Prevention of steroid-induced low bone mineral density in children with renal diseases: a systematic review

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ABSTRACT

Background. Children with renal diseases who are treated with glucocorticoids are at increased risk of developing osteoporosis and fractures. However, there is no common strategy for prevention of corticosteroid-induced osteoporosis. The present systematic review was performed to determine whether prevention of bone loss by calcium (Ca), vitamin D (vit D) and/or bisphosphonates is justified, safe and efficacious in children treated with steroids for various renal diseases.

Methods. Data sources: Medline, Embase, Central were searched from 1961 up to 2012. Randomized controlled trials (RCTs) and observational studies concerning children ≤18 years with renal diseases requiring steroids were included.

Results. The search strategy retrieved 2482 studies. Four RCTs including 166 patients and one observational study including 100 children met our eligibility criteria. One RCT and the observational study concerned treatment with Ca/vit D, one RCT with bisphosphonates and two RCTs with a combination of both therapies. All described a significant improvement in bone mineral density (BMD) in the treatment group compared with the control group.

Conclusions. Ca combined with vit D is recommended to prevent bone disease in children with renal diseases treated with steroids. Because of side effects, bisphosphonates should be reserved for the treatment of severe osteoporosis when Ca and/or vit D supplementation has failed.

INTRODUCTION

Children with renal diseases are often exposed to long-term steroid therapy, which is an important contributor to the development of osteoporosis [1–4]. Indeed, a long-term use of glucocorticoids induces a reduction of bone formation mainly by direct action on bone cells and antagonism of parathyroid hormone (PTH) and vitamin D (vit D) functions [5–7]. In addition, patients with nephrotic proteinuria lose 25-hydroxyvitamin D [25(OH)D] in urine and have low blood levels of this metabolite [8].

Children requiring repeated courses of corticosteroids have an increased risk of bone fractures [9, 10]. The measurement of the bone mineral density (BMD) by dual X-ray absorptiometry (DXA) is currently the most used technique to detect bone loss [11, 12]. An inverse relationship between steroid dose and BMD measured by DXA has been found in children with nephrotic syndrome (NS) who recently started with steroids [13, 14]. There is an association between reduced BMD and fractures in children [15–17]. Therefore, BMD measured by DXA seems to be an adequate technique to evaluate the risk of bone loss in children with steroid treatment for renal disease.

Alternate day dosing of prednisone has a less deleterious effect on vit D and calcium (Ca) metabolism than daily dosing [18], but does not exclude the risk of bone loss. Therefore, it has been suggested that patients initiating steroid therapy should receive preventive therapy such as Ca, vit D,
biphosphonates or a combination of these [19–22]. However, this strategy is not standardized and is not commonly used for children in the Netherlands.

Two systematic reviews have been performed by the Cochrane Collaboration on the prevention and treatment of corticosteroid-induced osteoporosis in adults presenting with various diseases [21, 22]. These reviews concluded that treatment with a combination of Ca and vit D is more effective in preventing bone loss when compared with placebo or Ca alone [21] and that bisphosphonates are effective in preventing and treating corticosteroid-induced bone loss [22].

To date, there are no guidelines on the prevention of bone disease in children with renal diseases treated with steroids. Moreover, no meta-analysis on Ca and vit D preventive treatment in children on steroids has been performed up to now.

The aim of the present systematic review is to evaluate the efficacy and safety of Ca and vit D supplementation or bisphosphonate administration in preventing or decreasing the occurrence of low BMD in children with renal diseases who are treated with steroids.

MATERIALS AND METHODS

Data sources

The search strategy was developed by three of the authors (A.B., M.G. and S.K.) and a clinical librarian. Embase, Medline and Central databases (from 1961 to 2012) were searched by a clinical librarian to identify studies related to the treatment or prevention of corticosteroid-induced bone disease in children with renal diseases. In this search, the keywords used to describe the study population are as follows: bone disease, pathologic bone demineralization, pathologic decalcification, osteomalacia, osteoporosis, osteopenia, or metabolic bone disease, corticosteroids and glucocorticoids. These words were combined with the different types of interventions considered (Ca, vit D and bisphosphonates). Additional strategies used to identify studies included searching the reference lists of review articles and included studies.

