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Effects of exercise training on bone health in elderly people with type 2 diabetes without osteoporosis: A randomised clinical trial

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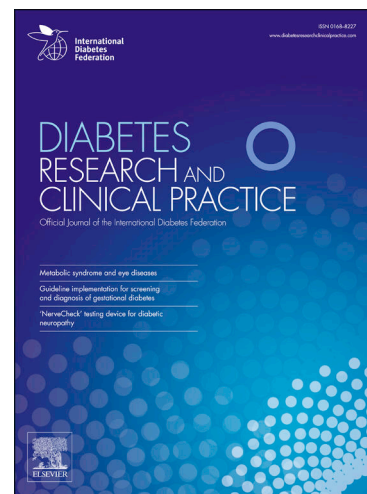
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Effects of exercise training on bone health in elderly people with type 2 diabetes without osteoporosis: a randomised clinical trial

Running Head: Effect of exercise on bone health.

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See Supplementary Material for a list of the SWEET-BONE Investigators.

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Abstract

Aims. To assess the effects of exercise on non-invasive measures of bone health in elderly individuals with type 2 diabetes without osteoporosis.

Methods. In this randomized clinical trial, 200 elderly individuals with type 2 diabetes without osteoporosis were randomized 1:1 to a two-year, specifically-designed exercise training program (Exercise group) or standard care (Control group). Coprimary outcomes were trabecular bone score (TBS), a surrogate measure of bone quality, and bone mineral density (BMD) at three sites. Secondary outcomes were other bone measures and muscle and physical function parameters.

Results. The coprimary endpoints increased in the Exercise group and decreased in the Control group. Significant between-group differences were observed for TBS (mean, 0.016 [95% confidence interval, 0.011-0.021], $p<0.0001$, which-disappeared after adjusting for abdominal fat indices), and lumbar spine (0.014 [0.005-0.024], $p=0.004$), femoral neck (0.017 [0.006-0.028], $p=0.003$), and total hip (0.020 [0.010-0.030], $p=<0.0001$) BMD. Significant between-group differences were observed also for other bone measures, body composition, muscle strength and quality, physical performance, and cardiorespiratory fitness. There were no between-group differences in adverse events.

Conclusions. A two-year exercise training improved several non-invasive measures of bone health, together with muscle and physical function parameters, potentially reducing fracture risk in people with type 2 diabetes.

Key words: type 2 diabetes; exercise; trabecular bone score; bone mineral density; fracture risk.

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1. Introduction

Individuals with senile osteoporosis are identified based on a low bone mass, as assessed by bone mineral density (BMD) T-score, which predicts fragility fractures [1]. In contrast, people with type 2 diabetes have an increased fracture risk despite normal-to-increased BMD [2, 3]. This has been attributed to decreased bone quality [1,2] in addition to increased risk of falls due to impaired vision, proprioception, and balance [4]. Bone quality is determined by bone architecture, including geometry and micro-architecture, and material properties, including mineralization and collagen cross-links, which ultimately affect bone strength and resistance to fracture independent of BMD [5]. However, even in people with type 2 diabetes, BMD is strongly associated with fracture risk, though risk is higher than in individuals without diabetes for a given BMD T-score and age [6].

These findings raised concerns on whether fracture preventing strategies for people with osteoporosis are effective also in individuals with type 2 diabetes, since these strategies have not been specifically tested in this population. However, observational studies and post hoc analyses of randomized clinical trials have shown that most osteoporosis medications have similar efficacy and safety profiles in people with and without diabetes [7]. Regarding physical activity (PA)/exercise, an independent inverse association has been demonstrated between PA level and incidence of fractures [8-10]. Moreover, exercise, particularly resistance exercise, has been shown to increase BMD [11,12], to prevent bone (and muscle) loss induced by intentional weight loss [13,14], and to decrease fractures [15] and falls [16]. While these findings were obtained in older adults from the general population who are at risk for or suffer from osteoporosis, as defined by decreased BMD T-score, evidence is sparse and clinical trials are lacking in people with type 2 diabetes without osteoporosis [17]. Furthermore, it is unclear which non-invasive measure(s) of bone health reflect(s) the benefits of exercise training in these individuals.

The “Study to Weigh the Effect of Exercise Training on BONE quality and strength in type 2 diabetes” (SWEET-BONE) aimed at investigating the effects of a two-year exercise program on bone health in elderly individuals with type 2 diabetes without osteoporosis. To this end, a wide range of non-invasive measures

of bone mass, quality, and strength were assessed, together with other determinants of fracture risk such as muscle and physical function parameters, which are known to improve with exercise [1].

Journal Pre-proofs

2. Methods

2.1. Design

The SWEET-BONE was a single-centre, open-label, assessor-blinded, parallel, superiority randomised clinical trial comparing a specifically designed exercise training program with standard care in elderly individuals with type 2 diabetes without osteoporosis.

The research protocol [18] complies with the Declaration of Helsinki and was registered at ClinicalTrials.gov (NCT02421393). It was approved by the Ethics Committee of Sant'Andrea University Hospital and participants provided written informed consent.

2.2. Participants

This study enrolled physically inactive and sedentary people with type 2 diabetes of both sexes, aged 65-75 years, with diabetes duration of ≥ 15 years, a BMI 27-40 kg·m⁻² and a Short Physical Performance Battery (SPPB) test score ≥ 4 , who are able to walk 1.6 Km without assistance, and became eligible after cardiologic evaluation.

The exclusion criteria are reported in Supplementary Table 1.

2.3. Recruitment and randomization

All individuals with type 2 diabetes attending the tertiary referral, outpatient Diabetes Clinic of Sant'Andrea University Hospital, Rome, Italy, were evaluated for eligibility.

