

REVIEW

Effect of inhaled corticosteroids on bones and growth

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ABSTRACT: Inhaled corticosteroids are recognized as the most effective anti-inflammatory therapy in patients with asthma and their early introduction is recommended by national and international guidelines. Concerns have been raised about potential adverse effects of inhaled corticosteroids on bones and growth, as these appear to be more important clinically than effects on the hypothalamic-pituitary-adrenal axis, which are more commonly measured. This review examines the effects of inhaled corticosteroids on biochemical bone markers, bone density and growth in adults and children with asthma, in view of the recent availability of a substantial amount of new clinical trial data.

Examination of relevant retrospective and prospective data, involving 11 studies (1,240 patients) on biochemical bone markers and 14 studies (373 patients) on bone density over a wide dose range, have largely indicated no significant or clinically important effect on these measurements in adults or children with asthma. Markers of bone formation and resorption need to be measured concurrently for a reliable assessment of bone turnover to be made.

Knemometry, measuring lower leg growth rate, is a sensitive technique for comparing the systemic activity of different inhaled corticosteroids, but does not relate to long-term growth. The majority of approximately 40 studies on inhaled corticosteroids and statural growth in children, over a wide recommended dose range, including a number of recent long-term, prospective studies, demonstrate little or no effect. Children taking above recommended doses of inhaled corticosteroids should have their growth monitored using stadiometry at least every 6 months by trained personnel.

Most of the areas reviewed, particularly the relatively new areas of biochemical bone markers and bone density, require further properly controlled, long-term, prospective investigation, although the long-term value of bone markers appears limited. In summary, the data as it currently stands, suggests that doses of inhaled corticosteroids up to 1,000 $\mu\text{g}\cdot\text{day}^{-1}$ in adults and 400 $\mu\text{g}\cdot\text{day}^{-1}$ in children have no significant effect on bones and growth in the large majority of patients with asthma.

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Asthma is a chronic inflammatory disease of the airways and current national and international asthma management guidelines advocate the early introduction of inhaled corticosteroids as the most effective anti-inflammatory therapy available [1–4]. However, inhaled corticosteroids are not entirely devoid of risk and their use in clinical practice entails a judgement that weighs the potential benefits against the risks of treatment [5–6]. The potential for systemic effects of inhaled corticosteroids is considered to be reflected in their activity of suppressing the hypothalamic-pituitary-adrenal (HPA) axis [7]. However, the clinical relevance of such suppression has been questioned [8] and concerns have been raised concerning the possible effects of inhaled corticosteroids on bones [9] and growth [10]. This review examines the effects of inhaled corticosteroids on bone metabolism, bone density and growth in adults and children with asthma, in view of the recent availability of a substantial amount of new information from clinical trials.

Effect of corticosteroids on bone metabolism

Corticosteroids may lead to a reduction in bone mass and osteopenia *via* several different mechanisms, including direct effects on bone formation and bone resorption and indirect effects *via* actions on the pituitary-gonadal and pituitary-adrenal axes, intestinal calcium absorption, renal tubular calcium reabsorption and secondary hyperparathyroidism (fig. 1) [11]. A number of biochemical markers have been used to assess the short-term effects of inhaled corticosteroids on bone turnover [12] (table 1). Bone formation has been evaluated by measuring blood concentrations of bone-specific alkaline phosphatase, osteocalcin and procollagen type-1 carboxy-terminal and amino-terminal propeptides (PICP and PINP, respectively). Bone resorption has been evaluated by measuring urinary excretion of hydroxyproline, calcium and pyridinium cross-links and by serum levels of type-1 carboxy-terminal telopeptide (1CTP) and tartrate-resistant acid phosphatase.