Study selection, data extraction, methodological quality and analysis

Two reviewers (A.B. and M.G.) independently screened titles and abstracts of all identified published articles for eligibility. Additionally, the full-text articles of all potentially relevant studies were retrieved and eligibility was determined independently by two authors (A.B. and M.G.). Differences regarding the inclusion were resolved through discussion. Randomized controlled trials (RCTs) provide stronger evidence than cohort studies. Therefore, first RCTs were selected regarding children (<18 years) with renal disease requiring systemic corticosteroid therapy that use calcium and/or vit D or bisphosphonates. The primary outcome measure was a change in BMD of the lumbar spine, distal radius, femoral neck or whole body. Secondary outcomes concerned growth, fracture rate and side effects of interventions. The risk of bias of the included RCTs was assessed using the risk of bias assessment tool from the Cochrane Collaboration [23]. The following items were assessed in the included RCTs: selection bias, performance bias, detection bias, attrition bias and reporting bias. Data were extracted by two reviewers (A.B. and M.G.), using a pre-developed data extraction form including the following items: age, gender, diagnosis, intervention, control group, treatment dose, frequency and intervention period. Since the studies were clinically heterogeneous (i.e. different populations, different interventions), study results could not be pooled, and data were therefore summarized narratively. We assessed the quality of evidence for the outcome BMD by discussing the five domains of the Grading of Recommendations assessment, Development and Evaluation Working Group (GRADE) assessment tool. These five domains are: risk of bias, imprecision, inconsistency, indirectness and publication bias [24].

Second, cohort studies were selected. The methodological quality of the included observational studies was evaluated by using the Newcastle–Ottawa quality assessment scale for cohort studies [25]. Three reviewers (A.B., M.G. and S.K.) independently assessed the quality of the included studies. Differences were resolved by discussion.

RESULTS

Description of studies

The search strategy retrieved 2482 studies (Figure 1). Five RCTs potentially met our eligibility criteria [26–30]. All five RCTs were blinded, except for the study by Brown et al. [26], which was excluded on the basis of failure of trial completion due to inadequate enrolment.

Two observational studies potentially met our eligibility criteria [19, 31]. The study from Noquera et al. [31] was excluded because only one child had a renal disease. The characteristics of included RCTs and the observational study are summarized in Table 1.

The four included RCTs were the studies by Kim et al. [27], Bak et al. [28], El-Husseini et al. [29] and Rudge et al. [30] and concerned a total of 166 children.

The treatment period in these trials varied from 8 weeks to 12 months. Three trials concerned children with renal disease [27–29], one contained a heterogeneous group of children on long-term prednisone therapy for different underlying clinical conditions such as juvenile idiopathic arthritis, Systemic lupus erythematosus, dermatomyositis, inflammatory bowel disease, kidney transplantation, autoimmune haemolytic anaemia and allergic bronchopulmonary aspergillosis with cystic fibrosis [30] (Table 1).

Treatments varied between studies: Ca and vit D [28], Ca and pamidronate [27], alendronate [30], alphacalcidol or alendronate or nasal calcitonin [29]. The study by El-Husseini et al. [29] included only patients with evident osteopenia or osteoporosis (T-score < −1 by DXA), whereas the others included all patients with steroids but not necessarily with obvious bone defects [27, 28, 30]. El-Husseini et al. [29] used the T-score instead of the Z-score. As a consequence of that, the occurrence of low BMD can initially be overestimated because the T-score is a score compared with young adults and not with age- and

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gender-matched controls [11]. Outcome measures included BMD using DXA in all of the four trials.

