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Exercise training and bone mineral density in postmenopausal women: an updated systematic review and meta-analysis of intervention studies with emphasis on potential moderators

Mohebbi, R., Shojaa, M., Kohl, M. et al.
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The aim of this systematic review and meta-analysis was (1) to determine exercise effects on bone mineral density (BMD) in postmenopausal women and (2) to address the corresponding implication of bone and menopausal status or supervision in postmenopausal women. A comprehensive search of eight electronic databases according to the PRISMA statement up to August 9, 2022, included controlled exercise trials ≥ 6 months. BMD changes (standardized mean differences: SMD) at the lumbar spine (LS), femoral neck (FN), and total hip (TH) were considered as outcomes. Study group comparisons were conducted for osteopenia/osteoporosis versus normal BMD, early versus late postmenopausal women, and predominantly supervised versus predominantly non-supervised study arms. We applied an inverse heterogeneity (IVhet) model. In summary, 80 studies involving 94 training and 80 control groups with a pooled number of 5581 participants were eligible. The IVhet model determined SMDs of 0.29 (95% CI: 0.16–0.42), 0.27 (95% CI: 0.16–0.39), and 0.41 (95% CI: 0.30–0.52) for LS, FN, and THBMD, respectively. Heterogeneity between the trial results varied from low (I2 = 20%, TH BMD) to substantial (I2 = 68%, LS-BMD). Evidence for publication bias/small study effects was negligibly low (FN-, TH-BMD) to high (LSBMD). We observed no significant differences (p > .09) for exercise effects on LS-, FN-, or TH-BMD-LS between studies/study arms with or without osteopenia/osteoporosis, early versus late postmenopausal women, or predominantly supervised versus non-supervised exercise programs. Using robust statistical methods, the present work provides further evidence for a positive effect of exercise on BMD in postmenopausal women. Differences in bone status (osteopenia/osteoporosis versus normal bone), menopausal status (early versus late postmenopausal), and supervision (yes versus no) did not significantly affect the exercise effects on BMD at LS or proximal femur.

Bariatric surgery and skeletal health: A narrative review and position statement for management by the European Calcified Tissue Society (ECTS)

Julien Paccou a, Elena Tsourdi b c, Christian Meier d et al.
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Context: Numerous studies have demonstrated detrimental skeletal consequences following bariatric surgery.

Methods: A working group of the European Calcified Tissue Society (ECTS) performed an updated review of existing literature on changes of bone turnover markers (BTMs), bone mineral density (BMD), and fracture risk following bariatric surgery and provided advice on management based on expert opinion.

Literature review: Based on observational studies, bariatric surgery is associated with a 21-44% higher risk of all fractures. Fracture risk is time-dependent and increases approximately 3 years after bariatric surgery. The bariatric procedures that have a malabsorptive component (including Roux-en-Y Gastric bypass (RYGB) and biliopancreatic diversion (BPD)) have clearly been associated with the highest risk of fracture. The extent of high-turnover bone loss suggests a severe skeletal insult. This is associated with diminished bone strength and compromised microarchitecture. RYGB was the most performed bariatric procedure worldwide until very recently, when sleeve gastrectomy (SG) became more prominent. There is growing evidence that RYGB is associated with greater reduction in BMD, greater increase in BTMs, and higher risk of fractures compared with SG but RCTs on optimal management are still lacking.

Expert opinion: In all patients, it is mandatory to treat vitamin D deficiency, to achieve adequate daily calcium and protein intake and to promote physical activity before and following bariatric surgery. In post-menopausal women and men older than 50 years, osteoporosis treatment would be reasonable in the presence of any of the following criteria: i) history of recent fragility fracture after 40 years of age, ii) BMD T-score ≤ -2 at hip or spine, iii) FRAX score with femoral neck BMD exceeding 20% for the 10-year major osteoporotic fracture probability or exceeding 3% for hip fracture. Zoledronate as first choice should be preferred due to intolerance of oral formulations and malabsorption. Zoledronate should be used with caution due to hypocemia risk. It is recommended to ensure adequate 25-OH vitamin D level and calcium supplementation before administering zoledronate.

Conclusions: The bariatric procedures that have a malabsorptive component have been associated with the highest turnover bone loss and risk of fracture. There is a knowledge gap on osteoporosis treatment in patients undergoing bariatric surgery. More research is necessary to direct and support guidelines.

The Importance of Recent Prevalent Fracture Site for Imminent Risk of Fracture – A Retrospective, Nationwide Cohort Study of Older Swedish Men and Women

Axelsson, K.F., Litsne, H. and Lorentzon, M. (2023)
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There is limited evidence regarding which fracture types carry the highest risk for subsequent fracture. The aim of this study was to investigate how the risk of imminent fracture depends on index fracture site. This nationwide retrospective cohort study utilized national registers in Sweden to determine the risk of fracture according to recent (≤2 years) index fracture site and according to an old (>2 years) prevalent fracture compared with the risk observed in controls without a fracture. All Swedes 50 years or older between 2007 and 2010 were included in the study. Patients with a recent fracture were designated a specific fracture group depending on the type of previous fracture. Recent fractures were classified as major osteoporotic fracture (MOF), including fractured hip, vertebra, proximal humerus, and wrist, or non-MOF. Patients were followed until December 31, 2017, censored for death and emigration, and the risk of any fracture and hip fracture was assessed. A total of 3,423,320 persons were included in the study, 70,254 with a recent MOF, 75,526 with a recent non-MOF, 293,051 with an old fracture, and 2,984,489 persons with no previous fracture. The median time of follow-up for the four groups was 6.1 (interquartile range [IQR] 3.0–8.8), 7.2 (5.6–9.4), 7.1 (5.8–9.2), and 8.1 years (7.4–9.7), respectively. Patients with a recent MOF, recent non-MOF, and old fracture had a substantially increased risk of any fracture (hazard ratio [HR] adjusted for age and sex 2.11, 95% confidence interval [CI] 2.08–2.14; HR 2.24, 95% CI 2.21–2.27; and HR 1.77, 95% CI 1.76–1.78, respectively) compared with controls. All recent fractures, MOFs, and non-MOFs, as well as older fractures, increase the risk of subsequent fracture, suggesting that all recent fractures should be included in fracture liaison services and that case-finding strategies for those with older fractures may be warranted to prevent subsequent fractures.

