




Effects of High-Intensity Resistance Training on Visceral Adipose Tissue and Abdominal Aortic Calcifications in Older Men with Osteosarcopenia – Results from the FrOST Study

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Purpose: To evaluate the effect of a high-intensity resistance training (HIT-RT) on visceral adipose tissue (VAT) and abdominal aortic calcifications (AAC).

Patients and Methods: We conducted a post hoc analysis of the Franconian Osteopenia and Sarcopenia Trial (FrOST). 43 community-dwelling men with osteosarcopenia aged 72 years and older were randomly allocated to a supervised high-intensity resistance training (HIT-RT) twice weekly for 18 months (EG; n=21) and a non-training control group (CG; n=22). Non-contrast enhanced 2-point Dixon MRI scans covering mid L2 to mid L3 were acquired to measure VAT volume inside the abdominal cavity. Volume of AAC and hard plaques in renal arteries, truncus celiacus and superior mesenteric artery was measured by computed tomography (CT) scans covering mid T12 to mid L3. Intention-to-treat analysis with imputation for missing data was used to determine longitudinal changes in VAT and AAC volume. Correlations were used to determine associations between VAT and AAC.

Results: Significant reduction of VAT volume in the EG (−7.7%; p<0.001) combined with no change in the CG (−1.3%; p=0.46) resulted in a significant 6.4% between group effect (p=0.022). We observed a significant increase of AAC volume in EG (+10.3%; p<0.001) and CG (12.0%; p<0.001). AAC differences between groups were not significant (p=0.57). In vascular outlets increases in volume of the hard plaques were observed in both groups, however, not all of them were significant. There was no significant correlation between changes in VAT and AAC volumes.

Conclusion: The study confirmed a positive impact of HIT-RT on the metabolic and cardiovascular risk profile with respect to reduction of VAT volume. No positive exercise effect on AAC was observed. However, there was a further progression of AAC volume independent of group affiliation. Whether different exercise regimen may show a positive effect on AAC remains subject to further studies.

Keywords: HIT-RT, VAT, AAC, osteopenia, sarcopenia

Introduction

Demographic changes and the ever increasing rate of metabolic and cardiovascular diseases are challenging individual health and healthcare systems worldwide. In general exercise is considered as an effective intervention to positively affect cardiometabolic and cardiovascular risk factors in various populations. There is a considerable body of evidence that regular exercise affects parameters such as the metabolic syndrome (MetSyn) as a cluster of cardiometabolic and cardiovascular risk factors,¹ predominately based on positive changes in visceral adipose tissue (VAT).² However, the effect of exercise on other hallmarks of metabolic and cardiovascular diseases such as aortic calcifications is less clear.

The complex interaction between the different risk factors has not been fully deciphered so far, however, it has been shown that different body composition features are specifically associated with cardiovascular events. Subjects with more advanced abdominal aortic calcifications (AAC) have a higher risk for cardiovascular events, especially those with a fatal outcome.³ It has also been shown that AAC is influenced by visceral adipose tissue inducing lipotoxic effects on the atherosclerotic processes, while subcutaneous adipose tissue may play a rather protective role.⁴

However, apart from positive effect on metabolic and cardiovascular risk factors, exercise also improves musculoskeletal diseases such as osteoporosis and sarcopenia that often occur in parallel in older peoples.⁵ This might explain the attractiveness of exercise as a multi-purpose prevention tool in the elderly. However in detail, exercise effects on various outcomes will differ dependent on the type of exercise and the strain composition applied. This might particularly refer to older physically limited cohorts. The FrOST-study, an 18 months high-intensity resistance training (HIT-RT) protocol reported positive effects on musculoskeletal⁶ and cardiometabolic risk⁷ in a population of older, community dwelling men with osteosarcopenia. Of importance, a high proportion of this cohort suffered from overweight/obesity, MetSyn and related parameters causative for cardiometabolic and cardiovascular risk. Considering further the high relevance of VAT and AAC for the latter aspect, led us to expand our research on the effects of HIT-RT on both risk factors in this older cohort at increased cardiometabolic and cardiovascular risk.