The observational study investigated the effect of 1-year Ca and vit D on BMD in 100 children with NS on steroid treatment [19].

**Methodological quality RCT**

El-Husseini et al. [29] documented a randomized and blind allocation of patients, Rudge et al. [30], Bak et al. [28] only described that patients were randomized and Kim et al. [27] assigned each patient to a group according to the order of admission for corticosteroid pulse therapy which is a quasi-randomization process. Only the study by El-Husseini et al. [29] documented adequate allocation concealment, although the blinding procedure was not fully described. Bak et al. [28] and Rudge et al. [30] did not provide information on the allocation concealment, and patients from the study by Kim et al. [27] were not randomized blindly. Blinding of patients was described only in the study by Rudge et al. [30]. Blinding of investigators and effect assessors was not documented in any of the studies. Patients in the study by Rudge et al. [30] received steroid therapy under different clinical conditions. Clinical diagnoses were not evenly distributed between treatment groups. This was also the case for the study by Kim et al. [27]. In the studies by Bak et al. [28] and El-Husseini et al. [29], groups were comparable with equal distribution of clinical condition, age, gender and mean steroid dose.

In the study by Rudge et al. [30], 4 of 22 patients failed to complete the study; three from the placebo group moved away and discontinued participation, one patient on alendronate died of pulmonary haemorrhage as a complication of systemic lupus erythematosus. The study by Bak et al. [28], El-Husseini et al. [29] and Kim et al. [27] did not mention any dropout. Three studies lacked information about intention-to-treat analysis [27–29]. All studies had an equal provision of care. Due to the judgement ‘high risk’ for one key domain (blinding) in the risk of bias assessment in the study by Bak et al. [28] and ‘unclear risk’ in the three other RCTs [27, 29, 30], we concluded that the validity of the RCTs was doubtful (Table 2).

**Methodological quality cohort**

In the observational study by Gulati et al. [19], 100 consecutive children with NS were recruited and 12 were excluded as they did not have a follow-up for renal function biochemistry or BMD assessment. Of the remaining 88 patients at the first follow-up visit, 15 patients were not initiated with Ca and vit D supplements at all. Since all of them were asymptomatic, they were not restarted on these supplements but were followed as a control group. Gulati et al. [19] did not mention any dropout and adverse events. Patients had an equal provision of care.

The quality of the observational study by Gulati et al. [19] was assessed as moderate and applicable with an average Ottawa–Newcastle score of seven (out of nine) (Table 3).

