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Review

Exercise effects on glucocorticoid-induced bone loss in adults: a systematic review and meta-analysis

Stephanie Kast[1], Franz Jakob[2], Matthias Kohl[3], Simon von Stengel[1],
Katharina Kerschan-Schindl[4], Uwe Lange [5], Friederike Thomasius[6], Wolfgang Kemmler [1,7,*]

[1]Institute of Radiology, FAU-Erlangen-Nürnberg, University Hospital Erlangen, Erlangen, Germany
[2]Bernhard-Heine-Centrum für Bewegungsforschung, University of Würzburg, Würzburg, Germany
[3]Department of Medical and Life Sciences, University of Furtwangen, Schwenningen, Germany
[4]Department of Physical Medicine, Rehabilitation and Occupational Medicine, Vienna, Austria
[5]Department of Rheumatology, Osteology und Physical Medicine, Justus-Liebig-University Gießen, Gießen, Germany
[6]Frankfurt Center of Bone Health, Frankfurt, Germany
[7]Institute of Medical Physics, Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany

*Correspondence to: Wolfgang Kemmler, Institute of Medical Physics, Friedrich-Alexander-Universität Erlangen-Nürnberg, Henkestrasse 91, 91052 Erlangen, Germany. E-mail: wolfgang.kemmler@imp.uni-erlangen.de

Abstract

Objectives: Due to their pronounced anti-inflammatory and immunosuppressive effects, glucocorticoids (GCs) are widely used in inflammatory conditions and organ transplants. Unfortunately, GC-induced osteoporosis is one of the most common causes of secondary osteoporosis. The aim of the present systematic review and meta-analysis was to determine the effect of exercise added to GC therapy on BMD at the lumbar spine or femoral neck in people on GC therapy.

Methods: A systematic literature search of five electronic databases included controlled trials with a duration of >6 months and at least two study arms [glucocorticoids (GCs) and GCs and exercise (GC + EX)] were conducted up to 20 September 2022. Studies involving other pharmaceutical therapies with relevant effects on bone metabolism were excluded. We applied the inverse heterogeneity model. Outcome measures were standardized mean differences (SMDs) with 95% CIs for BMD changes at the lumbar spine (LS) and femoral neck (FN).

Results: We identified three eligible trials with a total of 62 participants. In summary, the GC + EX intervention indicated statistically significantly higher SMDs for LS-BMD [SMD 1.50 (95% CI 0.23, 2.77)] but not for FN-BMD [0.64 (95% CI −0.89, 2.17)] compared with GC treatment alone. We observed substantial heterogeneity (LS-BMD $I^2 = 71\%$, FN-BMD $I^2 = 78\%$) between the study results.

Conclusion: Although more well-designed exercise studies are needed to address the issue of exercise effects on GC-induced osteoporosis (GIOP) in more detail, upcoming guidelines should pay more attention to the aspect of exercise for bone strengthening in GIOP.

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Lay Summary

What does this mean for patients?

Based on our research, we suggest that patients with glucocorticoid (GC)-induced osteoporosis should participate in regular exercise programs for osteoporosis and fracture reduction. This not only helps to prevent fall-related fractures, but also increases bone mineral density, particularly at the lumbar spine and proximal femur, which are skeletal sites very prone to fragility fractures. Nevertheless, more well-designed exercise trials are needed to address the issue of exercise effects on GC-induced osteoporosis in more detail and to look at different groups of people on GC therapy.

Key messages

- Exercise added to glucocorticoid therapy demonstrated significant effects on BMD at the lumbar spine.
- This finding should be verified by dedicated randomized controlled trials.

Introduction

Glucocorticoids (GCs), with their anti-inflammatory and immunosuppressive effects, are widely used for the treatment of acute and chronic inflammatory conditions or for preventing rejection after organ transplants [1]. Of European postmenopausal women, 2.7% are currently taking GCs (cortisone/ prednisone) [2]. However, GC-induced osteoporosis (GIOP) is one of the most common causes of secondary osteoporosis [3]. GC-induced bone loss is most prominent in trabecular bone. A trabecular bone loss of 8% at the lumbar spine (LS) was reported for the initial 5 months of GC therapy; however, after discontinuation of the treatment, this bone loss seemed to be (partially) reversible [4]. Nevertheless, vertebral fractures were observed in ≈37% of women under long-term (i.e. ≥3 months) GC administration, with >14% of the patients having two or more asymptomatic vertebral fractures [5]. Considering the dose-dependent effect of GC on bone, the relative risks (RRs) increase to a statistically significant 1.36 for non-vertebral and 2.59 for vertebral fractures for doses of 2.5–7.5 mg/day prednisolone equivalent, while doses of ≥7.5 mg/day double the adjusted relative risk for vertebral fractures (RR 5.18) [6, 7]. A number of antiresorptive and bone anabolic pharmaceutic agents (e.g. alendronate/risedronate/zoledronate, denosumab, teriparatide) were recommended for prevention [1] and therapy of GIOP [3, 8]. In addition, the general recommendations for vitamin D and calcium supplements apply [3, 8, 9]. However, many people are looking for non-pharmaceutical options to prevent GC-induced bone loss.