The hypotheses for this post hoc analysis were (1) that HIT-RT positively affect VAT and (2) the volume of AAC and hard plaques in the renal arteries, truncus celiacus and superior mesenteric artery in comparison with a non-exercising control group.

Materials and Methods

Study Design

FrOST is a randomized controlled longitudinal exercise study with 18 months of training. The project was initiated and performed by the Institute of Medical Physics (IMP), Friedrich-Alexander-University of Erlangen-Nürnberg (FAU), Germany. The project was registered under ClinicalTrials.gov: NCT03453463. Comprehensive details on study design, participants, exercise regimen, assessments and results have been published previously.^{6,8,9} Here we will only repeat information necessary to understand the specific post hoc analysis reported here.

Participants

In brief, one hundred and eighty community dwelling men 72 years and older were eligible and willing to participate in FrOST. Inclusion criteria were: a) morphometric sarcopenia (skeletal muscle mass index (SMI) ≤ 7.26 kg/m²,^{10,11} and b) osteopenia or osteoporosis according to WHO.¹² Exclusion criteria were: a) secondary osteoporosis, b) a history of hip fracture, c) (osteo)anabolic and antiresorptive pharmaceutical therapy, c) glucocorticoid therapy > 7.5 mg/d for more than four weeks during the last 2 years, d) participation in resistance type exercise (>60 min/week) during the last 2 years, e) cognitive impairments, f) limitations or problems that inhibit intense exercise and g) alcohol abuse of more than 60 g/d ethanol. 43 men were eligible and randomly assigned either to an exercise (EG, n=21) or a control (CG, n=22) group (Figure 1). Apart from study intervention described below all participants were encouraged to maintain their normal physical activity and exercise habits beside the study. Furthermore, they were asked not to change their dietary routines.

Resistance Exercise Training

The exercise group underwent a progressive, single-set HIT-RT at a local, well-equipped gym (Kieser-Training, Erlangen, Germany) twice weekly consistently supervised by licensed instructors. During the training period, 5 consecutive phases with a duration of 8–12 weeks were carried out in linear periodization. According to the approach of Steele et al,¹³ our training concept was based on a non-repetition maximum (nRM) and a repetition maximum (RM) as endpoints of the sets. The intensity of the exercises was determined by a range of repetitions per set (ie 8–10 or 5–7), aiming at different relative intensities between 65 and 80% 1RM. The first twelve weeks were characterized by a phase of briefing and initial familiarization eg learning of proper lifting techniques followed by conditioning of the practiced exercises. Subsequently in Phase 2, 14–15 out of 18 exercises (back extension, bench press, butterfly with extended

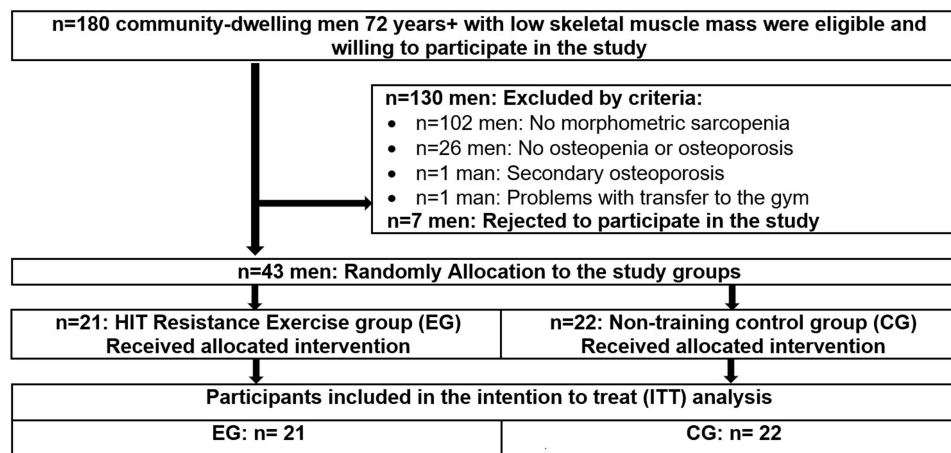


Figure 1 Participant study Flow.