**Effects of intervention RCT**

All studies reported a significant improvement in BMD in the treatment group compared with the control group. The results could not be pooled due to clinical, therapeutic and outcome measure heterogeneity. For this reason, data from the
<table>
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<th>Study</th>
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<td>Bak et al. [28]</td>
<td>Inclusion criteria: children with steroid-sensitive nephrotic syndrome (18 newly diagnosed and 22 relapsed) Sample size: 40 (20 Ca/vit D, 20 placebo) Mean age Ca/vit D 4.6 ± 1.9 years, placebo 4.6 ± 1.8 years</td>
<td>Ca 1000 mg/day and vit D 400 IU/day for 8 weeks</td>
<td>Lumbar (L2–4) BMD: absolute and relative change after 8 weeks of steroid treatment. Decrease of lumbar BMD significantly reduced in the treatment group compared with the non-treatment group (−4.6 ± 2.3% versus −13.0 ± 4.0%, P &lt; 0.001). Absolute BMD decreased in both the groups (treatment group median 0.54–0.51 g/cm², P = 0.001 versus control group 0.52–0.45 g/cm², P &lt; 0.001)</td>
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<td>El-Husseini et al. [29]</td>
<td>Inclusion criteria: kidney transplant and osteopenia or osteoporosis Sample size: 60 (15 control, 15 alfacalcidol, 15 alendronate, 15 calcitonine. Mean age: alfacalcidol 14.5 ± 4.3 years, alendronate 15.2 ± 3.5 years, control 14.6 ± 4.3 years</td>
<td>Alfacalcidol 0.25 g/day, alendronate 5 mg/day, nasal calcitonine 200 IU/day (not included in meta-analysis) or placebo. All patients were on Ca 500 mg/day</td>
<td>Lumbar (L2–4) and total body BMD (absolute, T-score) before and after 12 months of steroid treatment. Both treatment groups showed a significant improvement in the lumbar BMD T-score (group alfacalcidol −2.3 to −0.5, P &lt; 0.001, alendronate −2.3 to −1.9, P = 0.006) while the control group showed a significant bone loss (−2.4 to −2.8, P &lt; 0.001). Whole body BMD T-score improved in the alfacalcidol (−1.3 to 0.3, P &lt; 0.001) and alendronate (−1.4 to −0.9, P &lt; 0.001) group and decreased in the control group (−1.5 to −1.9, P &lt; 0.001)</td>
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<tr>
<td>Kim et al. [27]</td>
<td>Inclusion criteria: children with nephropathy receiving high doses of steroids Sample size: 44 subjects (22 controls (only Ca) and 22 study group (Ca and pamidronate) Mean age: pamidronate/Ca 8.5 ± 4.49 years, Ca 8.5 ± 2.39 years</td>
<td>Pamidronate 125 mg/day and Ca 500 mg/day or Ca 500 mg/day for 3 months, starting simultaneously with steroids</td>
<td>Lumbar (L2–4) BMD before steroid treatment and after 3 months. Significantly decreased mean lumbar BMD in the Ca group (0.654–0.631 g/cm², P = 0.0017), BMD not reduced in the Pamidronate group (0.644–0.647 g/cm², ns).</td>
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<td>Rudge et al. [30]</td>
<td>Inclusion criteria: long-term prednisone therapy Sample size: 22 (11 alendronate and 11 placebo) Median age: alendronate 8.7 years, placebo 8 years</td>
<td>Alendronate 1–2 mg/kg/week or placebo</td>
<td>Lumbar (L2–4) and mid-femoral BMD (g/cm², g/cm³, Z-score) before and after 6 and 12 months of steroid treatment. Mean lumbar volumetric BMD increased significantly in alendronate group after one year (0.266 to 0.307 g/cm³, P = 0.013) but not in the placebo group (0.255 to 0.276 g/cm³, P = 0.156).</td>
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<td>Gulati et al. [19]</td>
<td>Children with idiopathic nephrotic syndrome Sample size: 88 (73 Ca/vit D, 15 no intervention) Mean age Ca/vit D 8.9 ± 0.5 years, no intervention 9.6 ± 1.0 years</td>
<td>Ca 500 mg/day and vitamin D3 200 IU/day</td>
<td>Lumbar (L1–4) BMD, difference between the initial and final z scores. Children on supplements (n = 73) had a significantly improved z-score (+0.30 ± 0.11) when compared with those without supplements (n = 15) (−0.38 ± 0.12, P = 0.008)</td>
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different RCTs and observational study are presented separately (Table 1).

The results of the BMD measurements in the four studies are difficult to pool because different units are used. The study by Bak et al. [28] measured areal density in g/cm², the study by Rudge et al. [30] used Z-scores, the study by El-Husseini et al. [29] mentioned T-scores and the study by Kim et al. [27] reported neither Z- nor T-scores. The Z-score is preferred for paediatric patients as it standardizes BMD relative to an age- and gender-matched population, whereas the T-score standardizes BMD relative to healthy young adults [11].

In the study by Kim et al. [27], some patients receiving oral pamidronate complained of mild abdominal discomfort, but this did not cause any dropout. The study by El-Husseini et al. [29] described transient hypocalcaemia in two patients, one on alendronate and one on calcitonin. Bak et al. [28] did not observe any significant differences in hypercalciuria between the treated and untreated groups, although the urinary Ca
excretion increased significantly during steroid therapy in both groups. The study by Rudge et al. [30] and El-Husseini et al. [29] described the occurrence of fractures. In the study by Rudge et al. [30], one subject from the control group had a sustained fracture and one subject in the control group from the study by El-Husseini et al. [29] had a traumatic humerus fracture. Furthermore, the study by Rudge et al. [30] reported a similar mean height velocity in both the alendronate and the placebo group.