Two hundred individuals were finally enrolled and randomized 1:1 to receive exercise training on top of standard care (exercise, EXE, group; n=100) or standard care alone (control, CON, group; n=100) for two years. All participants were seen every 6 months for adjusting treatment and reporting adverse events.

Randomization was stratified by sex (males versus females), age (65-70 versus 71-75 years) and type of diabetes treatment (non-insulin versus insulin), using a permuted-block randomization software which randomly varies the block size (range 4-8).

Participants, physicians and exercise specialists were unblinded, whereas assessors of study outcomes were blinded to group assignment.

2.4. Intervention

The training program for the EXE group consisted of both gym and home sessions.

Two 75-min weekly sessions were supervised by an exercise specialist in the gym facility of the Metabolic Fitness Association and consisted of 5 min of warm up, followed by 20 min of aerobic training, 30 min of resistance (strength and power) training, and 20 min of core stability (8 min), balance (8 min) and flexibility (4 min) training (Supplementary Figure 1).

The unsupervised home sessions consisted of 3 series of 10 repetitions of step-up and sit-to-stand exercises at least three times a week on non-training days.

Starting at month 2, participants were asked to wear a weighted vest during and, as much as possible (at least for 30 min each day while standing or walking), outside the exercise sessions. Weight of vests was 2% of lean body mass weight and was then increased by 2% at each intermediate visit.

Participants were asked to report on a daily diary the exercises performed at home and the time spent wearing the weighted vest.

2.5. Standard care

All patients received a treatment regimen aimed at achieving glycaemic, lipid, blood pressure, and body weight targets, according to current guidelines [19] and including nutritional and drug therapy. A daily calcium intake of 1,200 mg was also recommended [1]. Treatment was adjusted at intermediate diabetes visits using a pre-specified algorithm [20].

2.6. Outcomes

The trabecular bone score (TBS), a grey-level texture measurement based on 2D projection images acquired during a dual-energy X-ray absorptiometry (DXA) lumbar spine scan, was originally identified as the primary outcome, because it was proposed as a reliable non-invasive measure of bone quality [21]. Moreover, it was shown to predict fracture risk independently of BMD [22] and to be decreased in people with type 2 diabetes compared to those without diabetes [22-24] as well as in individuals with fracture versus those without fracture [25]. However, while confirming the predictive value of TBS, a recent report

showed that it is artifactually lower in individuals with type 2 diabetes because its measurement using current algorithms is affected by increased abdominal tissue thickness due to excess fat mass [26]. For this reason, 4 DXA-derived coprimary endpoints were identified post hoc, including TBS and BMD at three sites (lumbar spine, femoral neck, and total hip).

Secondary outcomes included change in (a) measures of BMD and bone geometry and strength provided by quantitative ultrasound (QUS) and peripheral quantitative computed tomography (pQCT); (b) body composition; (c) muscle strength, mass, and quality; (d) physical performance; and (e) cardiorespiratory fitness. Additional secondary outcomes were musculo-skeletal disturbances, which were not analysed due to the high percentage of unfilled questionnaires, and number of falls and symptomatic and asymptomatic fractures, which are being evaluated over 7 years, including a 5-year post-trial follow-up (ending December 2028).

Ancillary outcomes included change in PA level, modifiable cardiovascular risk factors, and 10-year risk of cardiovascular events.

2.7. Measurements

Study parameters were assessed at baseline and end-of-study.

Bone mass, quality and strength. Areal BMD (aBMD) was assessed by lumbar spine and total femur DXA scans using Hologic Horizon Wi (Hologic, Bedford, MA, USA) and TBS was measured from lumbar spine DXA images using the TBS iNsite software version 3.0 (Medimaps, Plan-les-Ouates, Switzerland) [26,27].

Broadband ultrasound attenuation, speed of sound, and estimated BMD were assessed by calcaneal QUS using the Sahara® Clinical Bone Sonometer (Technologic, Turin, Italy) and the quantitative ultrasound index was then calculated [28]. Total, trabecular (Trab), and cortical (Cort) volumetric BMD (vBMD) and cross-sectional area (CSA) were measured in 2.5 mm-slices obtained at the 4% site of the nondominant radius and the 4%, 14%, 38%, and 66% sites of the left tibia using an XCT-2000 pQCT scanner (Norland Stratec, Pforzheim, Germany). Additionally, Cort-thickness, bone strength index (BSI), and stress-strain indexes (SSI), which are surrogate measures of resistance to bending (xSSI and ySSI) and torsional (pSSI) loads, were calculated [29].

Bone biochemistry. Serum calcium and phosphorus, alkaline phosphatase, 25OH Vitamin D, and parathyroid hormone were measured by standard methods.

Body composition. Body composition was evaluated by total body DXA, with measurement of appendicular (arm and leg), trunk and total body fat and lean mass and total body bone mineral content and BMD.

Muscle strength, mass and quality. Isometric upper and lower limb muscle strength was measured using a strain gauge tensiometer (Digimax, Mechatronic GmbH, Germany) [30] and muscle quality was then assessed as ratio of strength to DXA-derived arm or leg lean mass [31]. Leg muscle CSA was measured by pQCT at the 66% site of the tibia [32], together with muscle density and fat:muscle and bone:muscle area ratio, which also reflect muscle quality.

Physical performance. A SPPB test was performed for the assessment of balance (side-by-side stand, semi-tandem stand and tandem stand), gait (gait speed test), and lower limb muscle power (chair stand test) [33].

Cardiorespiratory fitness. Cardiorespiratory fitness was assessed by sub-maximal evaluation of oxygen consumption at 80% of the maximal heart rate to predict maximal oxygen consumption (VO_{2max}) [34].