Abbreviations: HIT, High-Intensity-Training; EG, exercise group; CG, control group; ITT, intention to treat; VAT, visceral adipose tissue; AAC, abdominal aortic calcifications.

arms, calf raises, crunches, hip extension, inverse fly, lateral crunches, lateral raises, latissimus front pulleys, leg adduction and abduction, leg curls, leg extension, leg press, pullovers, rowing, shoulder press) were performed on resistance-devices (MedX, Ocala, Florida, USA). Phase 3 was extended by an explosive movement in the concentric phase and the initiation of the repetition maximum approach.¹³ In the further course, the superset approach (phase 4) and drop sets (phase 5) were introduced in order to intensify the training protocol. For more details on the training procedure, please refer to Kemmler et al.¹⁴

Dietary Supplementation

According to recent recommendations¹⁵ individual supplementation of whey protein (Active PRO80, inkospor, Roth, Germany) was provided to all participants to generate a total protein intake of 1.5–1.6 in the EG and 1.2–1.3 g/kg body mass per day in the CG.

To ensure a daily calcium uptake of ≈ 1000 mg¹⁶ each participant was provided with calcium capsules (Sankt Bernhard, Bad Dietzenbach, Germany) based on a dietary calcium questionnaires (Rheumaliga, Switzerland) if calcium intake fell below 950 mg per/day.

On the basis of measured and analyzed 25-Hydroxy-Vitamin-D 3 (25-OH D3) concentrations of blood samples, participants with levels <30 ng/mL were provided with 10,000 IE per week (MYVITAMINS, Manchester, UK). Participants with 30–40 ng/mL were requested to ingest 5000 IE/week.

MRI to Assess VAT

MRI scans were acquired at baseline and after 16 months of HIT-RT. All scans were performed on a 3T scanner (MAGNETOM Skyra^{fit}, Siemens Healthineers AG, Erlangen, Germany) using a non-contrast enhanced 2-point Dixon Gradient Echo Volumetric Interpolated Breath-hold Examination (VIBE) sequence (TE: 1.29 ms; TR: 3.97 ms; matrix: 320x260; resolution: 1.2×1.2 mm²; slice thickness: 3.5 mm; slice gap: 0.7 mm). Twelve slices covered a total length of approximately 5 cm from mid L2 to mid L3.

Image analysis was performed by a single reader (KK, medical student) under the supervision of a board certified radiologist (SB, >10 years of experience) using MIAF (Medical Image Analysis Framework, University of Erlangen) as described before.¹⁷ The body surface was determined automatically. The contour of the abdominal cavity was manually segmented slice by slice using open source software 3D Slicer.¹⁸ Finally, VAT inside the abdominal cavity was automatically separated from inner organs such as kidney or intestines, and blood vessels using a threshold automatically calculated with the Otsu-Method¹⁹ from the intensity histogram (Figure 2). Volume of VAT was measured in cm³.

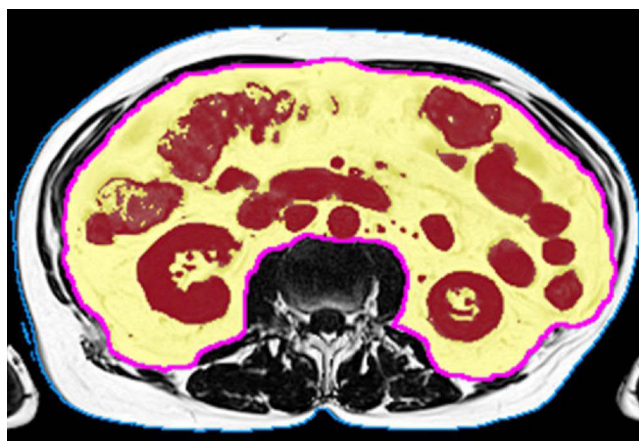


Figure 2 Segmentation of VAT in Dixon MRI fat image. Total abdominal volume is shown by the blue contour; visceral volume of interest is shown by the magenta contour; the Otsu threshold separates visceral adipose tissue VAT (yellow overlay) from inner organs (dark red overlay).

