied the strict high-intensity approach in phase 3 for 8 weeks, the outcome was still extraordinarily high. We raise the question of whether we can expect a further significant increase in outcomes from the remaining intervention, now continuously applying the classical HI-RT approach until the end of FrOST? Answers will be given by a later publication, which will be evaluating the endpoint outcomes along with focusing on the outcomes regarding osteopenia.

Secondly, the sample size of this trial might be considered as rather small ($n=21$ and $n=22$). Indeed, the project has been powered on BMD-changes at the LS as determined by QCT. However, a sample size calculation that addresses the Sarcopenia Z-Score provided power at 86% to detect a $p<0.05$ difference using validated assumptions. Thus, we consider the sample size and corresponding statistical power as appropriate in addressing our research topic.

Lastly, we used BIA for measuring the SMI, and there have been the arguments posing an overestimation of SMI by BIA¹⁰³ and consequently suggesting a higher cut-off value of 7.9 kg/m² for males than we did (7.177 kg/m²). We consider the BIA vs DXA discussion irrelevant for the quality of our study for several reasons: 1) In previous studies, Kemmler et al have determined a high interclass correlation between

their DSM-BIA (InBody770) and DXA scanner (Hologic 4500a) for ASMM^{49,104} and Ling et al have found an “excellent agreement” of BIA and DXA.¹⁰⁵ 2) We used BIA for both, baseline and FU, so a possible general overestimation of the SMI would have had no statistical impact. 3) As explained in the methods section of this publication, we used a specifically designed T-score⁴⁹ for our cohort, ensuring the inclusion of only eligible subjects.

Overall, we are delighted with the outcomes of FrOST. We followed a high-quality methodological and statistical approach, showed multiple significant improvements and provided a precise exercise protocol as asked for by reviews, eg, “Exercise interventions in healthy older adults with sarcopenia: A systematic review and meta-analysis” by Vlietstra²¹ to ensure comparability and generalizability.

Conclusion

In conclusion, we summarize that HI-RT in combination with protein supplementation is a favorable intervention strategy to reduce the risks, progression and burden of sarcopenia. The high changes in muscle mass and sarcopenia Z-score can be achieved in an inexpensive, time-efficient and safe manner. The high compliance and lack of injuries in our cohort proved that HI-RT is indeed feasible for the elderly. The present study, along with data from the FranSO-study indicates that there is some evidence, which proposes that protein doses ≥ 1.7 g/kg/day might be required for maintenance of muscle mass without resistance training. Furthermore, studies with a similar exercise protocol changing different variables (eg, trial duration, exercise frequency) should be conducted with more cohorts to have a higher comparable amount of HI-RT trials.

Data Sharing Statement

The authors will neither share the participants’ anonymized data nor other study-related documents.

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Disclosure

The authors report no conflicts of interest in this work.

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