PA level. The level of PA outside the sessions was evaluated using the Physical Activity Scale for the Elderly (PASE) questionnaire [35].

Cardiovascular risk factors and scores. Traditional cardiovascular risk factors were assessed by standard methods, whereas 10-year risk of cardiovascular events was estimated using the SCORE2-Diabetes [36].

2.8. Adverse events

Adverse events were reported at intermediate visits and, for EXE participants, also at supervised sessions.

2.9. Statistical analysis

Sample size calculation was based on a pilot study showing that TBS was 1.225 (0.085) in individuals with type 2 diabetes. To detect a between-group difference of 0.045 in TBS (i.e., effect size=0.50) with statistical power of 90% ($\alpha=0.05$) by two-sided two-sample equal-variance t-test, 86 patients per arm were needed and a sample of 100 patients per arm tolerated a 14% dropout rate.

The χ^2 or the Fisher's exact test as appropriate, for categorical variables, and the unpaired Student's t test or the corresponding nonparametric Mann-Whitney test, for continuous variables, were utilized to compare participants' characteristics at baseline.

To account for the potential influence of between-group differences in baseline to end-of-study changes in abdominal fat mass, TBS least squares means with 95% CI were estimated from generalized linear models adjusted for either waist circumference or trunk fat mass.

The intention-to-treat analysis was applied to all randomized participants with a baseline and end-of-study measure of study endpoints. Baseline to end-of-study changes in the primary and secondary endpoints in each group were analysed by paired Student's t test, whereas the efficacy of the intervention on these endpoints was assessed using the unpaired t-test or the Mann Whitney U test, by comparing between-groups changes from baseline to end-of-study.

Regardless of the study arm, univariate correlations between change in TBS or aBMD and their baseline value or change in each other and other relevant parameters were assessed by Pearson's or Spearman's correlations, as appropriate, whereas the independent predictors of change in TBS or aBMD were assessed by multivariable linear regression analysis with stepwise backward variable selection. Covariates were baseline TBS (or aBMD), age, sex, change in aBMD (or TBS), muscle density, fat:muscle area ratio, upper and lower body muscle strength, VO_{2max} , BMI (or, alternatively, waist circumference, total body or trunk fat mass), HbA_{1c} , and eGFR, and insulin treatment throughout the study. The models were further adjusted for study arm and baseline BMI (or waist circumference, total body or trunk fat mass), HbA_{1c} , eGFR, and insulin treatment.

Statistical analyses were performed using SPSS version 20 (SPSS Inc., Chicago, IL, USA) and SAS software release 9.3 (Cary, NC, USA). The statistical significance level was set at $\alpha < 0.0125$ (2-tailed) to account for the 4 coprimary endpoints.

Journal Pre-proofs

3. Results

3.1. Participants

A total of 321 individuals were assessed for eligibility from June 2018 to December 2021. Recruitment was interrupted from March to September 2020 and subsequently slowed down because of the COVID-19 pandemic. After excluding 121 individuals for various reasons, the remaining 200 were randomized (see Table 1 and Supplementary Tables 2-3 for baseline features). At the end of follow-up (December 2023), 176 participants (88%) had completed the study (EXE=89; CON=87) and were included in the intention-to-treat analysis, whereas 24 (12%) had withdrawn for various reasons (EXE=11; CON =13) (Figure 1).

Attendance at home sessions was satisfactory, with 80.4% of participants attending $\geq 50\%$ of sessions and 96.7% wearing a weighed vest. Conversely, attendance at gym sessions was relatively low, with only 51.1% of participants attending $\geq 50\%$ of these sessions, almost exclusively due to the fear of COVID-19 infection.

3.2. Coprimary outcomes

The TBS increased significantly by 0.62% in the EXE group and decreased significantly by 0.65% in the CON group, with a significant between-group difference (Table 2 and Figure 2). However, the between-group difference in TBS disappeared when adjusting TBS values for waist circumference or trunk fat mass (Table 2). Changes in TBS correlated significantly with changes in aBMD, muscle strength and density, PASE and SPPB test scores, VO_{2max} and, inversely, fat:muscle area ratio, BMI, and waist circumference at univariate analysis (Supplementary Table 4). Moreover, changes in TBS were independently predicted by changes in muscle strength, SPPB test score, VO_{2max} and, inversely, fat:muscle area ratio, but not by age, sex, baseline TBS and change in aBMD, BMI (or waist circumference, total body or trunk fat mass), HbA_{1c} , and eGFR, and insulin treatment throughout the study, at multivariable linear regression analysis (Supplementary Table 5). These results did not change when further adjusting for study arm and baseline BMI (or waist circumference, total body or trunk fat mass), HbA_{1c} , eGFR, and insulin treatment (not shown).

Lumbar spine, hip neck, and total hip aBMD increased significantly by 0.76%, 1.45% and 1.34%, respectively, in the EXE group, and decreased by 0.59%, 0.82%, and 0.78%, respectively (significantly only for total hip), in the CON group, with significant between-group differences (Table 2). Changes in aBMD at one site correlated significantly with changes in aBMD at another site, but not or less strongly with changes in TBS, muscle strength, physical performance, and cardiorespiratory fitness at both univariate (Supplementary Table 4) and multivariable linear regression (Supplementary Table 5) analysis.

3.3. Secondary outcomes

No between-group difference was observed in QUS parameters, with speed of sound and quantitative ultrasound index decreasing significantly and broadband ultrasound attenuation and eBMD showing no significant change in both groups (Supplementary Table 6). In contrast, significant between-group differences were detected for pQCT-derived Cort-CSA and pSSI at 14% tibia and total and Trab-vBMD, Cort-CSA and thickness, and pSSI at 38% tibia (Supplementary Table 6).