CT to Assess AAC

CT scans were acquired at baseline and after 12 months. All scans were performed on a Somatom Force (Siemens, Erlangen, Germany) using 120 kV, CAREdose 3D with an effective 100 mAs; 1 mm slice thickness, BR40s kernel and a field of view of 20 cm. The scans covered mid T12 to mid L3.

Calcifications were assessed by the same reader (KK) under the supervision of the same radiologist (SB). Segmentation of the abdominal aorta, the renal arteries, truncus celiacus and superior mesenteric artery was performed with 3D Slicer using an individually adapted threshold ranging from 145 to 160 Hounsfield Units (HU). The respective threshold in a patient was selected based on an Osteo phantom included in the images, which is typically used for calibration of bone mineral density. Identical thresholds were used for the BL and FU images of a given participant. For this purpose, BL and FU images of a given participant were segmented side by side. First the calcifications were cut out manually using the scissor function of 3D Slicer and then remaining artefacts were removed slice by slice using the eraser function. Subsequently, the segmented volume of the plaques was measured in the respective section in mm³ (Figure 3).

Statistical Analysis

Pearson correlations were used to describe associations between VAT and AAC volume as well as between both parameters and obesity and MetSyn. An intention-to-treat (ITT) with imputation for missing data analysis was performed. R statistics software (R Development Core Team Vienna, Austria) in combination with Amelia II²⁰ was used to apply repeatedly imputations. For ITT, the complete data set was utilized and imputed 100 times, which worked well in all cases. A normal distribution was tested using qq-plots. An ANCOVA adjusted for baseline values was performed to detect differences between the changes in the training and the control group. Results of the ITT analysis were compared with those of a per-protocol (PP) analysis, significances were similar. Therefore, the PP analyses are omitted in the following. All applied tests were 2-tailed with an accepted significance of $p < 0.05$.

Results

Baseline Characteristics

Table 1 shows participant characteristics at BL. Apart from body height and protein intake parameters were not significantly different in the two groups. Per inclusion all participants had osteosarcopenia. Accepting that a body fat rate of 27%–30% constitutes obesity in men²¹ most participants (75%–94%) can be considered as (osteosarcopenic) obese and one third of the subjects of the CG and EG respectively were affected by the MetSyn.²² At baseline VAT volume of the combined group was significantly correlated with BMI ($r = 0.66$) and MetSyn Z-Score⁷ ($r = 0.70$). In

