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Research Article

Efficacy of Physical Activity and Exercise added to Pharmaceutic Therapy with Denosumab, Romosozumab, Abaloparatide, or Teriparatide in Patients with Osteopenia

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Abstract

The present systematic review determined the effects of physical activity/exercise added to Denosumab, Romosozumab, Abaloparatide or Teriparatide-therapy on bone strength and fall incidence in middle-aged and older people with osteopenia/osteoporosis. A systematic literature search of five electronic databases and two registers (up to 30/05/2023) without language restrictions included studies with (a) postmenopausal women and men ≥45 years, with low bone mass that compared study arms with (b) combined interventions of physical activity/exercise and Denosumab or Romosozumab or Abaloparatide or Teriparatide versus (c) isolated pharmaceutical therapy on (d) Bone Mineral Density (BMD) and prospective fall and/or fracture events (e) applying a randomized controlled study design. Finally only one study that compared the effect of Teriparatide and whole-body vibration versus isolated Teriparatide therapy on bone strength parameters was eligible. This trial reported a significant effect of combined vs. isolated therapy for lumbar spine BMD however not for total hip-, radius- and tibia-BMD, bone microarchitecture or bone turnover biomarkers. Thus, reviewing the literature there is rather limited data on additive effects of exercise on novel pharmaceutic therapy for osteoporosis. Nethertheless, considering age, bone status and physical function of most people under corresponding therapies might already justify the recommendation of exercise programs dedicated to reduce number and impact of falls and fall impact that complement the effects of pharmacological therapy on bone strength. Due to the enormous socioeconomic importance of osteoporosis-induced low trauma fractures more studies should focus on the dissection of the impact of individualized exercise programs when combined with medical treatment.

Keywords: Exercise; Denosumab; Romosozumab; Teriparatide; Bone Mineral Density.

Introduction

Osteoporosis and corresponding low-trauma fractures are increasingly critical problems of the health care systems in our over-aged societies [1,2]. Pharmaceutical therapy is an effective cornerstone in the prevention and therapy of osteoporosis. More recent pharmaceutics i.e. Denosumab, Teriparatid, Abaloparatide or Romosozumab also overcome the limitations of bisphosphonates [3] as the most frequently applied osteoporosis therapy to date[4]. With respect to Bone Mineral Density (BMD) changes, "exercise" was on average less effective [5] compared to the pronounced increases in BMD after Denosumab, Teriparatide, Abaloparatide or Romosozumab treatment. However, a combination of pharmaceutical agents with anabolic potential (there is some evidence for anabolic effects of the antiresorptive agent Denosumab on cortical bone[6-8]. and mechanical stimuli applied by exercise might trigger additive effects on bone strength and particularly aid fracture prevention [9]. Corresponding additive effects might apply to falls. As there are some data reported on intrinsic effects of advanced osteoporosis treatment on falls reduction and amelioration of sarcopenia measures during treatment with Denosumab[10], the combination of exercise and pharmaceutical therapy might augment the pronounced fall preventive effect of exercise even further [11], and might thus be a promising strategy for reducing fragility fractures. Accordingly, the aim of this review was to provide evidence for the efficacy of physical activity and exercise added to pharmaceutical therapy with Denosumab, Romosozumab, Abaloparatide or Teriparatide on BMD and fall incidence in middle-aged and older people with osteopenia/osteoporosis, compared to isolated pharmaceutical therapy.

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Materials and Methods

This systematic review was reported according to the PRISMA 2020 statement (Page et al., 2021). The present systematic review was registered under PROSPERO ID: CRD42023440581. Since finally only one eligible study could be identified, we limited the methodology section to the systematic review approach [Figure 1].