Vitamin D and parathyroid hormone levels increased significantly in both groups with no between-group differences, whereas alkaline phosphatase, calcium and phosphorus levels did not change (Supplementary Table 6).

Significant between-group differences were detected for appendicular lean mass, which increased in the EXE versus CON group, and trunk and total body fat mass, which increased in the CON versus EXE group (Supplementary Table 7).

Muscle strength at the upper and lower body level significantly increased (by 3.5% and 8.5%, respectively) in the EXE group and decreased (by 10.3% and 12.6%, respectively) in the CON group, with significant between-group differences. Likewise, strength:mass ratio at the upper and lower body level significantly increased (by 5.1% and 9.3%, respectively) in the EXE group and decreased (by 8.5% and 11.4%, respectively) in the CON group, with significant between-group differences. No baseline to end-of-study change or between-group difference were observed for muscle CSA and bone:muscle area ratio. Conversely, muscle density significantly increased by 3.7% in the EXE group and decreased by 3.3% in the

CON group, whereas opposite changes (-10.1% and +24.8%, respectively) were observed for fat:muscle area ratio, with significant between-group differences for both parameters (Table 2).

The SPPB test score and VO_{2max} significantly increased by 6.2% and 24.9%, respectively, in the EXE group and decreased by 5.5% and 3.8%, respectively, in the CON group, with significant between-group differences (Table 2).

3.4. Ancillary outcomes

The level of PA outside the sessions decreased significantly in the CON group (-19.5%), but did not change significantly in the EXE group (-3.05%), with a significant between-group difference (Table 2).

Significant decreases were observed for BMI, waist circumference, HbA_{1c} , total and LDL cholesterol, and systolic BP in the EXE group, whereas total and LDL cholesterol, blood urea nitrogen, creatinine, and albumin:creatinine ratio increased and eGFR decreased significantly in the CON group, resulting in significant between-group differences in BMI, waist circumference, HbA_{1c} , systolic BP, blood urea nitrogen, creatinine, and albumin:creatinine ratio (Supplementary Table 8). Ten-year risk of cardiovascular events increased significantly in both groups, but less in the EXE versus CON group, with a significant between-group difference (Supplementary Table 8).

3.5. Adverse events

No between-group differences were observed in adverse events (Table 3), none of which occurred during the exercise sessions. Though musculo-skeletal disturbances might have been favoured by participation in the training program, the rate of these events was similar between the two groups. Two traumatic fractures occurred among the EXE participants.

4. Discussion

This randomised clinical trial concurrently investigated the effects of exercise on a wide range of non-invasive measures of bone health, body composition, muscle strength, mass and quality, physical performance, and cardiorespiratory fitness in elderly people with type 2 diabetes without osteoporosis. The study results showed that a two-year exercise training program, consisting of supervised gym sessions (including aerobic, muscle strength and power, core stability, balance, and flexibility training) combined with unsupervised home sessions and use of weighted vests, was effective in improving TBS, BMD, and several pQCT-derived measures, suggesting a beneficial effect on bone mass, quality, and strength.

The TBS decreased in the CON group by 0.65% over the two-year follow-up, consistent with previous studies reporting a yearly reduction of ~0.3% [37,38], and increased to approximately the same extent (0.62%) in the EXE group. However, this increase is similar to that reported with antiresorptive treatment [38], but much lower than that observed with osteoanabolic therapies [39,40]. Furthermore, the between-group difference of 0.016 is likely not clinically significant. In fact, this difference is slightly lower than that observed in a cross-sectional analysis of the NHANES 2005-2006 data between older adults with low versus intermediate-high level of moderate-to-vigorous PA [41], but much lower than that between individuals with and without type 2 diabetes reported in previous studies [22-24]. More importantly, the between-group difference in TBS disappeared when values were adjusted for waist circumference or trunk fat mass, which were significantly reduced in the EXE but not CON group. This confirms that measurement of TBS using current algorithms is affected by abdominal fat and suggests that changes in TBS with exercise were not due to changes in bone microarchitecture.

Conversely, BMD at lumbar spine, femoral neck, and total hip decreased by 0.59%, 0.82%, and 0.78%, respectively, in the CON group, and increased by 0.76%, 1.45%, and 1.34%, respectively, in the EXE group, with statistically and clinically significant between-group differences, consistent with previous reports on the effect of exercise training in the general aging population with or at risk for osteoporosis [11-14]. Our findings indicate that the training program resulted in a meaningful improvement in bone mass also in individuals with normal-to-increased BMD such as those with type 2 diabetes, which has important clinical

implications given the higher fracture risk for the same T score. This interpretation is supported by the pQCT data, which suggest a beneficial effect also on bone geometry and strength.

The training program resulted also in significant improvements in muscle strength, physical performance, cardiorespiratory fitness, body composition, and cardiometabolic risk profile. Moreover, muscle strength:mass ratio and muscle density increased, whereas fat:muscle area ratio decreased, indicating improved muscle quality. Conversely, muscle CSA was unchanged, which however is consistent with the concepts that this measure includes not only muscle but also inter and intramuscular fat [42], thus explaining why it is not a good predictor of fracture risk, unlike muscle strength and physical performance [43]. Indeed, the unchanged muscle CSA associated with increased muscle density and decreased fat:muscle area ratio suggests that muscle mass was actually increased in the EXE group. Moreover, though the intervention did not increase the amount of PA performed outside the exercise sessions, it was able to prevent the known age-dependent decline in PA level observed in the CON participants and previously documented by the use of an accelerometer in the control group of the Italian Diabetes and Exercise Study (IDES)₂ [34]. In any case, the overall PA increased in the EXE group considering the amount of PA performed during the supervised gym and unsupervised home sessions.