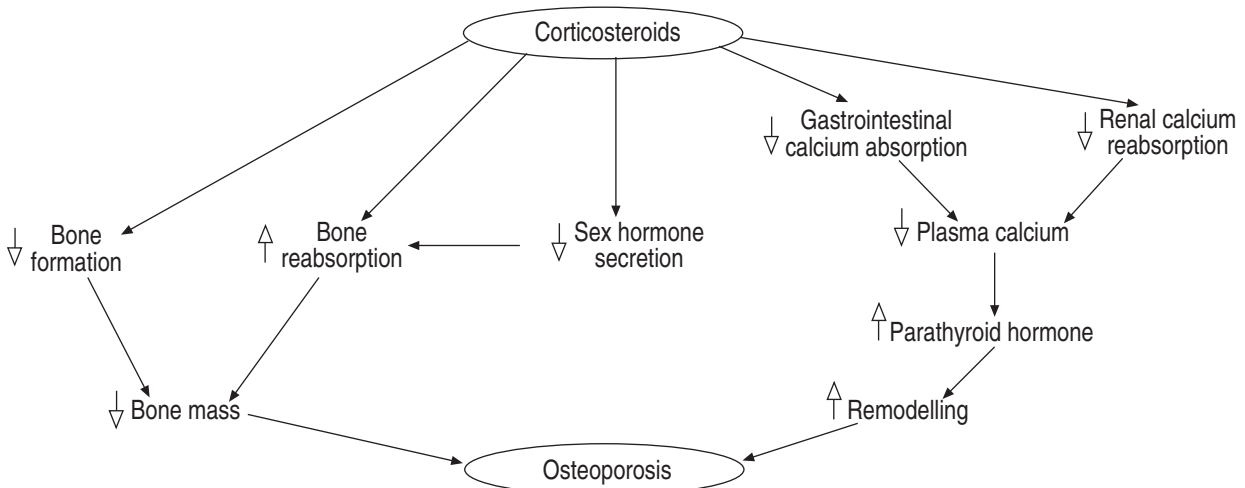


Fig. 1. – Possible effects of corticosteroids on bone metabolism and bone mass. \uparrow : increase; \downarrow : decrease.

Table 1. – Biochemical markers of bone formation and resorption

| Bone formation | Bone resorption |
|--|---|
| Blood | |
| Alkaline phosphatase (bone specific) | Acid phosphatase (acid resistant) |
| Osteocalcin | Type-1 carboxy-terminal telopeptide |
| Procollagen type 1 carboxy-terminal propeptide | |
| Procollagen type 1 amino-terminal propeptide | |
| Urine | |
| | Calcium |
| | Hydroxyproline |
| | Pyridinium cross-links (pyridinoline and deoxypyridinoline) |

Bone formation and resorption may both play a major role in the development of osteopenia, but it has become clear that the coupling mechanism between the two is more important [13, 14]. Individual biochemical markers, therefore, are likely to be of limited value and also seem largely to reflect on an individual's most recent corticosteroid exposure rather than to any important cumulative effect [14–19]. A combination of measurements of markers of both bone formation and resorption are therefore necessary to reliably determine the effect of corticosteroids on overall bone turnover.

In trying to interpret the effects of any treatment on bone metabolism in patients with asthma, it is also important to consider the effect of age, diet, physical activity and the sensitivity and specificity of the test. For example: the excretion of pyridinium cross-links in children is considerably higher than in adults [20]; urinary hydroxyproline levels are susceptible to dietary influences, whereas pyridinium cross-links are not and the latter are also a more true measure of bone as opposed to soft tissue collagen [21]; when physical activity of patients with rheumatoid arthritis improves following treatment with prednisolone, bone loss may fall and bone density actually increase [22]; and urinary cross-links are more sensitive than ICTP to changes in trabecular bone, as seen with corticosteroid therapy, and deoxypyridinoline is more specific for osseous

tissue than are pyridinoline crosslinks [21]. In addition, when assessing possible corticosteroid effects, it is essential to include an appropriate control group, as asthma itself may have an important effect on some variables, as for example, on plasma osteocalcin levels which may be reduced [15].

Adults

In adults, inhaled corticosteroids at doses of up to 2,000 $\mu\text{g}\cdot\text{day}^{-1}$ have no effect on urinary calcium excretion. However, reversible dose-related suppression of plasma osteocalcin, a protein synthesized primarily by osteoblasts, has been reported with inhaled beclomethasone dipropionate (BDP) and budesonide at doses above 1,000 $\mu\text{g}\cdot\text{day}^{-1}$ in normal volunteers [16–18] and rarely in patients with asthma [23], although the clinical significance of such changes remains unknown [24]. Other studies with inhaled corticosteroids have not confirmed this effect on plasma osteocalcin or other markers of bone formation in patients with asthma [25, 26] (table 2). High doses of BDP have also been shown to increase urinary hydroxyproline excretion, at least in normal male subjects [19]. Urinary excretion of pyridinium cross-links, a more sensitive marker of bone collagen resorption, however, is not increased, even in patients also taking intermittent courses of oral corticosteroids [27]. In adults, the magnitude of the effect of inhaled corticosteroids on markers of bone metabolism is significantly less than that of therapeutically equivalent doses of prednisolone. For budesonide, 2,000 $\mu\text{g}\cdot\text{day}^{-1}$ has a similar effect in suppressing osteocalcin production to that of prednisolone 15 $\text{mg}\cdot\text{day}^{-1}$ [28].

