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A systematic review and meta-analysis of glucocorticoid-induced osteoporosis in children

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ABSTRACT

Objective: To summarize the published effects of systemic glucocorticoid therapy on bone mineral density (BMD) and fractures in children.
Methods: We performed a systematic review and meta-analysis of existing literature, using Medline, CINAHL, and Cochrane databases to identify studies of BMD or fractures in children ≤18 years taking systemic glucocorticoid therapy. We excluded studies of inhaled glucocorticoids, chemotherapy, and organ transplantation. Two authors reviewed abstracts for inclusion, read full-text articles to extract data, and rated each study using the Downs–Black scale.
Results: A total of 16 studies met eligibility criteria, including 10 BMD (287 children) and six fracture (37,819 children) studies. Spine BMD was significantly lower (−0.18; 95% CI = −0.25; −0.10 g/cm^2) in children taking glucocorticoid therapy, compared to age- and gender-matched healthy controls. Spine BMD was also lower (−0.14; 95% CI = −0.27; 0.00 g/cm^2) in children taking glucocorticoids, compared to children with the same disease not taking glucocorticoids. Incident clinical fracture rates varied from 2% to 33%. Morphometric vertebral fracture incidence ranged from 6% to 10%, and prevalence was 29–45%.
Conclusion: Published data suggest that children treated with glucocorticoid therapy have lower spine BMD compared to healthy children. Whether children receiving glucocorticoid therapy have lower spine BMD compared to children with milder disease not requiring such therapy is not certain. Clinical and morphometric vertebral fractures are common, although only one study assessed fracture rates in healthy controls. Additional well-designed, prospective studies are needed to evaluate the skeletal effects of glucocorticoid therapy in children.

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Introduction

Glucocorticoid-induced osteoporosis (GIO) is the most common form of secondary osteoporosis [1]. Systemic glucocorticoid therapy is associated with an initial increase in bone resorption [2,3] and more importantly, subsequent reduced bone formation [4], leading to microarchitectural deterioration and increased fracture risk. Epidemiologic studies have unequivocally established a higher risk of fracture among adults taking systemic glucocorticoid therapy [1,5–7]. The risk of fracture in adults is dose-dependent, with higher daily doses of oral glucocorticoids conferring a greater risk of fracture. Several medications are FDA-approved for the prevention and treatment of GIO in adults, and guidelines from the American College of Rheumatology can inform clinical decisions about whom to treat and which medication to select [8]. However, no evidence-based guidelines exist to assist clinicians caring for children who require long-term oral glucocorticoid therapy.

The absence of a synthesized evidence base regarding glucocorticoid use in children is a barrier to guidelines to monitor bone health in this patient population [4]. Glucocorticoid use in growing children might decrease peak bone mass and increase life-long risk of fracture. However, in the disease for which glucocorticoid

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therapy is given might also adversely affect skeletal health, glucocorticoid therapy might improve appetite, increase physical activity, control the underlying disease, and/or reduce inflammatory cytokines, thereby improving skeletal health [9].

The aim of this study was to examine the effect of systemic glucocorticoid therapy on skeletal health in children by systematic review and meta-analysis. We hypothesized that children taking systemic glucocorticoid therapy would experience higher rates of symptomatic (clinical) and morphometric vertebral fractures and lower bone mineral density (BMD) and/or content (BMC), compared to baseline measures, age-matched healthy peers, and children with the same disease who were not taking glucocorticoids.

Methods

With assistance from an academic librarian, we searched PubMed, CINAHL, and Cochrane databases from January 1, 1966 to February 5, 2013 to identify relevant articles published in any language on children 0–18 years. We used the MeSH terms glucocorticoids, corticosteroids, methylprednisolone, prednisone, prednisolone, hydrocortisone, triamcinolone, and dexamethasone crossed with the following terms: fracture(s), bone density, bone mineral density, and bone mineral content. To identify additional articles we added the following search terms: juvenile rheumatoid arthritis, juvenile idiopathic arthritis (JIA), juvenile systemic lupus erythematosus (SLE), inflammatory bowel disease, and juvenile dermatomyositis. We also reviewed the reference lists of the full-length articles undergoing level 2 review to identify additional articles meeting predefined inclusion criteria. Literature was reviewed again in October 2013 to identify interim publications.