**Effects of intervention cohort**

Gulati et al. [19] used the Δz-score. This study demonstrated a significant correlation between the BMD Δz-score and Ca and vit D supplementation. None of the patients developed pathological fractures.

### DISCUSSION

**Quality of evidence and recommendations**

Children with various renal diseases are often exposed to long-term steroid therapy and to its side effects on bone [1–3, 9]. Prevention and treatment with Ca, vit D, bisphosphonates or a combination of these have been suggested by different studies [20–22].

This review shows that RCTs on prevention of steroid side effects on bone in children with various renal diseases are not abundant, display a limited sample size and are not of high methodological quality. All of these factors are clear limitations of the current meta-analysis and in fact prevented a statistical meta-analysis. As there are disease-specific effects on steroid-induced bone disease, this may be a limitation in our approach. Importantly, however, all the eligible studies of this systematic review report the efficacy of intervention to improve BMD measured by DXA.

It may be obvious that a decreased BMD constitutes an indication for intervention, but a recommendation may be less clear when the BMD remains in the normal range, because of potential side effects of treatments.

The side effects of bisphosphonates are not negligible, but the use of Ca and vit D is safe as long as recommended dosages and follow-up are adhered to [28, 29]. Since Ca supplements alone have not been tested in RCTs, the combination of Ca and vit D should be preferred.

According to GRADE, the quality of evidence of the effectiveness of Ca/vit D compared with placebo for the outcome BMD was classified as low [24].

As a consequence of that, the grade of recommendation for the Ca/vit D therapy is weak [32]. However, all studies reported a significant improvement in BMD in the treatment group compared with the control group. Therefore, we suggest Ca and vit D supplementation from the start of steroid therapy.

The dosage of Ca given in the studies of this review varied between 500 and 1000 mg. The recommended daily Ca intake for healthy children ranges between 30 and 75 mg/kg per day depending on age [33]. The first of our prevention treatment policy in children with renal diseases treated with steroids will be improving dietary Ca intake. If the latter is not possible, supplementation of 250 mg elementary Ca per day for a bodyweight <10 kg, 500 mg for >10 kg and 1000 mg for >40 kg [33, 34] is advised. The duration of Ca supplementation should be at least the period of steroid treatment and longer when dietary Ca intake remains too low. The dosage of vit D given in the study by Bak et al. [28] was 400 IU of vitamin D3. El-Husseini et al. [29] treated their patients with 0.25 μg of 1α-OH-vitamin D3 (alphacalcidol) because they did not have a normal renal function after kidney transplantation and therefore, a diminished renal 1α-hydroxylase activity. In the observational study by Gulati et al. [19], patients were treated with vit D3 (cholecalciferol). Vit D3 at a dosage of 400–800 IU should be preferred in the case of normal renal function because of a decreased risk of hypercalcaemia [33, 35, 36]. Monitoring of 25(OH)D serum levels is advised, besides serum Ca, phosphate, alkaline phosphatase, PTH and urine Ca/creatinine ratio. Since magnesium and zinc are also involved in bone mineralization and might be reduced in children with renal disease, monitoring of these serum levels can be considered [37, 38]. Higher dosages of vitD3 should be given when serum 25(OH)D levels are too low, aiming at levels >50 nmol/L (20 ng/mL) [33, 39].

We assessed the quality of evidence of the effectiveness of bisphosphonates compared with Ca or placebo for the outcome BMD as low. The grade of recommendation is weak [32]. Currently, bisphosphonate therapy should be reserved for children with low BMD and bone fractures that have not responded to the combination treatment of Ca and vit D.