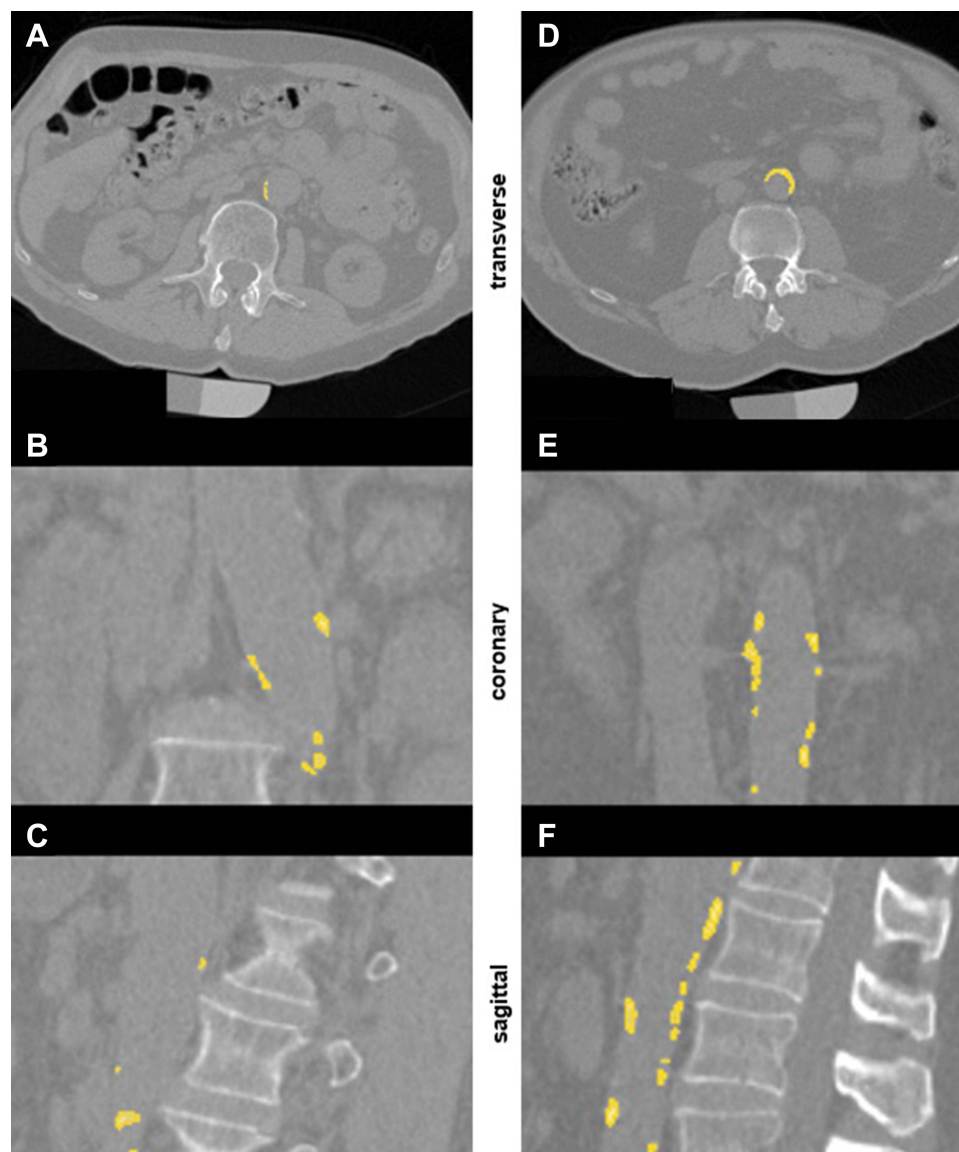


Figure 3 Segmentation of baseline AAC volume in CT images. (A-C) Participant with low BL AAC of 1468 mm³ and an increase of Δ 11.97%; (D-F) Participant with high BL AAC of 5208 mm³ and an increase of Δ 8.8%. (A and D) transverse section; (B and E) coronary section; (C and F) sagittal section.

contrast there were no significant correlations between AAC volume of the combined group with BMI ($r = 0.1$) and MetSyn Z-Score ($r = 0.05$). VAT volume was also not significantly correlated with AAC volume ($r = 0.18$).

Participants attended the HIT-RT sessions at a high rate of $95\% \pm 4\%$ indicating the high attractiveness and feasibility of the training protocol. No serious adverse effects or injuries were observed during the study period.

Study Endpoints

Table 2 shows VAT results. After 16 months of training, VAT volume significantly decreased (-7.7% ; $p < 0.001$) in the EG, while in the CG VAT volume did not considerably change (-1.3% ; $p = 0.46$). Absolute changes in VAT volume were significantly higher in the EG compared with the CG ($p = 0.022$).