In general, dedicated physical exercise is a recognized agent for increasing bone strength [10] and preventing low-trauma fractures [11]. Nevertheless, although physical exercise was recommended for preventing fall-related fractures, none of the recent recommendations [1, 3, 12] on prevention and treatment of GIOP refer to exercise as an agent for maintaining or increasing BMD. Considering the few exercise trials with their limited statistical power to address this issue, this reticence is understandable. Thus, in order to determine the effect of exercise on bone during GIOP, the aim of the present systematic review and meta-analysis is to summarize the existing literature and to quantify the exercise effect on BMD at the LS and femoral neck (FN) in cohorts undergoing GC therapy.

Methods

The literature search for the present systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement and was registered in the International Prospective Register of Systematic Reviews [13] (PROSPERO; CRD42022308155).

Studies from five electronic databases (PubMed/ MEDLINE, Scopus, Web of Science, Cochrane and CINAHL) published up to 31 January 2022, with an update on 20 September 2022, were used for this review without language restrictions. A standard search protocol was developed using a standardized vocabulary.

Synonyms, truncations and subject headings (MESH terms for MEDLINE) were used to sensitize the following search query: ('osteoporosis' or 'osteopenia' or 'bone mass' or 'bone turnover' or 'bone mineral content' or 'bone mineral density' or 'BMD' or 'BMC' or 'bone density' or 'bone loss' or 'bone resorption' or 'bone strength' or 'demineralized bone' or 'bone defect') AND ('exercise' or 'training' or 'sports' or 'physical activity' or 'physical fitness' or 'weight bearing' or 'weight lifting') AND ('glucocorticoids' or 'corticosteroid' or 'steroid' or 'prednisolone' or 'prednisone' or 'cortison' or 'corticosteron').

The reference lists of the identified studies were reviewed and a manual search was performed in Google Scholar to identify additional relevant articles. To exclude duplicate publications, author names, title, abstract and date of publication were checked by the same reviewer (S.K.).

Inclusion and exclusion criteria

Based on our research question ('In people with GOIP, what is the effect of exercise added to GC therapy compared with isolated GC therapy on BMD at the LS and hip use in controlled trials'), we considered studies/study arms with the following inclusion criteria: studies with at least one exercise group *vs* a control group without additional physical training, both receiving the same GC treatment; studies that determined areal BMD or bone mineral content (BMC) of the LS and/or FN at baseline and end of the study as determined by DXA or DPA; studies with an intervention duration ≥6 months and randomized and non-randomized controlled trials.

Human studies with pharmaceutical agents other than GCs with a relevant influence on bone metabolism, cancer patients, all kinds of intense physical activity or exercise prior to the exercise intervention and participants exposed to weightlessness in space or permanent bed rest were excluded. Review articles, case reports, editorials, conference abstracts and letters were also excluded.

Data extraction

Two reviewers (S.K. and W.K.) independently evaluated full-text articles and extracted data from all eligible publications. An extraction form was used to sample the relevant data of the publications, including publication characteristics (e.g. author's name, year of publication, country); study details (e.g. study design, sample size, dropout rate); participant characteristics (gender, health status, age, anthropometric data including baseline BMD values; Table 1); pharmacologic therapy characteristics (Table 2), including details on GC therapy, dietary supplements (calcium and vitamin D) and other medications; and exercise training characteristics (pre-intervention training status, monitoring/supervision of exercise, intervention duration, exercise protocol, type of exercise, intensity progression, attendance rate, activity in the non-exercise group) (Table 3).

Study outcomes

The outcome measure was BMD at the LS and/or FN determined by DXA.

Quality assessment

Eligible studies were assessed for risk of bias by two independent reviewers (S.K. and W.K.) using the Physiotherapy Evidence Database (PEDro) Scale Risk of Bias Tool [14] and the Tool for the Assessment of Study Quality and reporting in Exercise (TESTEX) [15], both specifically dedicated to physiotherapy/exercise studies. In case of inconsistencies, a third independent reviewer (S.v.S.) decided.