In contrast to some of the above results, are the findings of two recent prospective studies in patients involving fluticasone propionate (FP) [23, 29], a new potent inhaled corticosteroid which clinical studies have suggested is as effective as twice the dose of BDP [30–32] and budesonide [29, 33, 34]. In the first of these studies [23], clinically equivalent doses of FP and BDP (*i.e.*, 750 $\mu\text{g}\cdot\text{day}^{-1}$ and 1,500 $\mu\text{g}\cdot\text{day}^{-1}$, respectively) were compared in a double-blind, crossover study consisting of two 6 week treatment periods in patients with moderate to severe asthma. BDP decreased serum levels of both osteocalcin and ICTP

Table 2. – Studies of the effects of inhaled corticosteroids on markers of bone formation and resorption in adults and children with asthma

| Treatment | R/P | Daily dose µg | Delivery device | Patients n | Treatment duration | Effect on bone formation | Effect on bone resorption | First author | [Ref.] |
|-----------------|-----|------------------|--------------------|---------------|-----------------------|------------------------------|------------------------------|-----------------|--------|
| Adults | | | | | | | | | |
| FP BDP | P | 750 | MDI | 21 | 6 weeks | Nil | Nil | BOOTSMA | [23] |
| BDP | R | 1500 | MDI | 70 | 2.5 yrs | Ost & P1CP reduced | Nil | KERSTJENS | [25]* |
| BDP | R | 1000–2000 | MDI+S | 57 | >1 yr | Nil | Nil | PACKE | [27] |
| BDP | P | 200–2000 | MDI | 7 | 3 weeks | Nil on P1CP, P1NP reduced | Nil | PUOLIJOKI | [26] |
| FP BDP | P | 1000–2000 | MDI+S | 671 | 6 weeks | Nil | Nil | AYRES | [29] |
| FP BDP | P | 1000 | MDI+S | 24 | 2 yrs | Nil | Nil | EGAN | [39] |
| BDP | P | 2000 | MDI+S | | | Nil | Nil | | |
| Children | | | | | | | | | |
| Bud | P | 800 | DPI | 14 | 4 weeks | Ost & P1CP reduced | 1CTP & UPC reduced | SORVA | [14] |
| BDP | R | 300–800 | MDI | 18 | 25 months | Nil | TRAP reduced | KONIG | [15] |
| Bud | P | 400–800 | MDI+S | 15 | 5 months | Ost & P1CP reduced | ND | SORVA | [36] |
| Bud | P | 200–800 | MDI | 14 | 2 weeks | Nil | Nil | WOLTERS | [35] |
| FP BDP | P | 400 | DPI | 229 | 8 weeks | Nil | Nil | HOECKX | [37] |

R: retrospective; P: prospective; BDP: beclomethasone propionate; MDI: metered-dose inhaler; +S: plus spacer; P1CP: procollagen type-1 C-terminal propeptide; P1NP: procollagen type-1 amino-terminal propeptide; Ost: osteocalcin; 1CTP: type-1 carboxy-terminal telopeptides; TRAP: tartrate resistant acid phosphatase; UPC: urinary pyridinium cross-links; FP: fluticasone propionate; Bud: budesonide; ND: not done; DPI: dry powder inhaler. *: patients with asthma and COPD included in this study.

significantly, although FP did not. Neither BDP nor FP increased markers of bone resorption. Interestingly neither treatment affected mean morning cortisol levels, indicating a separation between the response of the HPA axis and that of biochemical markers of bone formation. In the second study [29], a large, randomized, double-blind trial in 671 adults with severe asthma, FP 1,000 µg·day⁻¹ and 2,000 µg·day⁻¹ and budesonide 1,600 µg·day⁻¹ had no effect on a range of markers of bone formation and resorption after 6 weeks of treatment. Curiously, an overall index of bone formation relative to bone resorption (*i.e.*, P1CP: 1CTP ratio), showed a small increase following treatment with FP 2,000 µg·day⁻¹. This suggests, if anything, a beneficial effect on bone turnover, possibly related to an improvement in physical activity, as previously reported in patients with rheumatoid arthritis treated with prednisolone [22].