Table 3 shows AAC results. We observed a significant increase in AAC volume in the EG ($+10.3\%$; $p < 0.001$) as well as in the CG ($+12.0\%$; $p < 0.001$). The between group difference was not significant ($p = 0.57$). Between-group differences were also not significant for the vascular branches of the abdominal aorta (Right renal artery $p = 0.52$; Left renal artery $p = 0.60$; Truncus

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

Variable	CG (n=22)	EG (n=21)	p-value
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 Index [kg/m ²]	24.5 ± 1.9	25.0 ± 3.0	0.515
Total body fat [%] ^a	33.6 ± 4.0	34.5 ± 6.1	0.563
SMI [kg/m ²]	6.89 ± 0.31	7.01 ± 0.27	0.671
Metabolic Syndrome Z-Score [Z]	-4.22 ± 3.70	-3.14 ± 4.66	0.322
Physical activity [Index] ^b	4.15 ± 1.53	4.45 ± 1.32	0.490
Energy intake [kJ/d] ^c	9393 ± 2419	8836 ± 1706	0.407
Protein intake [g/kg/d] ^c	1.29 ± 0.34	1.10 ± 0.25	0.043
25 (OH)D [nmol/l] ^d	54.0 ± 21.1	43.8 ± 17.5	0.126
Calcium intake [mg/d] ^e	833 ± 282	802 ± 226	0.636

Notes: ^aVia dual-energy X-ray absorptiometry (DXA). ^bScale from (1) “very low” to (7) “very high”.⁴⁶ ^cAs determined by dietary records. ^dRoche Diagnostics, Mannheim, Germany. ^eAs determined by a Calcium Questionnaire provided by Rheumaliga, Switzerland.

Abbreviation: SMI, skeletal muscle mass index.

Table 2 Absolute and Relative Changes of Visceral Adipose Tissue (VAT) in Control (CG) and Exercise Group (EG) After 16 Months of High Intensity Resistance Training

Variable		Baseline (SD)	Δ Absolute (SD)	Δ [%]	p
VAT [cm ³]	CG	1095 (405)	-14.7 (19.5)	-1.3	0.46
	EG	1067 (440)	-82.4 (20.5)	-7.7	<0.001

Notes: p: within-group differences (follow-up vs baseline). Δ: percent change between baseline and 16 months. Results obtained from intention to treat analysis. At baseline no data were available for 2 subjects of the control group and 5 subjects of the exercise group. At 16 months follow-up no data were available for 3 subjects of the control group and 7 subjects of the exercise group.

Abbreviations: SD, standard deviation; VAT, visceral adipose tissue.

Table 3 Absolute and Relative Changes of AAC, Hard Plaques in Renal Arteries, Truncus Celiacus and Superior Mesenteric Artery in Control (CG) and Exercise Group (EG) After 12 Months of High Intensity Resistance Training

Variable		Baseline (SD)	Δ Absolute (SD)	Δ [%]	p
AAC [mm ³]	CG	2133 (2331)	255 (60.6)	12.0	<0.001
	EG	2441 (2720)	251 (62.3)	10.3	<0.001
Right renal artery [mm ³]	CG	56 (94)	4.8 (5.38)	8.5	0.384
	EG	102 (146)	12.3 (5.8)	12.1	0.045
Left renal artery [mm ³]	CG	52 (90)	8.1 (3.59)	15.7	0.031
	EG	139 (215)	14.9 (3.66)	10.7	<0.001
Truncus celiacus [mm ³]	CG	54 (86)	3.7 (1.74)	6.8	0.043
	EG	34 (37)	2.8 (1.79)	8.1	0.14
Superior mesenteric artery [mm ³]	CG	48 (84)	8.9 (5.16)	18.4	0.09
	EG	74 (124)	15.0 (5.13)	20.2	0.006

Notes: p: within-group differences (follow-up vs baseline); Δ: percent change between baseline and 12 months. Results obtained from intention to treat analysis. At baseline no data were available for 5 subjects of the control group and 3 subjects of the exercise group. At 12 months follow-up data were available for all subjects of the control group but data were missing for 4 subjects of the exercise group.

Abbreviations: AAC, abdominal aortic calcifications; SD, standard deviation.

celiacus $p=1.00$; Superior mesenteric artery $p=0.64$). The individual vascular outlets showed both significant and non-significant increases in hard plaques.