Table 1. Baseline characteristics of the studies and participants

Author, year	Study arm	Participants, n (gender)	Health status	Age, years, mean (s.d.)	Body height, cm, mean (s.d.)	Body mass, kg, mean (s.d.)	BMD-LS (baseline), g/cm^3, mean (s.d.)	BMD-FN (baseline), g/cm^3, mean (s.d.)	Dropout rate, %
Braith et al., 1996	GC	8 (male)	Heart transplant recipients	56 (6)	173 (9)	85 (11)	0.716 (0.087)	0.921 (0.078)	n.g.
	GC + exercise	8 (male)		56 (6)	173 (5)	78 (8)	0.701 (0.064)	0.972 (0.085)	
Mitchell et al., 2003	Glucocorticoids	8 (female: 1, male 7)	Lung transplant recipients	55 (6)	173 (13)	81 (20)	0.528 (0.180)	–	n.g.
	GC + exercise	8 (female: 2, male 6)		49 (7)	173 (10)	72 (19)	0.543 (0.170)	–	
Westby et al., 2000	GC	16 (female)	RA	56 (11)	164 (7)	63.4 (13.6)	1.004 (0.141)	0.755 (0.055)	7
	GC + exercise	14 (female)		56 (10)	162 (8)	61.7 (10.8)	0.969 (0.118)	0.726 (0.118)	

Table 2. Medication characteristics of the studies

Author, year	GC	Start of pharmaceutic therapy	Calcium	Vitamin D	Other medication
Braith et al., 1996	Progressive reduction from 1000 to 10 mg/day oral methylprednisolone after 20 weeks, in case of acute rejection ($n = 20$) higher doses	During surgery, i.e. 2 months pre-exercise	n.g.	n.g.	n.g.
Mitchell et al., 2003	Progressive reduction from 500 (surgery) to 10–15 mg/day oral methylprednisolone during the intervention	During surgery, i.e. 2 months pre-exercise	n.g.	n.g.	Ciclosporin, azathioprine, details n.g.
Westby et al., 2000	Continuously 2.5–7.5 mg/day prednisone	n.g. (taking continuous low-dose prednisone)	Calcium carbonate 1000 mg/day	400 IU/day	DMARDs, NSAIDs, details n.g.

n.g.: not given.

Data synthesis

Authors were contacted to provide missing data. When no reply was received or data were not available, CI or s.e. were converted to s.d. [16]. Only s.e.% had to be converted to absolute s.d. in the present study. One basically eligible study [17] that addresses our research questions within a subgroup analysis (GC + EX: $n = 3$ vs GC: $n = 12$) was not considered due to a lack of data on absolute changes and variance of the changes (the authors were contacted, but data were no longer available). Due to the small number of studies, we did not perform subgroup analyses.

Statistical analysis

We conducted a meta-analysis using the metafor package [18] that is included in the statistical software R (R Foundation for Statistical Computing, Vienna, Austria) [19]. Effect size values were presented as standardized mean differences (SMDs) in combination with the 95% CI. We applied the inverse heterogeneity model proposed by Doi et al. [20]. Heterogeneity between the studies was checked using I^2 statistics. An I^2 of 0–40% was considered 'low', 30–60% as 'moderate', 50–90% as 'substantial' and 75–100% as 'considerable' heterogeneity [21]. Assessment of small study/publication bias was conducted using funnel plots with trim-and-fill analyses applying the L0 estimator proposed by Duval et al. [22]. Funnel plot asymmetry was further checked using a regression test and their standard errors using the t-test and Kendall's τ statistic for potential publication bias. Additionally, we used Doi plots

and the Luis Furuya–Kanamori index (LFK index) [23] to check for asymmetry. LFK values within ±1 were considered negligible, while values ≥±1–±2 were considered as showing minor asymmetry. Values >±2 indicate major asymmetry. P-values <0.05 were considered significant for all the tests. SMD values of 0.2, 0.5 and 0.8 were considered as small, medium and large effects [24].

Results

Study selection

Fig. 1 illustrates the process of the study. After removing 283 duplicates, 1180 articles were screened based on title and abstract. The full texts of 11 potentially relevant articles were screened and finally a total of three articles [26–28] from two research groups were included in this systematic review and meta-analysis.