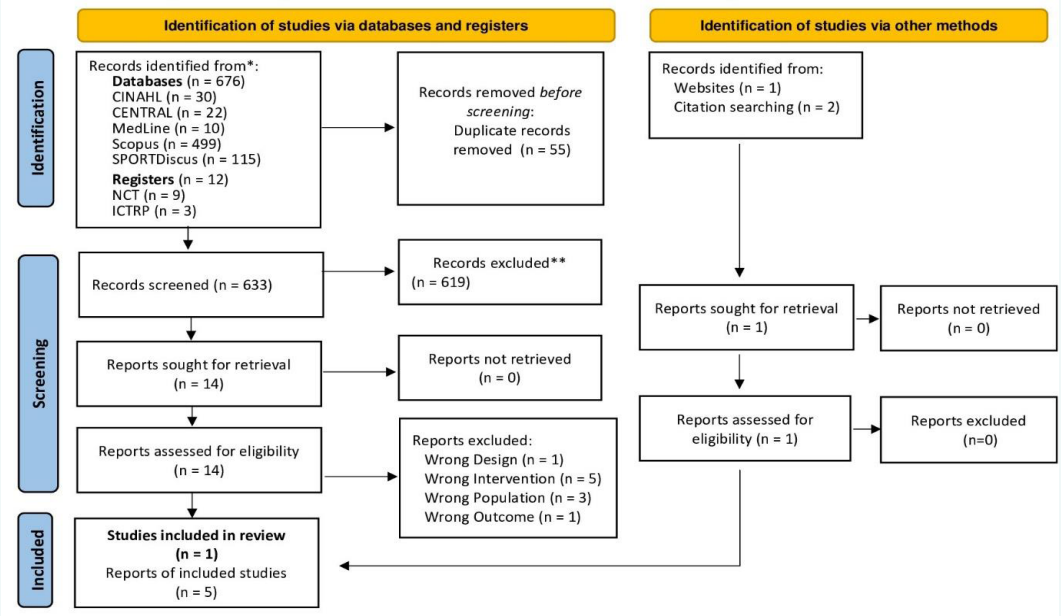

Figure 1 Prisma 2020 flow diagram for new systematic reviews, which included searches of databases, registers and other sources.

Information Sources and search strategy

Literature search strategies applied medical subject headings and key words related to participants, intervention, medication, and outcome. Study reports from the five electronic databases (Medline [PubMed], The Cochrane Central Register of Controlled Trials [CENTRAL], Cumulative Index to Nursing & Allied Health [CINAHL via Ebsco Host], SPORTDiscus (via Ebsco Host) and The Physiotherapy Evidence Database [PEDro]) published up to 16th April 2023 were searched without language restrictions. The International Clinical Trials Registry Platform (ICTRP) and clinicaltrials.gov was also screened for unpublished and ongoing trials. Reference lists of relevant reviews and eligible studies were also searched for additional articles. A standardized search protocol was developed for each database; an example of the search strategy for the MedLine medical database was given in supplement 1.

Eligibility Criteria

Eligibility criteria were specified following the PICOS scheme. Population: Studies that exclusively focus on (a) middle-aged and older human participants (i.e. postmenopausal women or men ≥45 years) with (b) low bone mass (i.e. Osteopenia, Osteoporosis) and (c) without diseases or conditions with impact on bone metabolism. Studies with mixed premenopausal/postmenopausal or healthy/osteopenic cohorts without separate BMD analysis were excluded. Intervention: Study arms with all kinds of physical activity or exercise in combination with either Denosumab or Romosozumab or Abaloparatid or Teriparatide therapy. Clinical trials that included participants with mixed pharmaceutic therapies (i.e. Denosumab/Bisphosphonates [12,13], or other pharmaceutical therapies with impact on bone metabolism (e.g. bisphosphonate, glucocorticoids) were also excluded. This does not refer to vitamin-D, calcium and protein supplementation; these were included in the analysis. Comparators: Study arms that received the identical, albeit isolated pharmaceutical therapy. Outcomes: Bone Mineral Density (BMD) of the lumbar spine (LS) or/and proximal femur as assessed by dual-energy X-ray absorptiometry (DXA), dual-photon absorptiometry (DPA) or quantitative computed tomography (QCT) and prospective fall and/or fracture events reported as primary, secondary, experimental or adverse (e.g. falls) outcome. Studies: Only randomized controlled trials (RCTs) were included. Trials that reported follow-up results of completed exercise interventions, duplicate studies, preliminary data from later published study, editorials, conference abstracts and letters were excluded.

Data management

Search results were downloaded and imported to Endnote. Duplicates were identified and excluded based on the method proposed by Bramer et al.[14]. Before the formal screening process, a pilot was conducted with the first 50 titles and abstracts based on manuscript titles. Title, abstract and full-text screening was conducted using Endnote. Data extraction was applied using Microsoft Excel.

Selection Process

Two independent reviewers screened the article titles and abstracts yielded by the search against the eligibility criteria. We obtained full articles for all titles that appeared to meet the inclusion criteria or where there was any uncertainty. If necessary, the corresponding authors were contacted twice by email, and the study was excluded if no response was forthcoming.

Data collection process

One reviewer extracted the information of the eligible studies, another reviewer checked the corresponding results. A pre-piloted Excel spreadsheet was used for data extraction. If more information was needed, we intended to contact the authors twice by e-mail (n=0).

Quality Assessment

Two reviewers evaluated the methodological quality of the trial utilizing the PEDro (Physiotherapy Evidence Database scale risk of bias tool) (Sherrington et al., 2000) and TESTEX (Smart et al., 2015) score, both specifically dedicated to physiotherapy (PEDro) and exercise (TESTEX) trials.