Children

Studies on biochemical markers of bone turnover in children treated with inhaled corticosteroids have mostly been reassuring and daily doses of 800 µg of BDP and budesonide and 200 µg of FP have been found not to affect serum levels of bone-specific alkaline phosphatase, osteocalcin, parathyroid hormone or urinary hydroxyproline excretion [5, 15, 35]. One small, prospective study, however, demonstrated a significant reduction in osteocalcin and P1CP, at both 1 and 5 months following treatment with budesonide at doses of 400 µg·day⁻¹ and 800 µg·day⁻¹ [36]. Unfortunately markers of bone resorption were not measured in this study. A further open study by the same group in 14 newly diagnosed children with asthma, dem-

onstrated a significant fall in serum osteocalcin and P1CP, as well as a fall in 1CTP and urinary pyridinium cross-links following 4 weeks treatment with budesonide [14]. This result suggests the operation of a coupling process between bone formation and resorption, so that net bone loss may not occur. Low doses of oral corticosteroids in children, even as low as 2.5 mg·day⁻¹ of prednisolone, decrease plasma osteocalcin and urinary hydroxyproline excretion [35], again indicating preservation of normal coupling of bone formation with resorption.

Bone markers were extensively investigated in a recent prospective study comparing the safety and efficacy of FP 400 µg·day⁻¹ by Diskhaler with budesonide 400 µg·day⁻¹ by Turbuhaler [37]. This large, double-blind, study examined the effects of these corticosteroids in 229 prepubescent children, with mild to moderate asthma over 8 weeks of treatment. Biochemical markers of bone formation (*i.e.*, serum osteocalcin and P1CP) and bone resorption (*i.e.*, serum 1CTP and urinary hydroxyproline excretion) changed very little, with no consistent pattern of change. In addition, bone formation relative to bone resorption (*i.e.*, P1CP: 1CTP ratio), did not change from baseline and there was no difference between the two treatment groups. This study supports the low systemic activity of FP and budesonide at 400 µg·day⁻¹ in children and in particular demonstrates the absence of significant effects on a range of biochemical markers of bone formation and resorption and on an index of overall bone turnover.

Besides the sparsity of data in children, the interpretation of any effects of inhaled corticosteroids on markers of bone formation and resorption, is made difficult by the lack of information on age, sex and activity matched normal controls. It remains to be shown how biochemical

markers of bone formation and resorption relate to long-term changes in bone density and growth, although there are already indications that they may not predict corticosteroid induced changes in bone mass, at least not as measured by quantitative computed tomography (QCT) in adult patients with asthma [38, 39]. Patients receiving high doses of inhaled corticosteroids (i.e., $50.8 \text{ mg}\cdot\text{day}^{-1}$ in children and $52 \text{ mg}\cdot\text{day}^{-1}$ in adults), may initially experience a reduction in bone turnover. However, compensatory mechanisms soon become activated, including an increase in some aspects of bone formation [25] and a reduction in bone resorption [14, 29], which return an equilibrium to the bone remodelling units and hence bone turnover. This may reconcile why short-term changes in bone metabolism do not necessarily result in long-term changes in bone density.

Markers of bone formation and resorption need to be measured together for a reliable assessment of any effect of corticosteroids on bone turnover to be made. Serum osteocalcin and P1CP for bone formation and serum 1CTP and urinary pyridinium cross-links are currently the bone markers of choice.

Effect of corticosteroids on bone density

Oral corticosteroid therapy is a recognized cause of osteoporosis and increases the risk of vertebral and rib fractures [40]. However, there are no data to suggest that long-term treatment with inhaled corticosteroids is associated with an increased risk of fractures. Reduction in bone density in patients with asthma treated with high doses of inhaled corticosteroids for at least 6 months has been shown in some retrospective studies in adults [26, 41, 42], but not in others in either adults [43–46] or children [47–49] (table 3). One retrospective study demonstrated there were no significant differences in bone density between patients with asthma who were and those who were not on inhaled steroids, although cumulative inhaled steroid dose was associated with a small reduction in lumbar spine bone density in women [50].