Alendronate [30] and pamidronate [27] were administered orally. A disadvantage of daily oral dosing is that the patient has to remain upright for 30 min and is not allowed to eat 2 h before and 30 min after ingestion of the bisphosphonates to reduce the risk of oesophagitis [40]. El-Husseini et al. [29] administered alendronate at a dosage of 5 mg daily, and Rudge et al. [30] used 80 mg weekly, 40 mg weekly or every other week depending on the age, whereas Kim et al. [27] used 125 mg of pamidronate daily. The lack of RCTs comparing different bisphosphonate medications for various dosages and durations of treatment makes it impossible to prefer one therapeutic regimen over another. The treatment duration of bisphosphonates in the reviewed studies in this article varied between 3 months [27] and 1 year [29, 30].

The Cochrane review on bisphosphonate therapy in children with secondary osteoporosis [41] concerned not only children treated with corticosteroids but also children with chronic illness such as cerebral palsy. The authors concluded
that data are insufficient to support the use of bisphosphonates as standard therapy, but the results justify further evaluation of bisphosphonates among children with secondary osteoporosis. However, a Cochrane review on adults with secondary osteoporosis concluded that bisphosphonates are indeed effective in preventing and treating corticosteroid-induced bone loss [22].

Concerning the side effects, the authors of the above-mentioned Cochrane review on children conclude that bisphosphonate use was generally well tolerated in the short term. Harms data from 23 case series (n = 241 children) were used. One patient withdrew due to an adverse event. Five deaths were reported, but they were not attributed to the bisphosphonate treatment [41]. Adverse events mentioned in the case series from the Cochrane review on bisphosphonates are hypocalcaemia, acute phase reactions, gastrointestinal side effects, oesophageal erosions, bone/muscle pain, dizziness, rash and memory loss [41].

Other possible side effects of bisphosphonate treatment are: osteonecrosis of the jaw (never reported in any child), over-suppression of bone turnover, acute inflammatory response, uveitis and diarrhoea [42]. To reduce the risk of hypocalcaemia, adequate vit D stores and Ca intake must be ensured before and throughout bisphosphonate treatment. There are concerns of potential adverse effects on reproductive health in teenage girls [42]. In patients with impaired renal function, dosages of bisphosphonates should be adjusted, and in patients with a creatinine clearance of <30 mL/min, bisphosphonates must be used very cautiously [40].

DXA is the most widely used technique for BMD determination in children. Several observations suggest that BMD measured by DXA, despite its limitations, may be used to define strategies to prevent and treat bone loss in children with NS and receiving corticosteroids [13–17]. It is generally accepted that DXA results should be preferably expressed in Z-score [11]. From the present review, we conclude that evaluation of BMD by DXA is advisable in case of frequent or prolonged steroid use, even though clear recommendations of BMD target values or best timing of measurements cannot be deducted from the reported RCTs. The International Society of Clinical Densitometry guidelines for assessment, interpretation and reporting of BMD specify that DXA must always be performed before starting a bone-specific therapy [11]. A baseline BMD as part of serial DXA measurements can be considered a valuable aid in monitoring the effects of therapy.

CONCLUSIONS

Based on this systematic review, children with various renal diseases that are treated with steroids may benefit from prevention or treatment of decreased BMD. We suggest preventing steroid-induced bone disease in children by Ca and vit D supplementation. Bisphosphonates should be reserved for treatment of severe osteoporosis when the combination therapy with Ca and vit D has failed. More RCTs are required to establish evidence-based recommendations concerning dosages, monitoring of Ca and vit D, side effects and the standardization of BMD follow-up.

AUTHORS’ CONTRIBUTION

All authors have contributed substantially to conception and design, acquisition of data or analysis and interpretation of data; have drafted the article or revised it critically for important intellectual content and have approved the final version to be published.

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CONFLICT OF INTEREST STATEMENT

None declared.

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