An important finding is that change in TBS was not independently predicted by changes in aBMD (and vice versa, except for lumbar spine aBMD), but rather by changes in muscle strength and quality, physical performance and cardiorespiratory fitness, which in turn showed no or only weak associations with changes in aBMD. These findings might suggest that the improvements in muscle strength and quality, physical performance, and cardiorespiratory fitness may exert beneficial effects on bone quality more than mass, via mechanisms involving the bidirectional biochemical interaction between bone and muscle through which these two endocrine organs may influence one another independently of mechanical loading [44]. This interpretation is consistent with previous reports showing that muscle strength, but not mass was associated with TBS [45] or pQCT parameters [46], whereas changes in muscle mass, but not strength in response to lifestyle intervention correlated with changes in aBMD [47]. However, a meta-analysis showed concomitant increases in muscle strength and BMD following progressive resistance

training programs in older adults [48]. Moreover, both muscle mass and strength were shown to be associated with BMD in the US general population from the NHANES 1999-2002 [49] and cardiorespiratory fitness was found to be inversely related with BMD in postmenopausal women [50].

Strengths of this study include the focus on individuals with type 2 diabetes without osteoporosis, the randomized design, the type and duration of the intervention consisting of a two-year combined supervised and unsupervised training program and use of weighted vests, and the assessment of a wide range of parameters. However, this study has several limitations. First, non-invasive surrogate measures of bone quality and strength may not reliably reflect geometry and microarchitecture, since TBS values are influenced by the excess abdominal fat characterizing individuals with type 2 diabetes [26]. Second, participation in the gym sessions was suboptimal, though the increases in muscle strength and VO_{2max} were of the same extent of those observed in the IDES, in which ~10-year younger individuals with type 2 diabetes were engaged in a supervised aerobic and resistance training program of one-year duration with a much higher attendance at exercise sessions [20]. This suggests that even a relatively low number of supervised gym sessions was sufficient for ameliorating fitness and bone parameters and that home sessions and use of weighed vests also contributed to obtain these effects. Nevertheless, the effects would probably have been greater with a higher attendance at the supervised exercise sessions. Third, the generalizability of this (or any other) exercise intervention is limited to individuals without conditions limiting or contraindicating exercise or affecting the safety of the intervention. Therefore, implementation in real-world settings of this approach is feasible only in a subset of individuals with type 2 diabetes. Fourth, diet was not considered in data analysis, though patients received dietary prescriptions and adherence to diet was verified at intermediate visits.

In conclusion, a two-year exercise training program combining supervised gym sessions with unsupervised home sessions and use of weighted vests significantly improved a wide range of non-invasive measures of bone health in elderly individuals with type 2 diabetes without osteoporosis. This was associated with amelioration of body composition, muscle strength and quality, physical performance, and

cardiorespiratory fitness. All-together, these effects might result in long-term reduction of fractures in individuals at high fracture risk despite normal-to-increased BMD.

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CRedit authorship contribution statement

Stefano Balducci: Conceptualization - Data curation- Formal analysis- Funding acquisition – Investigation – Methodology – Project administration – Resources – Validation – Writing–review & editing. **Jonida Haxhi:** Conceptualization – Data curation– Formal analysis– Investigation – Methodology – Visualization – Writing–review & editing. **Lorenza Mattia:** Data curation– Investigation – Visualization – Writing–review & editing. **Martina Vitale:** Data curation– Investigation – Visualization – Writing–review & editing. **Luca Pugliese:** Data curation– Investigation – Visualization – Writing–review & editing. **Giuseppe Argento:** Data curation– Investigation – Visualization – Writing–review & editing. **Massimo Sacchetti:** Data curation– Investigation – Methodology – Writing–review & editing. **Giorgio Orlando:** Data curation– Investigation – Methodology – Writing–review & editing. **Lucilla Bollanti:** Data curation– Investigation –Writing–review & editing. **Nicolina Di Biase:** Data curation– Investigation – Writing–review & editing. **Giuseppe Lucisano:** Data curation– Formal analysis – Software – Visualization – Writing–review & editing. **Antonio Nicolucci:** Conceptualization – Data curation– Formal analysis – Software. **Giuseppe Pugliese:** Conceptualization – Data curation– Formal

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: **Stefano Balducci**: lecture fees from Astra-Zeneca, Eli Lilly, Novo Nordisk, and Takeda. **Jonida Haxhi**: lecture fees from Boehringer Ingelheim. **Martina Vitale**: lecture fees from MundiPharma and Novo Nordisk. **Antonio Nicolucci**: consulting fees from AstraZeneca, lecture fees from Eli Lilly, Medtronic, and Novo Nordisk, and grant support from AlfaSigma, Novo Nordisk, Pikdare, Sanofi, Shionogi, SOBI, and Theras. **Giuseppe Pugliese**: consulting fees from Bayer and lecture fees from Boehringer Ingelheim, Eli Lilly, and Novo Nordisk. No other disclosures were reported.

Data availability

All data associated with this study are present in the paper or the Supplementary Material. Deidentified participants' data will be accessible upon reasonable request to the corresponding author via a data sharing agreement.

Nonstandard abbreviations used

BMD = bone mineral density; CON = control; Cort = cortical; DXA = dual-energy X-ray absorptiometry; EXE = exercise; Italian Diabetes and Exercise Study; PA = physical activity; pQCT = peripheral quantitative computed tomography; QUS = quantitative ultrasound; SPPB = Short Physical Performance Battery; SWEET-BONE = the Study to Weigh the Effect of Exercise Training on BONE quality and strength in type 2 diabetes; TBS = trabecular bone score; Trab = trabecular; VO_{2max} = maximal oxygen uptake.