There is a paucity of well designed, prospective studies investigating bone density with the use of inhaled corticosteroids in patients with asthma. This relationship is further confounded by the fact that these patients have also usually taken intermittent courses of oral corticosteroids in the past, and physical activity and exercise levels are not adequately considered. In addition, there are a number of different methods for accurately measuring bone density. Dual energy radiographic absorptiometry (DEXA) provides precise measurements of overall bone mass, but QCT is the only sensitive method that measures true bone density. Moreover, QCT can distinguish trabecular from cortical bone, which is important, as the former being more metabolically active, is more sensitive to the effects of corticosteroids [51]. Dual energy, as apposed to single energy QCT can also distinguish trabecular bone from marrow fat, providing for still greater specificity and accuracy [39].

Adults

A recent retrospective study, in which bone density of the lumbar spine was determined by DEXA and the prevalence of lumbar vertebral fractures was measured in 69

adult asthmatic patients, specifically aimed to differentiate between the effect of high doses of inhaled steroids and that due to past or current oral steroid therapy [9]. This study showed that the daily dose, but not the cumulative lifetime dose of inhaled steroid therapy, may adversely affect bone density. Bone density was also lower in association with the duration of past oral prednisolone therapy. Larger cumulative inhaled steroid doses were shown to be associated with higher bone densities and a reduction in the numbers of patients at risk of fracture. It appeared there were two opposing effects of inhaled steroid therapy on bone density and vertebral fractures, one a direct negative effect of the current daily dose and the other an indirect and protective effect of prolonged use associated with a reduction of oral steroid use.

To date, three well-controlled, long-term, prospective studies have been reported. The first, a randomized, double-blind, parallel group study, compared the effects of FP $1,000 \text{ }\mu\text{g}\cdot\text{day}^{-1}$ with BDP $2,000 \text{ }\mu\text{g}\cdot\text{day}^{-1}$ in patients with moderate to severe asthma, on bone density using QCT and DEXA over 2 yrs [39]. Prior oral steroid use was comparable between the two groups. Twenty four patients (12 male, 12 premenopausal female) with a mean age of 36 yrs completed 2 yrs of treatment. Spinal (T12 to L3) vertebral trabecular bone density as measured by dual energy QCT was normal at baseline and remained unaltered following 2 yrs of treatment with FP, but fell by 3.3% in absolute terms (i.e., in milligram per cubic centimetre) following treatment with BDP, though remaining well within the normal range. The treatment difference was significant in favour of FP at both 1 and 2 yrs. In addition, there was no change in bone density as measured by QCT or DEXA at any other limb or spinal site or in any of the biochemical markers of bone formation and resorption. This study suggests that high doses of inhaled steroids long-term may only have a negligible effect on bone density, although there may be a differential effect between different corticosteroids.

The second, a randomized, double-blind, parallel group study, compared the effects of FP $400 \text{ }\mu\text{g}\cdot\text{day}^{-1}$ with BDP $800 \text{ }\mu\text{g}\cdot\text{day}^{-1}$ and FP $750 \text{ }\mu\text{g}\cdot\text{day}^{-1}$ with BDP $1,500 \text{ }\mu\text{g}\cdot\text{day}^{-1}$ in 69 patients with asthma on bone density, using QCT of the radius and tibia and DEXA of the lumbar spine, over 1 yr [52]. Little or no evidence of any important differences between these equipotent doses of FP and BDP on bone density or bone metabolism were seen.

The third, prospective study carried out in 19 predominantly postmenopausal women with newly diagnosed asthma treated with BDP $1,000 \text{ }\mu\text{g}\cdot\text{day}^{-1}$ for 1 yr, showed no effect on bone density of the lumbar spine or proximal femur as measured by DEXA [53]. This result suggests that moderate doses of inhaled corticosteroids may not have an important effect on bone density over a 1 yr treatment period, even in predisposed patients.

Children

Few studies have investigated the effect of inhaled corticosteroids on bone density in children. In the first fully reported cross-sectional study [15], bone density was measured by radiographic absorptiometry of the hand and by DEXA of the whole body, radius and lumbar spine, in eight patients with asthma, aged 5–18 yrs, treated with BDP in doses between 300 to $800 \text{ }\mu\text{g}\cdot\text{day}^{-1}$ and in eight