Study and participant characteristics

The three studies included in this systematic review and meta-analysis comprise three isolated GC groups and three combined GC and exercise (GC + EX) groups (Table 1). All the studies were randomized controlled trials. The pooled number of participants was 62 (GC: 32, GC + EX: 30) and the sample sizes in individual studies ranged from 8 to 16 participants per group (Table 1). One study each included only women [28] or men [26], another study [27] included both genders. The mean age of the cohorts ranged from 49 ($n = 7$) [27] to 56 years ($n = 11$) [28]. Participants suffered from RA [28] or

Table 3. Exercise characteristics of the studies {start}

Author, year	Pre-intervention exercise status	Design/ supervision	Intervention length (months)	Type of exercise	Exercise protocol	Progression of intensity	Attandance	Activity in control group
Braith *et al.*, 1996	n.g. presumably (DRT) untrained	RCT consistently supervised	6	DRT, all main muscle groups at machines	3 sessions per week: 1× per week lumbar extension on specific MedX device and 2× per week 8 upper and lower body exercises with 1 set of 10–15 reps at RM, walking training with similar intensity and volume (n.g.) in both groups	Yes	n.g.	Walking
Mitchell *et al.*, 2003	Untrained	RCT, consistently supervised	6	DRT lumbar extension training on machine	1 session per week lumbar extension on specific MedX device; 1 set with 15–20 reps to voluntary muscle fatigue, time under tension/rep: 2 s concentric, 1 s isometric, 4s eccentric; walking training with similar intensity and volume (n.g.) in both groups	Yes	n.g.	Walking
Westby *et al.*, 2000	Untrained	RCT, predominately unsupervised	12	Aerobic dance and DRT (major peripheral muscle groups)	3× week, 15–20 min of moderate intensity aerobic dance, 10–15 min of floor exercises, cuff weight exercises with low intensity; more details n.g.	n.g.	71%	n.g.

n.g.: not given; RCT: randomized controlled trial; reps: repetitions; RM: repetition maximum (i.e. work to failure).

were lung [27]/heart transplant recipients [29] with the surgical procedure 2 months prior to the exercise intervention (Table 1). In contrast to the cohort with RA [28], baseline BMD at the LS was low or very low in the studies that included heart [26] or lung transplant [27] recipients, respectively. Moreover, in the latter cohorts a statistically significant BMD loss of 12–15% at the LS (5–6% for FN-BMD [29]) occurred during the 2 months between transplantation and the start of the intervention.

GC treatment characteristics

Table 2 gives the characteristics of the GC therapy. In summary, in all studies prednisone/methylprednisolone was administered, albeit in different modes and diverging doses. In the two studies with the lung or heart transplant recipients, GC therapy started with high doses during and immediately after surgery and then successively decreased to doses of ≈10 mg/day after 5–6 months [26, 27]. Westby *et al.* [28], which included RA patients, scheduled a lower and continuous GC administration of 2.5–7.5 mg/day. Due to the well-documented GC therapy–induced reductions in calcium absorption in both the gut and the renal tubule of importance [30], only Westby *et al.* [28] supplemented calcium (1000 mg/day) and vitamin D (400 IU/day), while baseline data or data on calcium were not reported by Braith *et al.* [26] or Mitchell *et al.* [27].

Exercise characteristics

Characteristics of the exercise protocols of the included studies are presented in Table 3. Briefly, all the studies included untrained participants. Apart from the intervention of Westby *et al.* [28] that applied a mixed moderate-intensity aerobic dance and low-intensity dynamic resistance exercise training, the two other studies [26, 27] focus on isolated dynamic resistance exercise training (DRT) on machines, with special emphasis on lumbar extension exercises to muscle failure/ repetition maximum. Braith *et al.* [26] and Westby *et al.* [26, 27] scheduled three sessions per week, while Mitchell *et al.* [27] scheduled one session with a single set of 15–20 repetitions (7 s/repetition) to muscle fatigue on the MedX lumbar extension device. At 6 [26, 27] and 12 months [28], the interventions of the studies can be considered short to moderately long. Although of short duration, Braith *et al.* [26] and Mitchell *et al.* [27] considered progression of exercise intensity in their protocols.

Study outcomes

All three studies determine BMD of the LS, two of them [26, 28] additionally address BMD at the FN, consistently via DXA.