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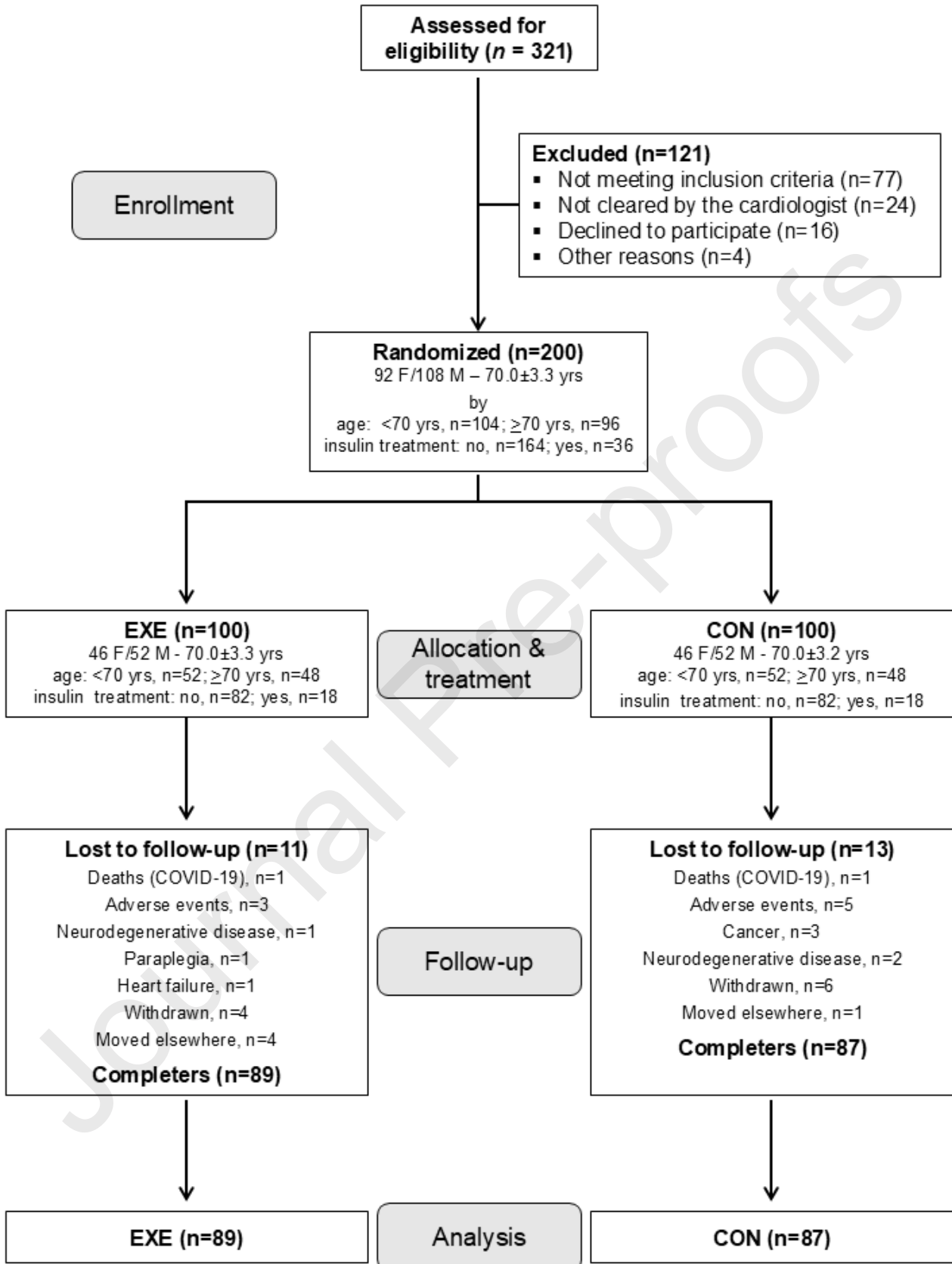


Figure 1. Study flow chart. Flow of participants through the study. EXE = exercise; CON = cont.