Data synthesis

Results are displayed for all studies in tables showing publication and study characteristics, participant and cohort characteristics and exercise

and pharmaceutic therapy characteristics of the study. One reviewer extracted the information of the eligible studies, another reviewer checked the corresponding results.

Results

Study characteristics

Despite our systematic search identified only one eligible study [15]. The "PArathyroid hormone (1–34) and Whole-Body Vibration (WBV) exercise in the treatment of postmenopausal OSteoporosis (PAVOS) project is a 12-month multicenter RCT with two parallel study groups. PAVOS compared the effects of Teriparatide and WBV versus Teriparatide alone on areal BMD at the LS and the total hip region of interest (ROI) volumetric BMD and bone microarchitecture (cortical thickness, bone volume/total volume, trabecular number and thickness) at the radius and tibia [16], and bone turnover markers i.e. c-terminal telopeptide (CTX) and total procollagen type 1 amino-terminal propeptide (P1NP) [16]. The study included predominately sedentary postmenopausal women ≥50 years with one vertebral fracture and T-Score <-3 SD at LS or total hip or at least 2 vertebral fractures without T-Score based criteria were included [Table 1]. Methodological quality of the study according to the PEDro [17] and TESTEX [18], score can be classified as moderate-high (PEDro: 7 of 10, TESTEX: 12 of 15 score points) [19] [Table 1].

All study participants received subcutaneous Teriparatide treatment (20 µg/d) from study start and were advised to take cholecalciferol and calcium [Table 1]. Previous bisphosphonate use was reported for 29% of the participants of the Teriparatide+WBV and 55% in the Teriparatide only group.

Table 2 displays the exercise protocol of the study. During the 12 months of WBV interventions (Power Plate My5, UK) three home training sessions of 12 min were applied using a frequency of 30 Hz and an amplitude of 1 mm with bent knee and without voluntary movements during WBV.

Study outcomes

After 12 months of intervention the authors reported significant effects for the combined Teriparatide+WBV (8.90%) versus the isolated Teriparatide study arm (6.65%) for areal BMD-LS, however not for aBMD-total hip (-0.18% vs. 0.81%), volumetric BMD at the radius or tibia-ROI, parameters related to bone microarchitecture and CTX or P1NP [16]. A secondary analysis of the PAVOS study [15], albeit with lower statistical power displayed inconsistent effects on functional parameters related to fall risk. Applying the Short Physical Performance Battery (SPPB), the Timed-Up-and-Go test (TUG), leg extensor power and hand grip strength, a significant superiority of the combined Teriparatide and exercise intervention vs. Teriparatide alone was reported for the chair rise test only.

Discussion

In the present work we clearly failed to answer our research question on "efficacy of physical activity and exercise added to pharmaceutical therapy with Denosumab, Romosozumab, Abaloparatide or Teriparatide on BMD and fall incidence in middle-aged and older people with osteopenia/osteoporosis, compared to isolated pharmaceutical therapy". As described above, there is a conspicuous lack of research into the combined effect of advanced osteoporosis pharmaceutics and exercise on

Table 1: Study, participant and pharmaceutic therapy characteristics of the included studies

Author, year	Study arm	Number of participant (gender) [n]	Health status	Age [years]	BMI [kg/m²]	BMD-LS baseline [g/cm³]	BMD- Hip baseline [g/cm³]	Drop-out [%]	Methodo-logical quality
Jepsen et al. 2019	Teriparatide (PTH 1-34), 20 microgram/day subcutaneous	18	Osteoporosis: T-Score < -3 SD or ≥2 vertebral Fractures	69 ± 8	24.1 ± 4.3	0.729 ± 0.137	0.615 ± 0.106	5,7	PEDro: 7
	PTH (1-34) + Exercise (WBV)	17		69 ± 5	24.5 ± 4.1	0.674 ± 0.103	0.618 ± 0.096		TESTEX: 12

Table 2: Exercise protocol of the included studies

First author, year	Pre-study exercise status	Design, Duration Supervision	Main type(s) of exercise	Exercise composition per session	Progression of Intensity	Attendancerate
Jepsen et al. 2019	n.g.	RCT, 12months Consistently-NS	Whole body vibration	3x 12 min/week multidimensional (3 planes) WBV on "Power plate My5" platform with 1 min of vibration and 1 min of rest (duty cycle 1-1) with 30 Hz. Amplitude: 1 mm, peak acceleration: 35.53 ms-2 (3.6 g)	yes[a]	≥75%b

fracture risk factors in people with osteopenia/osteoporosis. Considering that the application of newer antiresorptive (i.e. Denosumab) and particularly (bone-)anabolic agents in people with advanced osteoporosis will increase considerably [20], it is more than unfortunate that only one eligible study was identified. Furthermore, this applied WBV, an exercise technology hardly representative for conventional, voluntary exercise.