Our primary outcomes were spine and/or total body less head BMD or BMC measurements [10] and clinical and/or morphometric fractures associated with systemic glucocorticoid therapy. We included studies in which children age ≤ 18 years taking systemic glucocorticoid therapy underwent clinical and/or radiographic evaluation for fracture and/or measurements of lumbar spine and/or total body BMD (less head), with comparison to their baseline measurements or controls. Inclusion required that authors report the dose and duration of glucocorticoid therapy. We excluded studies related to inhaled or topical glucocorticoid therapy, concurrent glucocorticoid and chemotherapy, and organ or bone marrow transplant. We excluded the treatment arm of prospective studies involving bone active medications such as bisphosphonates or vitamin D, which could potentially obscure the true effects of glucocorticoids on skeletal health. We excluded case series and case reports due to potential for selection and detection bias. We included cross-sectional, cohort, and interventional studies.

Two authors reviewed all the abstracts to determine potential eligibility for inclusion (level 1 review, Fig. 1). Next, two authors read the full text of all articles reaching level 2 review. During level 3 review, two authors independently extracted data from each study using a standardized form to record the populations, interventions (form, dose, and duration of glucocorticoid therapy), main outcome measures (bone mineral density and fractures), and study design. The first author of each study publication was contacted twice by email for missing data (e.g., standard deviation for mean values) if the overall study design was otherwise acceptable.

Two reviewers rated the quality of each study using the Downs and Black [11] checklist which assesses five domains: reporting, external validity, bias, confounding, and power. We resolved discrepancies in data extraction and scoring by consensus. The

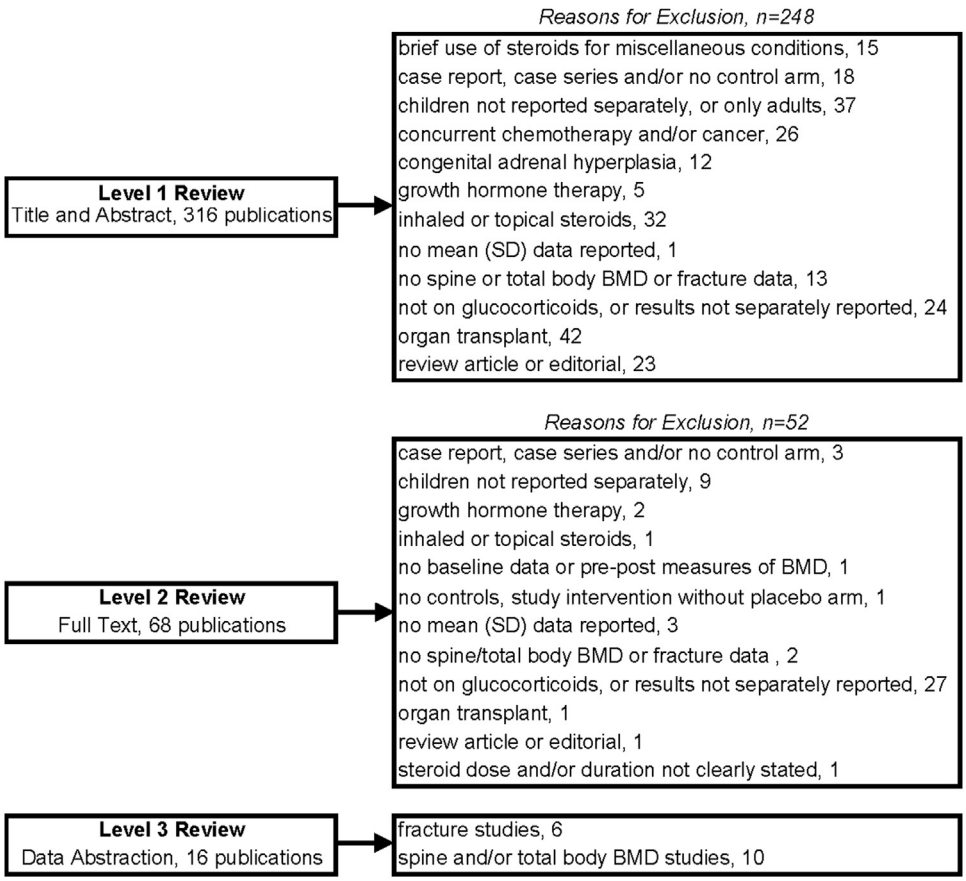

Fig. 1. Summary of articles reviewed.

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