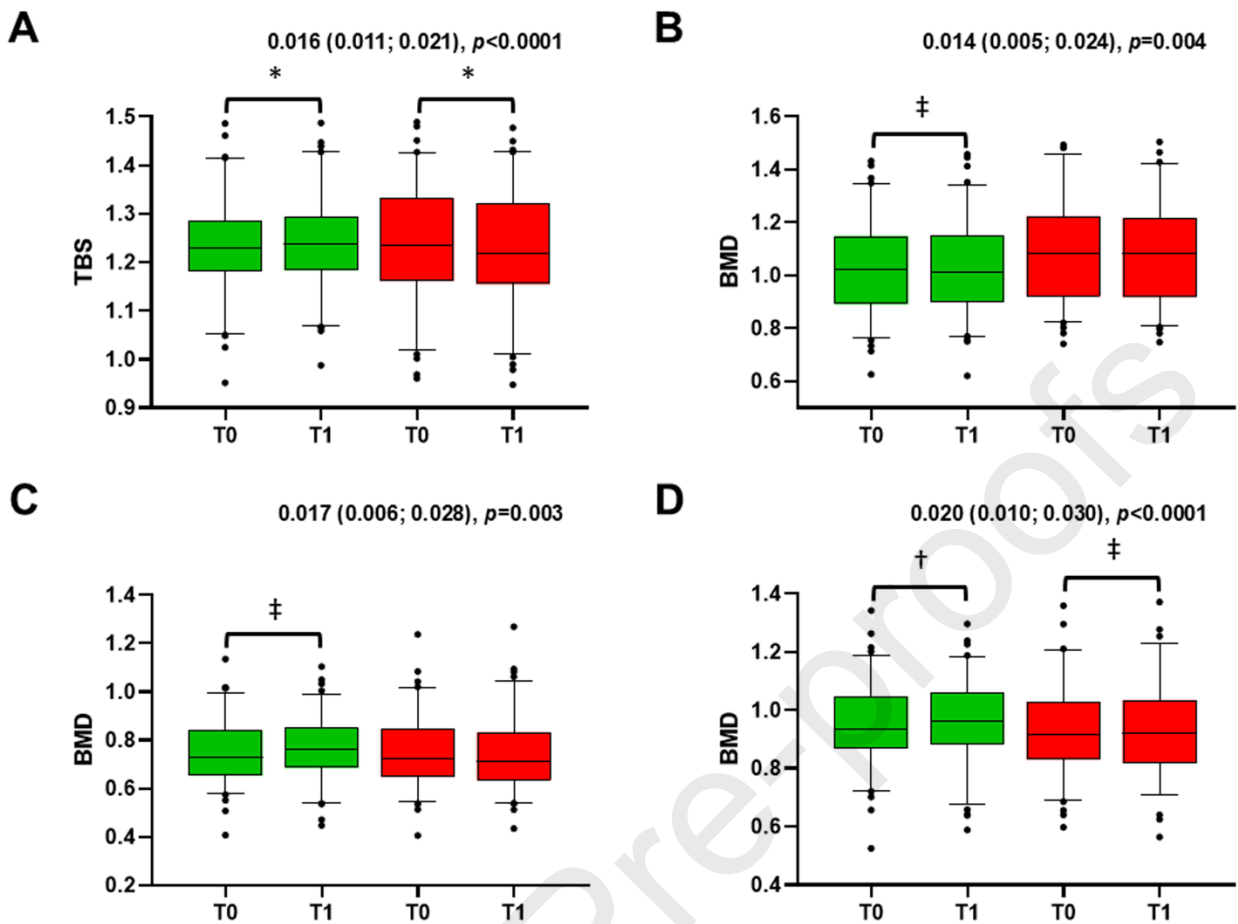


Figure 2. Effect of intervention on TBS by study arm and individual participant. Boxplots of baseline (T0) and end-of-study (T1) TBS (A), and lumbar spine (B), femoral neck (C), and total hip (D) BMD values in the EXE (green) and CON (red) group with median (middle line of the boxes), 25th and 75th percentiles (ends of the boxes), 95% CI (whiskers), and outliers (circles) for each group (* $p < 0.0001$, † $p < 0.01$ or ‡ $p < 0.05$ T1 vs T0); between-group mean difference (95% CI) and p value are shown. TBS = trabecular bone score; BMD = bone mineral density; EXE = exercise; CON = control.

Table 1. Baseline demographic and clinical features. Baseline demographic and clinical features of the EXE vs CON participants.

	EXE	CON	p
N	100	100	
Age, years	70.0±3.3	70.0±3.2	0.880
Sex, n			NA
Females	46	46	
Males	54	54	
Marital status, n			0.212
Single	0	2	
Married/cohabitant	87	80	

Widowed/separated/divorced	13	18	
Cohabitation, n			0.332
Alone	10	15	
With parents	0	1	
With spouse/offsprings	90	84	
Schooling, n			0.445
Primary school	26	25	
Intermediate school	42	47	
Secondary school	17	20	
Degree	15	8	
Occupation, n			0.989
Employed	5	5	
Retired	58	57	
Housewife	37	38	
Smoking, n			0.501
Never	57	50	
Former	31	33	
Current	12	17	
Diabetes duration, years	13.4±7.7	14.6±8.1	0.287
Retinopathy, n	19	19	1.000
Nephropathy, n	37	44	0.313
Neuropathy, n	14	15	0.841
CVD, n	19	20	0.858
BMI, kg·m ⁻²	29.3±5.0	30.1±4.8	0.245
Waist circumference, cm	101.2±12.7	103.9±12.4	0.135
HbA _{1c} , %	6.9±1.0	7.0±1.2	0.688
(mmol/mol)	(51.9±10.9)	(53.0±13.1)	
Triglycerides, mg·dl ⁻¹	137.6±62.3	157.4±202.7	0.353
Total cholesterol, mg·dl ⁻¹	175.0±37.2	172.2±45.9	0.626
HDL cholesterol, mg·dl ⁻¹	47.4±10.2	48.6±10.5	0.436
LDL cholesterol, mg·dl ⁻¹	102.1±36.7	97.1±40.6	0.356
Systolic BP, mmHg	135.8±14.9	135.7±16.3	0.942
Diastolic BP, mmHg	75.1±7.9	77.2±8.4	0.069
BUN, mg·dl ⁻¹	39.9±12.3	42.1±16.9	0.315
Creatinine, mg·dl ⁻¹	0.99±0.24	1.00±0.25	0.801
eGFR, mg·ml ⁻¹ ·1.73 m ⁻²	70.5±15.5	69.8±17.1	0.774
ACR, mg·g ⁻¹	18.4±26.2	22.7±26.7	0.250
10-year CV risk, %	14.5±3.4	14.8±3.6	0.572

EXE = exercise; CON = control; CVD = cardiovascular disease; BUN = blood urea nitrogen; ACR = albumin:creatinine ratio; CV = cardiovascular.