There was no significant correlation between changes in VAT volume and changes in AAC volume.

Discussion

The current post hoc analysis of the effect of HIT-RT on metabolic and cardiovascular risk factors in FrOST confirmed the hypothesis of positive training effects on VAT in elderly men with osteosarcopenia. The second hypothesis was rejected – positive effects on AAC were not observed in the observation period. Numerous metabolic and cardiovascular risk factors exist that contribute to a negative impact on health. For the FrOST study, we had previously investigated parameters of adiposity and the effect of HIT-RT on body composition and showed a positive training effect on total body fat mass and abdominal body fat percentage.^{7,23}

It is known that an enhanced VAT volume contributes to the development of obesity and that it is a more sensitive marker to detect changes in adiposity than total body weight or waist circumference.²⁴ Here we showed that at baseline VAT volume was moderately correlated with the MetSyn and obesity and that the positive effect of the HIT-RT on body composition reported earlier also applied to VAT. This was confirmed by a significant decrease in VAT in the EG ($p<0.001$) and a significant between-group difference ($p=0.022$).

Our results are consistent with other studies. Arciero and colleagues²⁵ reported a significant reduction of about -8% in VAT in an exercise group and a non-significant decrease in the CG group. The participants were middle-aged and of mixed gender and were also provided with whey protein, but in a smaller quantity than ours. Only 16 weeks of the intervention took place, but 4 times a week instead of 2 times a week as in our study. Meta-analyses showed that aerobic endurance training with moderate or high intensity had a greater effect on VAT than resistance training.^{26,27} However, there is a great heterogeneity among strength training studies in terms of training protocols, cohort characteristics and study designs.²⁶ Furthermore, Vissers et al included fewer strength training than aerobic exercise studies in their meta-analysis.²⁶

A more recent CT study of subjects of mixed gender and an average age in the early sixties by Yan et al²⁸ showed that both strength and aerobic exercise led to reductions in VAT volume over a 12-month period with no statistical difference between the different training groups. The change in VAT volume within one year was consistent with our results.

In contrast using single slice CT at the L3 level, Turcotte and colleagues²⁹ did not observe significant changes in VAT (-1.9%) during 18 months of progressive resistance training. Their sample size of male-only participants, ranging in age from 50–79 years was larger than ours but the training protocols were similar. Potentially the larger age range, particularly including younger subjects and a lower total body fat mass at baseline, could explain the different outcome compared to the studies discussed above.

An important point regarding VAT is precision of longitudinal assessments due to motion of internal organs, partly caused by respiration. In contrast to other studies²⁹ that only used a single slice we employed a volumetric analysis, which reduces the movement effect of the internal organs. We used a total scan length of 5 cm between vertebrae L2 and L3 as suggested by others.^{30–32} Meta-analyses showed that many previous exercise studies only used a single-slice measurement of VAT,²⁷ which simplified imaging but increased precision errors.

Studies on the effect of physical activity on vascular calcification (eg in coronary arteries) are inconclusive.³³

While results on VAT are in line with other studies, the investigation of exercise on AAC is novel. While our study showed changes of AAC volume over time our study data did neither demonstrate a significant effect of training on AAC nor on hard plaque calcifications in the small arterial outlets of the abdominal aorta. Over the observation period, both groups demonstrated a similar progression without significant differences, however, with considerable inter individual differences. It is also interesting that in contrast to earlier studies^{4,34} in the FrOST cohort AAC volume was not correlated with MetSyn or with obesity and there was no correlation between AAC and VAT volume although AAC volume was similar to volumes of $1950 \pm 2300 \text{ mm}^3$ reported in by Fuji et al³⁵ in subjects with comparable age (but a different gender distribution).