In contrast, several animal studies provided robust evidence for additive effects particularly for Teriparatide (…and to a lesser extent for Romosozumab und Blosozumab [21], and mechanical loading [22-25], on bone parameters. In a preclinical setting, Ronney et al.[26], observed different Teriparatide-induced alterations of endocortical and periosteal bone formation parameters in the tensile versus compressive regions of the femoral neck after mechanical loading. Applying a mechnobiological model, Martinez-Reina et al. [27], predicted reduced Denosumab-induced BMD changes after inactivity ("mechanical disuse"), a finding that further emphasised the combined application of exercise and Denosumab. In this context there is some evidence that the combination of exercise added to pharmaceutical interventions shared simlar underlying mechanisms but different intracellular pathways compared with the combination of different pharmaceutic agents [28].

One may argue that our search strategy that focused on middle aged and older participants with osteopenia and/or osteoporosis contributed to the low number of eligible studies. We agree in so far as exercise studies that specifically included osteopenic/oste-oporotic participants are rare [5]. However, since pharmaceutic therapy with Denosumab, Romosozumab, Abaloparatid or Teriparatide therapy is restricted to osteopenic/osteoporotic conditions, we doubt that this eligibility criterion affected the reliability and completeness of our literature review. Nevertheless, we had to exclude one study that compared the effect of WBV+Teriparatide vs. Teriparatide alone on BMD [29], in people with spinal cord injury due to our age specification. We also refrained from a joint analysis of antiresorptive pharmaceutic agents (e.g. bisphosphonates and Denosumab; [13],without separate analysis due to differences in their potential to increase bone and their mechanism of action [30].

The present systematic review on additive effects of physical activity/ exercise on pharmacologic therapy with Denosumab, Romosozumab, Abaloparatid or Teriparatide was conducted within the framework of the (German) National guideline on exercise and fracture prevention. Apart from systematic reviews and meta-analyses in the area of exercise and BMD [5,31-36], this guideline sets out to address additive effects of exercise and hormone replacement therapy [37], bisphosphonate therapy [38], glucocorticoids [39], or vitamin-D supplementation [40], on BMD and falls. The increasing relevance of advanced antiresorptive (i.e. Denosumab) and particularly anabolic agents (Romosozumab, Abaloparatid or Teriparatide) for bone strength [20], encouraged our intention to focus on the present issue not addressed so far. Since we felt that only few studies might focus on this research question, we opted to summarize several advanced pharmaceutic agents within a joint search of the literature.

In summary, due to a conspicuous lack of studies, the evidence for recommending a combination of exercise with advanced pharmaceutical therapy with Denosumab, Romosozumab, Abaloparatid or Teriparatide to further augment the already pronounced BMD increases in human adults with low bone mass [41], is very limited. And although some studies reported fall-reducing effects of pharmaceutical agents dedicated to bone strength [10,42,43], definite evidence is still scarce –, or relevant studies have yet to been carried out [44]. In parallel, apart from grip strength increases after Denosumab therapy [45], and increases in leg extension power after Teriparatide therapy [15], positive evidence for favorable effects of advanced pharmaceutical agents on functional parameters related to falls is low [44]. In contrast, many systematic reviews and meta-analyses [11,46], reported a pronounced effect of dedicated exercise on fall number and impact. Having said this, along with the increased fall risk in the usually older cohorts predominately treated with advanced pharmaceutical agents, a better approach is probably to align the power of bone strengthening medications with the primary training aim of the exercise protocols so as to reduce the number and severity of falls[11]. Moreover, the fact that exercise protocols addressing falls were less intense, more bone friendly and customizable compared to bone strengthening, such protocols [47], might encourage older people to start and/or maintain exercise along with their pharmacological therapy.

Conclusions

Due to the lack of eligible studies, we were unable to contribute to increasing the evidence on optimum fracture reducing therapy. Nevertheless the present work at least (a) indicates the research gap in this increasingly important area and thus might encourage increased research activity and (b) points out that further systematic reviews on this issue planned for the nearst future might also fail as our search in study registries gave no indication that new studies with combined exercise-Denosumab/Romosozumab/ Abaloparatide/Teriparatide therapy with BMD or falls as an outome have been identified.

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Conflict of Interest

The authors declare that the research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

Data Availability

The data that support the findings of this study are available from the corresponding author (WK), upon reasonable request.

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