Safety of Inpatient Zoledronic Acid in the Immediate Postfracture Setting

WuQiang Fan, Benjamin Z Leder, Michael Mannstadt et al.
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Context: Zoledronic acid (ZA) administered during the initial hospitalization for a fragility fracture improves the osteoporosis pharmacotherapy rate. Distinguishing the safety profile of inpatient ZA (IP-ZA) in this context is crucial if this approach is to be widely adopted.
Objective: To study the acute safety profile of IP-ZA.
Design, setting and patients: An observational study of patients admitted to the Massachusetts General Hospital with fragility fractures who were eligible to receive IP-ZA.
Intervention: Patients were treated with or without IP-ZA. Acetaminophen, either as a single pre-ZA dose or standing multiple-doses-per-day for 48 hours or longer after ZA infusion, was also administered along with protocolized vitamin D and calcium supplementation.
Main outcome measures: changes in body temperature, serum creatinine and serum calcium.
Results: 285 consecutive patients, meeting inclusion and exclusion criteria, are included in this analysis. 204 patients received IP-ZA. IP-ZA treatment was associated with a transient mean rise of body temperature of 0.31oC on the day following its administration. 15% of patients in the IP-ZA group and 4% in the non-treated group had temperatures above 38oC. Standing multiple-doses-per-day, but not a single pre-ZA dose of acetaminophen, effectively prevented this temperature increase. IP-ZA did not affect serum creatinine levels. Mean levels of serum total calcium and albumin-corrected calcium decreased by 0.54 mg/dl and 0.40 mg/dl, respectively, at their nadirs (Day 5). No patient experienced symptomatic hypocalcemia.
Conclusions: IP-ZA along with standing multiple-doses-per-day acetaminophen, administered to patients in the immediate post-fracture period, is not associated with significant acute adverse effects.

The Clinical Effectiveness of Denosumab (Prolia®) for the Treatment of Osteoporosis in Postmenopausal Women, Compared to Bisphosphonates, Selective Estrogen Receptor Modulators (SERM), and Placebo: A Systematic Review and Network Meta-Analysis

Moshi, M.R., Nicolopoulos, K., Stringer, D. *et al.*
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To assess the effectiveness and safety of denosumab (Prolia®) compared to bisphosphonates (alendronate, ibandronate, risedronate, zoledronate), selective estrogen receptor modulators (SERMs; bazedoxifene, raloxifene) or placebo, for the treatment of osteoporosis in postmenopausal women (PMW). Systematic searches were run in PubMed, Embase & Cochrane Library on 27-April-2022. Randomized controlled trials (RCTs) that included osteoporotic PMW allocated to denosumab, SERMs, bisphosphonates, or placebo were eligible for inclusion. RCTs were appraised using Cochrane Risk of Bias 2.0. Bayesian network and/or pairwise meta-analyses were conducted on predetermined outcomes (i.e. vertebral/nonvertebral fractures, bone mineral density [BMD], mortality, adverse events [AEs], serious AEs (SAEs), withdrawals due to AEs, AEs caused by denosumab discontinuation). A total of 12 RCTs ($k = 22$ publications; $n = 25{,}879$ participants) were included in the analyses. Denosumab, reported a statistically significant increase in lumbar spine (LS) and total hip (TH) BMD, compared to placebo. Similarly, denosumab also resulted in a statistically significant increase in TH BMD compared to the raloxifene and bazedoxifene. However, relative to denosumab, alendronate, ibandronate and risedronate resulted in significant improvements in both femoral neck (FN) and LS BMD. With regards to vertebral fractures and all safety outcomes, there were no

statistically significant differences between denosumab and any of the comparator. Relative to placebo, denosumab was associated with significant benefits in both LS and TH BMD. Additionally, denosumab (compared to placebo) was not associated with reductions in vertebral and nonvertebral fractures. Finally, denosumab was not associated with improvement in safety outcomes, compared to placebo. These findings should be interpreted with caution as some analyses suffered from statistical imprecision.

Fibroblast Growth Factor 23 Bone Regulation and Downstream Hormonal Activity.

Clinkenbeard, E.
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Mineral homeostasis of calcium and phosphate levels is one critical component to the maintenance of bone mineral density (BMD) and strength. Diseases that disrupt calcium and phosphate balanced have highlighted not only the role these minerals play in overall bone homeostasis, but also the factors, hormones and downstream transporters, responsible for mineral metabolism. The key phosphaturic hormone elucidated from studying rare heritable disorders of hypophosphatemia is Fibroblast Growth Factor 23 (FGF23). FGF23 is predominantly secreted from bone cells in an effort to maintain phosphate balance by directly controlling renal reabsorption and indirectly affecting intestinal uptake of this mineral. Multiple factors have been shown to enhance bone mRNA expression; however, FGF23 can also undergo proteolytic cleavage to control secretion of the biologically active form of the hormone. The review focuses specifically on the regulation of FGF23 and its secretion from bone as well as its hormonal actions under physiological and disease conditions.