Limited literature is available for longitudinal volumetric assessments of AAC. Particularly with higher age, there is an increase in the prevalence and the severity of plaques.^{36–38} In our study, the average age was 77.8 ± 3.6 years in EG

and 79.2 ± 4.7 years in CG. It has been further suggested, that the age related increase of AAC in men is more pronounced than in women.^{37,39} Graffy et al⁴⁰ reported an increase in the age-specific Agatston score of 10% per year in an observational study without training. This is comparable to the change of 12.0% in the CG of our study. However, Graffy's study was a mixed female-male cohort with an average age younger than ours. Another study described a progression of plaques of around 8% in one year measured by MRI, slightly lower than our observation.⁴¹ A lack of positive effects on AAC progression using training intervention, however, with a different training protocol, has previously also been described by Zhou et al³⁸ demonstrating a significant progression despite training, as in our results. Whilst Zhou et al did only use radiography and no control group our study included CT and a control group allowing for a more detailed analysis. One might argue, that the calcium substitution may have influenced our results since it has been reported to influence calcified vascular plaques⁴² but the majority of studies do not describe a significantly increased risk of cardiovascular outcomes due to calcium substitution⁴³ and substitution was only at nutritional recommendation levels.

Study Strengths and Limitations

Strengths of the study are the randomized study design, the long duration of the HIT-RT exercise program and the quantitative assessment of VAT and AAC volume using advanced 3D imaging techniques. The main limitations of the study are the relatively small number of participants and the post hoc approach of the project. Furthermore, some study and participant characteristics (e.g. high age, osteosarcopenic status, male gender, protein supplementation, specific exercise protocol) might prevent a proper generalization of our results to other (older) cohorts and/or conditions. No evaluation of reproducibility of the segmentations was conducted. Imaging was performed in a limited body area, thus we cannot draw conclusions eg with regards to the influence of other vessels or fat tissue locations in the body. No contrast agents were given limiting the assessment of soft plaques within the AAC and the outlets, which apparently differs in contrast and non-contrast enhanced CT scans.⁴⁴

Conclusion

HIT-RT is an attractive, time effective and feasible training modality for elderly men with osteosarcopenia in terms of VAT reduction. However, the progression of AAC and its vascular branches could not be prevented in the FrOST study. Therefore, in combination with the results published earlier^{7,23} we conclude that HIT-RT has a positive effect on the metabolic and cardiovascular risk profile but at least in the FrOST study not on AAC. Perhaps a variation of the exercise protocol with further emphasis on endurance may be more effective for targeting AAC resulting in further optimization of an integrated and cost-effective exercise approach for the elderly.

Abbreviations

HIT-RT, high-intensity resistance training; VAT, visceral adipose tissue; AAC, abdominal aortic calcifications; EG, exercise group; CG, control group; MRI, magnetic resonance imaging; CT, computed tomography; FrOST, Franconian osteopenia and sarcopenia trial; DXA, dual x-ray absorptiometry; BMD, bone mineral density; SMI, skeletal muscle mass index; MetSyn, metabolic syndrome; IMP, Institute of Medical Physics; FAU, Friedrich-Alexander-University of Erlangen-Nürnberg; WHO, world health organization; nRM, non-repetition maximum; RM, repetition maximum; TE, time to echo; TR, repetition time; ITT, intention-to-treat; PP, per-protocol; BL, baseline; FU, follow-up; SD, standard deviation.

Data Sharing Statement

Data sharing has not been approved by the study participants.

Ethics Approval and Informed Consent

The FrOST study was approved by the University of Erlangen Ethics Committee (number 67_15b and 4464b) and the Federal Bureau of Radiation Protection (BfS, number Z 5 – 2246212-2017-002). All study participants gave their written informed consent. The trial fully complies with the Helsinki Declaration.⁴⁵

Consent for Publication

The current contribution does not include any details that would allow conclusions to be made about the identity of the participants.

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Disclosure

Dr Sebastian Bickelhaupt reports personal fees, non-financial support from Siemens Healthineers, outside the submitted work; In addition, Dr Sebastian Bickelhaupt has a pending patent in the field of MRI. The other authors report no conflicts of interest in this work.

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