Methodologic quality

Following the suggestion of Ribeiro de Avila *et al.* [31], the methodologic quality of the studies according to PEDro [14]
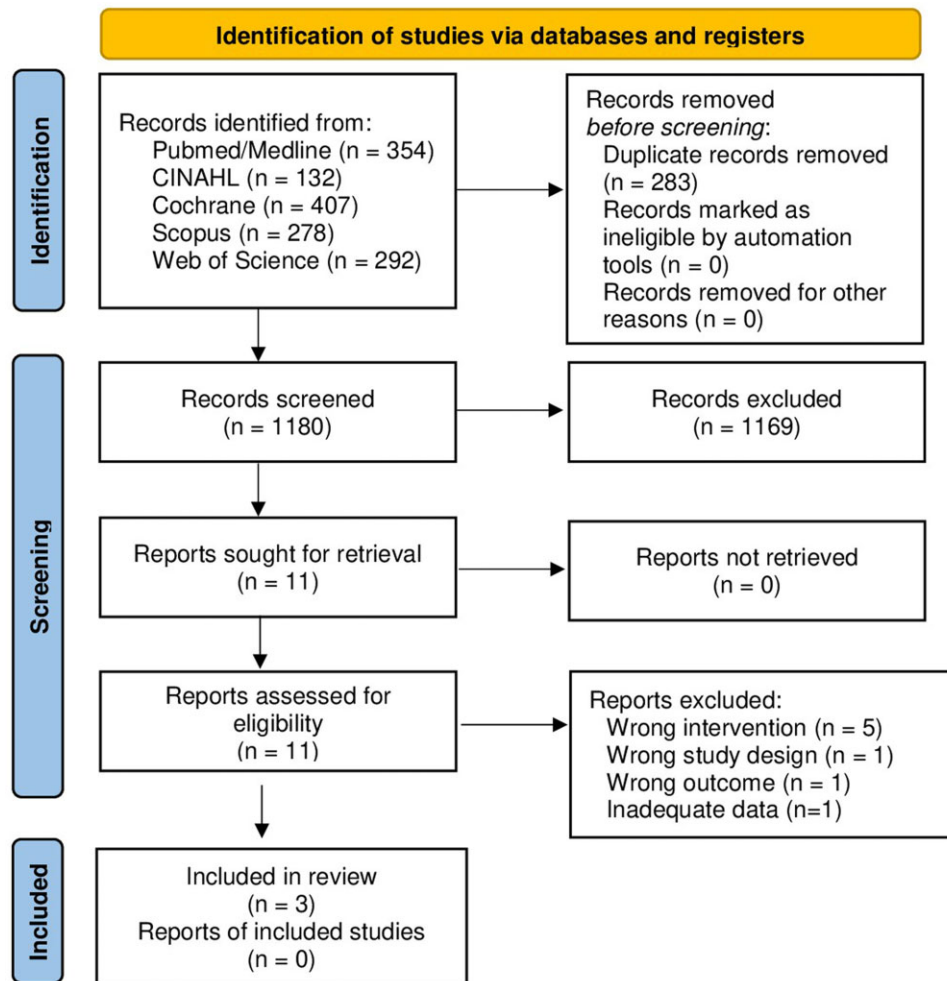
Figure 1. Flow diagram according to PRISMA [25]

can be considered low (<5 points) to moderate (5–6 points) (Supplementary Table S1, available at *Rheumatology Advances in Practice* online). In particular, aspects related to blinding/allocation concealment were not satisfied or not reported. With respect to TESTEX [15], the study scores ranged from 7 to 9 of 15 available points. Of note, no study reported information concerning adverse effects of the intervention or activity monitoring in the control groups (Supplementary Table S1, available at *Rheumatology Advances in Practice* online).

Study outcomes

BMD of the LS was maintained [28] or decreased (statistically) non-significant [26] or significant [27] in the combined GC + EX group, while LS-BMD decreased (statistically) significant [26, 27] in the isolated GC group. Apart from the study of Westby *et al.* [28], differences between GC + EX and GC were statistically significant [26, 27]. In parallel, the two studies [26, 28] that address FN-BMD reported statistically non-significant reductions in their exercise and GC groups. While Braith *et al.* [26] reported statistically significant greater reductions in their isolated GC groups, no relevant FN-BMD differences between GC + EX and GC were observed by Westby *et al.* [28].

Meta-analyses results

Three comparisons addressed exercise effects at LS-BMD (Fig. 2a). In summary, the inverse heterogeneity model (Fig. 2a) with imputation of the mean correlation demonstrated a statistically significant effect ($P < 0.021$) of exercise on GC + EX *vs* GC at the LS [SMD 1.50 (95% CI 0.23, 2.77)]. Heterogeneity between the trial results ($I^2 = 71\%$) can be classified as substantial (Fig. 2a).

Fig. 2b displays results for the effect GC + EX therapy *vs* isolated GC therapy on FN-BMD. Based on only two eligible studies, we observed no statistically significant positive effect ($P = 0.412$) of the combined therapy [SMD 0.64 (95% CI −0.89, 2.17)]. Heterogeneity between the trial results was substantial (78%) (Fig. 2b).