Table 2. Effect of intervention on bone, muscle, and physical performance, activity, and fitness parameters. Baseline (T0) and end-of-study (T1) values of bone quality and mass, body composition, muscle mass, quality and strength, physical performance, physical activity, and cardiorespiratory fitness in the EXE and CON group and between-group differences.

Variables	EXE			CON			EXE vs CON	
	T0	T1	<i>p</i>	T0	T1	<i>p</i>	Mean diff (95% CI)	<i>p</i>
<i>Bone quality and mass</i>								
TBS	1.236±0.102	1.243±0.099	<0.0001	1.239±0.117	1.231±0.118	<0.0001	0.016 (0.011; 0.021)	<0.0001
adjusted for waist circumference	1.240±0.039	1.244±0.031	0.024	1.232±0.037	1.20±0.031	0.243	0.007 (0.001; 0.012)	0.014
adjusted for trunk fat mass	1.239±0.044	1.243±0.038	0.053	1.231±0.049	1.229±0.043	0.259	0.006 (0.000; 0.011)	0.036
Lumbar spine aBMD, g·cm⁻²	1.030±0.175	1.037±0.176	0.017	1.088±0.201	1.082±0.200	0.078	0.014 (0.005; 0.024)	0.004
Femoral neck aBMD, g·cm⁻²	0.751±0.132	0.762±0.131	0.013	0.748±0.147	0.742±0.153	0.111	0.017 (0.006; 0.028)	0.003
Total hip aBMD, g·cm⁻²	0.946±0.146	0.959±0.148	0.002	0.941±0.162	0.934±0.165	0.018	0.020 (0.010; 0.030)	<0.0001
<i>Muscle mass, quality, and strength</i>								
Muscle CSA, cm²	74.1±17.6	74.1±17.2	0.992	75.5±19.1	75.2±18.2	0.856	0.25 (-3.38; 3.88)	0.893
Muscle density, mg·cm⁻³	71.6±4.8	74.3±6.2	<0.0001	70.4±4.1	68.1±5.9	0.001	4.92 (3.08; 6.76)	<0.0001
Fat:muscle area ratio, %	28.3±21.8	25.5±20.7	<0.0001	23.5±22.5	29.3±25.7	<0.0001	-8.67 (-11.70; -5.64)	<0.0001
Bone:muscle area ratio, %	4.94±1.14	6.06±10.12	0.338	5.00±1.33	4.74±1.11	0.072	1.38 (-1.25; 4.01)	0.300
Upper body muscle strength, Nm	201.9±73.9	208.9±68.9	0.015	197.1±71.6	176.8±69.9	<0.0001	27.30 (19.75; 34.86)	<0.0001
Upper body strength:mass ratio, Nm/kg	41.3±11.9	43.4±11.1	0.002	39.0±11.0	35.7±10.3	<0.0001	5.69 (3.83; 6.96)	<0.0001
Lower body muscle strength, Nm	121.7±43.3	132.1±44.7	<0.0001	123.7±47.5	108.2±40.7	<0.0001	25.97 (19.38; 32.57)	<0.0001
Lower body strength:mass ratio, Nm/kg	8.46±2.48	9.25±2.63	<0.0001	8.42±2.49	7.46±2.15	<0.0001	1.75 (1.30; 2.19)	<0.0001
<i>Physical performance, activity and fitness</i>								
SPPB test score	10.7±1.4	11.4±1.0	<0.0001	10.4±1.6	9.9±2.0	<0.0001	1.24 (0.87; 1.62)	<0.0001
PASE score	129.7±46.3	125.8±35.4	0.429	119.3±48.6	96.0±30.2	<0.0001	19.35 (7.30; 31.40)	0.002
VO_{2max}, ml·min⁻¹·kg⁻¹	19.7±5.5	24.6±5.8	<0.0001	19.9±6.1	19.2±5.7	0.017	5.66 (4.67; 6.65)	<0.0001

EXE = exercise; CON = control; TBS = trabecular bone score; aBMD = areal bone mineral density; CSA = cross-sectional area; SPPB = Short Physical Performance Battery; PASE = Physical Activity Scale for the Elderly; VO_{2max} = maximal oxygen uptake.

Table 3. Adverse events. Adverse events in the EXE vs CON participants.

	EXE	CON	<i>p</i>
Total	20	25	0.397
Cancer	1	5	0.212
Lung cancer	1		
Rectal cancer		1	
Prostate cancer		2	
Uterine		1	
Chronic myeloid leukemia		1	
Cardiovascular	3	6	0.498
Myocardial infarction with revascularization	1	1	
Revascularization only		1	
Atrial fibrillation		2	
Heart failure	1	1	
TIA	1	1	
Neuropsychiatric	5	4	1.000
Neurodegenerative disease	2	3	
Paraplegia	1		
Depression	2	1	
Musculo-skeletal	6	4	0.748
Herniated disk	2		
Rotator cuff lesion	1	1	
Fracture	2*		
Ankle sprain	1		
Hip prosthesis		1	
Knee prosthesis		1	
Knee pain		1	
Infection	5	4	1.000
Pneumonia		1	
COVID-19	5 (1 death)	3 (1 death)	
Other	0	2	0.497
Diabetic ketoacidosis		1	
Extensive burn		1	

EXE = exercise; CON = control; TIA = transient ischemic attack. * Traumatic fractures, caused by a fall from a ladder (distal radius) and a car accident (leg), respectively.

Declaration of interest statement

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Stefano Balducci: lecture fees from Astra-Zeneca, Eli Lilly, Novo Nordisk, and Takeda.

Jonida Haxhi: lecture fees from Boehringer Ingelheim.

Martina Vitale: lecture fees from MundiPharma and Novo Nordisk.

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