Publication/small study bias

The funnel plot analysis with trim and fill suggests considerable evidence for a publication/small study bias for the LS-BMD analysis (Fig. 3). The analysis imputes two missing studies on the lower right-hand side (i.e. small studies with negative outcome). The corresponding asymmetry was confirmed when inspecting the LFK Index (1.1 = minor asymmetry). Additionally, the regression ($P = 0.026$) but not the rank correlation test ($P = 0.333$) observed statistically significant funnel plot asymmetry.
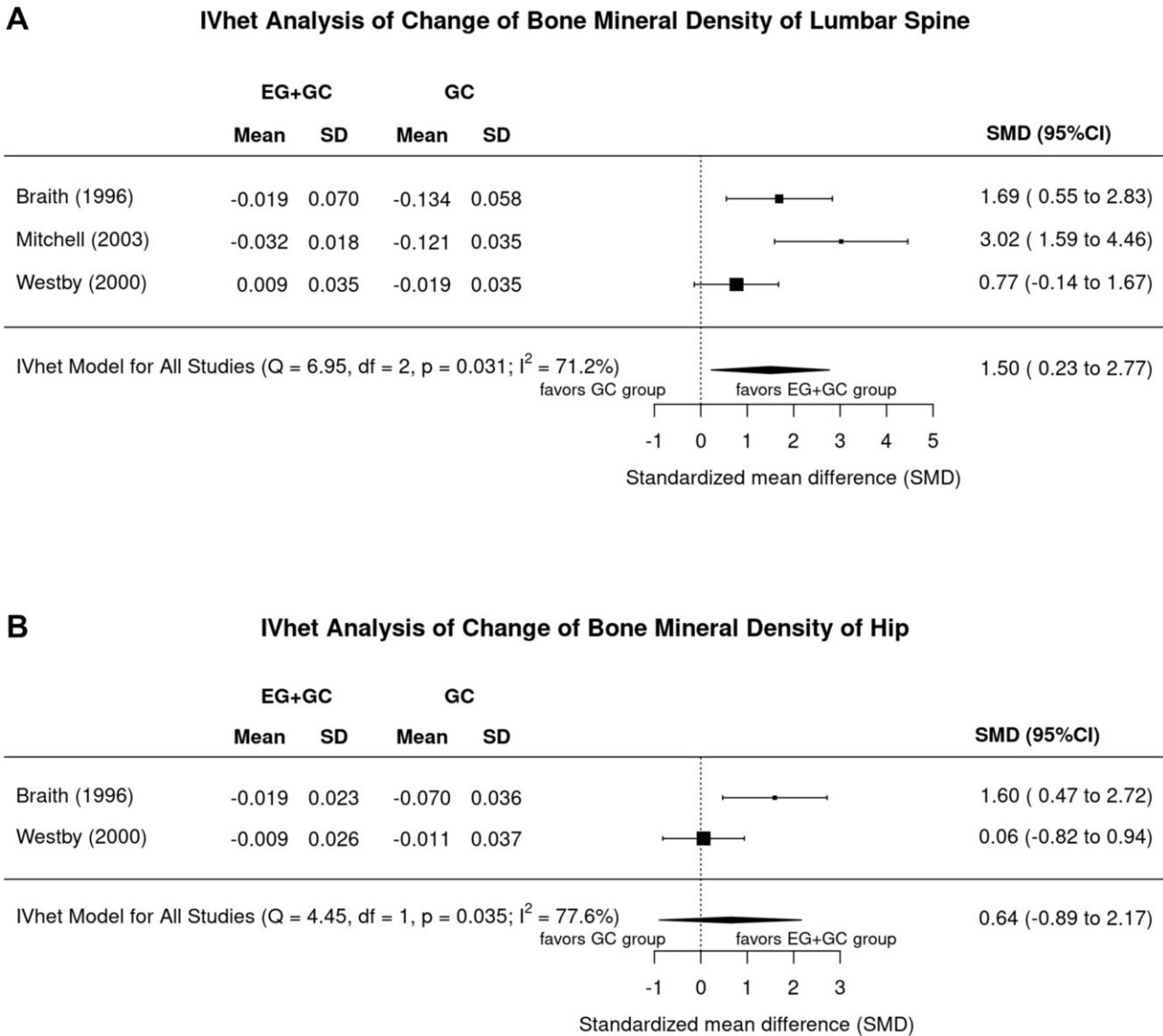
A   **IVhet Analysis of Change of Bone Mineral Density of Lumbar Spine**

	EG+GC		GC			SMD (95%CI)
	Mean	SD	Mean	SD		
Braith (1996)	-0.019	0.070	-0.134	0.058		1.69 (0.55 to 2.83)
Mitchell (2003)	-0.032	0.018	-0.121	0.035		3.02 (1.59 to 4.46)
Westby (2000)	0.009	0.035	-0.019	0.035		0.77 (-0.14 to 1.67)

IVhet Model for All Studies (Q = 6.95, df = 2, p = 0.031; I^2 = 71.2%)   1.50 (0.23 to 2.77)

favors GC group   favors EG+GC group

-1   0   1   2   3   4   5

Standardized mean difference (SMD)

B   **IVhet Analysis of Change of Bone Mineral Density of Hip**

	EG+GC		GC			SMD (95%CI)
	Mean	SD	Mean	SD		
Braith (1996)	-0.019	0.023	-0.070	0.036		1.60 (0.47 to 2.72)
Westby (2000)	-0.009	0.026	-0.011	0.037		0.06 (-0.82 to 0.94)

IVhet Model for All Studies (Q = 4.45, df = 1, p = 0.035; I^2 = 77.6%)   0.64 (-0.89 to 2.17)

favors GC group   favors EG+GC group

-1   0   1   2   3

Standardized mean difference (SMD)

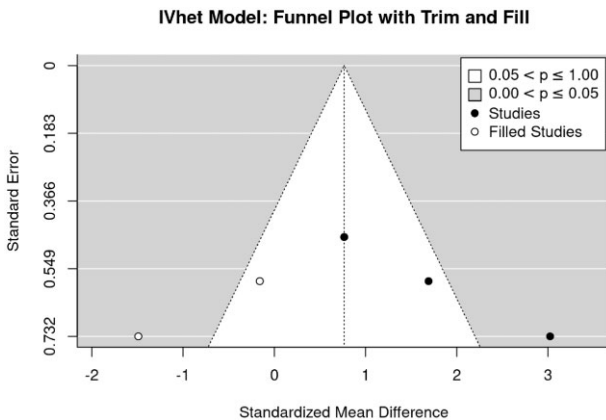**Figure 2.** Forest plot of meta-analysis results for **(A)** LS-BMD and **(B)** FN-BMD

Figure 3. Funnel plot with trim and fill on the effect of exercise on BMD at the LS

Funnel plot analysis (not shown) and other diagnostic tests do not indicate evidence for a publication/small study bias for the FN-BMD. However, due to the low number of studies included in the analysis ($n = 2$), the tests predominantly failed to generate reliable data.

Discussion

Reviewing current guidelines on GIOP [1, 3, 12], exercise is considered in the area of fall prevention, if at all. However, the potentially more important aspect of GOIP is the pronounced bone loss, particularly during the first year of treatment [32]. Thus, the aim of the present systematic review and meta-analysis was to provide evidence for the effect of exercise on BMD at the LS and proximal femur in people with ongoing GC therapy. After a comprehensive search process, only three studies were eligible to be included in the analysis. One may argue that this low number might prevent a meaningful meta-analysis on the effect of exercise on GC effects in people with GIOP. However, because the trials included featured comparable study designs (randomized controlled trials), participant age and sample size and two [27, 29] of the three studies were very similar, we opted to conduct a joint

(meta-)analysis, albeit applying the robust inverse heterogeneity model (see below).

In summary, we observed a statistically significant positive effect of exercise on BMD at the LS but not at the FN. We mainly attribute this result to the greater amount of trabecular bone at the LS predominantly affected by GIOP [4, 7]. The two studies that determined BMD at the LS and FN [26, 28] did in fact report considerably higher bone loss at the LS (Fig. 2) compared with the FN region of interest (Fig. 3), enabling a higher potential of positive effects for LS-BMD. Thus one may argue, that differences in baseline BMD (Table 1) contribute to the study outcomes. However, there is only limited evidence [33] that cohorts with (very) low baseline BMD (i.e. [27, 29]) benefit more from exercise compared with cohorts with normal BMD. Also of note, those two studies with high-dosed GC therapy (Table 2) administered after heart [29] or lung transplants [27] were the ones that revealed significant positive BMD effects. Both exercise studies were only 6 months in duration and thus might have predominately addressed the pronounced bone resorption observed during the first 5–7 months of GC treatment [32]. Surprisingly however, in two studies [27, 29] the exercise intervention not only slowed down GC-induced bone loss, but restored LS- and FN-BMD close to pre-GC-therapy levels. There is some evidence that the tapering of GC doses during the intervention contributed to this result (Table 2). Indeed, the GC group of the study of Braith et al. [29] revealed a maintenance of BMD at the LS and FN after 3 months of intervention. Reviewing the exercise protocols of both studies on transplant recipients [27, 29], a common component was back-strengthening exercise on a dedicated lumbar extension resistance device once per week. Of note, Mitchell et al. [27] prescribed only sets of 15–20 repetitions to voluntary muscle fatigue, with particular emphasis on the eccentric component (2 s concentric–1 s isometric–4 s eccentric) of the movement—a time-effective exercise protocol feasible even for people with low enthusiasm for exercise. However, the sedentary and physically limited status of the heart and lung transplant recipients might have contributed to the significant exercise effects on LS-BMD and FN-BMD. Thus it is debatable whether this finding can be transferred to cohorts with higher baseline fitness levels and higher baseline BMD, i.e. cohorts with RA.

The study that addressed RA with low-dose prednisone (2.5–7.5 mg/day) [28], i.e. a much more common scenario for GC treatment compared with the immunosuppressive approach discussed above, displays non-significant results for LS-BMD ($P = 0.09$) and FN-BMD (not given). In contrast to the studies with transplant recipients that applied dedicated back-strengthening programs on resistance machines specifically constructed for this purpose, the exercise protocol of Westby et al. [28] focused on aerobic dance without high-impact components and low-intensity DRT for 'major peripheral muscles'. It is likely that this non-(site)-specific low-intensity exercise protocol and the small sample size of the study ($n = 10$/group) included in the final BMD analysis might have prevented statistically significant results.

Of further importance, two [26, 27] of the three studies applied exercise protocols of 6 months, usually too short for determining the full amount of mineralized bone during a remodelling cycle [34, 35]. However, considering the mode of action of GIOP with rapid and pronounced bone loss during the first 5–7 months of GC supplementation [32], an exercise-induced reduction of GC-triggered bone loss might explain the corresponding 'short-term' effects.

Our positive meta-analysis result on exercise-induced effects on BMD, at least at the LS, could not necessarily be expected. As discussed, chronic administration of GCs can have significant catabolic effects on muscle [36, 37] and bone [37, 38]. Apart from dedicated effects on bone cells [1, 39], systemic effects of GC therapy might prevent positive effects of exercise/mechanical loading on bone. This refers to calcium malabsorption in the gut/renal tubule [30], hyperparathyroidism [40] and, in particular, the suppression of the somatotropic–gonadotropic axis [1, 41]. It is also possible that the resorptive potency of sclerostin and receptor activator of nuclear factor κB, which show an elevated expression with GCs, are counteracted at the cellular level.

Apart from the very limited number of eligible studies and their small sample sizes, other limitation and study particularities should be considered to properly interpret our results. First, two of the three studies [26, 27] focus on the immunosuppressive effects of GC therapy. Both trials started GC therapy immediately during/after heart and lung transplant and correspondingly administered (very) high initial GC doses (Table 2) that were successively reduced to ≈10 mg/day by the study end (8 months). In contrast, Westby et al. [28] applied a continuous dose of 2.5–7.5 mg/day in the RA cohort for 12 months. Although no corresponding information was provided for the latter study, it is likely that GC therapy was initiated years before the study start, i.e. the initial phase of rapid osteoclast-induced bone loss was already terminated [1, 32]. This feature might have reduced the effect of exercise to positively address BMD in this cohort. Second, baseline BMD varied between the exercise trials, with low [29] to very low [27] LS-BMD values in the transplant cohorts and normal BMD in the RA group [28]. There is some evidence that low baseline BMD might be related to higher exercise-induced BMD increases [33], which would be in line with the results of the present analysis. Third, unfortunately, two of the three studies (Tables 1 and 2) did not report dropout or exercise attendance rates, aspects that indicate the feasibility and acceptance of the training protocol. However, bearing in mind the high level of suffering and limitation due to heart or lung transplants, we assume that the attractiveness of the exercise training program is negligible in this context. Fourth, we applied the inverse heterogeneity model [20], which is less susceptible to underestimation of statistical error in heterogeneous studies; i.e. the results are more reliable in heterogeneous studies, especially with respect to the coverage probability of CIs [42].

Conclusion

In summary, the present systematic review and meta-analysis provided evidence for a positive effect of exercise on bone health during GC therapy. Our meta-analysis is based on only three randomized controlled trials. Further, the two studies that reported statistically significant results focus on immunosuppressive therapy after heart or lung transplants, which is a less common scenario for GC treatment. Thus, generalization of our results to other cohorts with GIOP is limited and the present finding should be carefully interpreted. As a consequence, further well-designed exercise trials will have to focus on the effect of exercise on BMD in GIOP to provide a definite conclusion on this issue. Nevertheless, considering the

time effectiveness of present exercise protocols on BMD, we feel that upcoming recommendations and guidelines on GIOP should more prominently include exercise as a tool for bone strengthening.

Supplementary material

Supplementary material is available at *Rheumatology Advances in Practice* online.

Data availability

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

Authors' contributions

S.K. and W.K. initiated the present meta-analysis and performed the literature search. Data analysis and interpretation was conducted by S.K., S.v.S., M.K., U.L. and W.K. All the authors contributed to quality assessment and drafted and revised the manuscript. S.K. and W.K. accept responsibility for the integrity of the data sampling, analysis and interpretation.

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