Table 3. – Studies of the effects of inhaled corticosteroids on bone density in adults and children with asthma

| Treatment | R/P | Delivery device | Daily dose* µg | Patients n | Treatment duration | Effect on bone density | First author | [Ref.] |
|-----------------|-----|-----------------|-------------------|---------------|-----------------------|--|-----------------|--------|
| Adults | | | | | | | | |
| BDP, Bud | R | MDI + S | 0–3200 | 69 | Š1 yr | Reduced sinal BD by DEXA with higher daily doses Increased spinal BD with higher cumulative doses | TOOGOOD | [9] |
| BDP | R | MDI + S | 1000–2000 | 57 | Š1 yr | Small reduction in spinal BD by DEXA | PACKE | [27] |
| FP BDP | P | MDI + S | 1000 | 24 | 2 yrs | Nil on spinal or femoral BD by QCT an DEXA Small reduction in spinal BD by QCT for BDP | EGAN | [39] |
| BDP, Bud | R | MDI, DPI | 750–2000 | 11 | Š1 yr | Reduced spinal & limb BD by DPD | STEAD | [41] |
| BDP, Bud | P | MDI, DPI | 750–2000 | 11 | 7 months | Nil on spinal or limb BD by DPD | STEAD | [41] |
| BDP, Bud | R | MDI, DPI | 800–2000 | 18 | Š1 yr | Reduced femoral, but not spinal BD by DEXA | HANANIA | [42] |
| BDP | P | MDI | 735 | 10 | 1 yr | Nil on limb BD by QCT | MEDICI | [43] |
| BDP | R | MDI | 164–172 | 10 | Š1 yr | Nil on limb or spinal BD by DPA | WOLF | [44] |
| BDP, Bud | R | MDI, DPI | 1000–2000 | 37 | Š18 months | Nil on femoral or spinal BD by QCT | BOULET | [45] |
| BDP, Bud | R | MDI, DPI | 300–1000 | 48 | 2 yrs | Nil on spinal BD by DEXA | LUENGO | [46] |
| BDP, Bud | R | MDI, DPI | 100–3000 | 47 | Š5 yrs | No difference in limb or spinal BD by DEXA between those on to those not on IHS | WISNIEWSKI | [50] |
| FP BDP | P | MDI + S | 400 & 800 | 69 | 1 yr | No clinically important effects on limb or spinal BD by QCT and DEXA | MEDICI | [52] |
| BDP | P | MDI + S | 750 & 1500 | 19 | 1 yr | Nil on spinal or femoral BD by DEXA | HERRALA | [53] |
| Children | | | | | | | | |
| BDP | R | MDI | 300–800 | 36 | Š6 months | Nil on limb or spinal BD by DEXA | KONIG | [15] |
| BDP | P | MDI + S | 300–400 | 14 | 6 months | Nil on spinal BD by DEXA | BARALDI | [47] |
| BDP | R | MDI | 100–600 | 15 | Š1 yr | Nil on limb or spinal BD by DEXA | HOPP | [48] |
| BDP | R | MDI | 150–600 | 44 | Š6 months | Nil on limb or spinal BD by DPA and DEXA | MARTINATI | [49] |

R: retrospective; P: prospective; BDP: beclomethasone propionate; MDI: metered-dose inhaler; +S: plus spacer; FP: fluticasone propionate; Bud: budesonide; DPI: dry powder inhaler; BD: bone density; DEXA: dual energy x-ray absorption; QCT: quantitative computed tomography; DPD: dual photon densitometry; DPA: dual photon absorptiometry; IHS: inhaled corticosteroid. *: patients with asthma and COPD included in this study.

age and sex-matched control children with asthma not treated with corticosteroids. No significant differences in bone density measured by either technique were found between the two groups. Moreover, whole body bone density measured by DEXA was in the normal range or above for all 16 children with asthma, compared with 61 age- and sex-matched normal control children. In another cross-sectional study [48], total and regional (spinal and leg) bone density measured by DEXA, were assessed in 15 children with moderate to severe asthma, aged 6–13 yrs and 15 age- and sex-matched normal controls. In the group with asthma the mean dose of BDP was 327 µg·day⁻¹ for boys and 250 µg·day⁻¹ for girls. BDP had been used for a mean of 24 months in boys and 19 months in girls. No significant differences were found between the children with asthma and the control children for height, weight, total, spinal or leg bone density, bone age or Tanner stage.

These cross-sectional studies suggest that inhaled corticosteroids in doses between 250–800 µg·day⁻¹ do not affect total or regional bone density in children with asthma.

In the only longitudinal study in children [47], lumbar vertebral bone density measured by DEXA was assessed in 14 asthmatic subjects, mean age 9.1 yrs, taking BDP in doses between 300 to 400 µg·day⁻¹ for 6 months. A control group of 16 age- and sex-matched asthmatic children not taking corticosteroids were also studied. During the observation period, bone density increased by 2.3% in the BDP group and by 4% in the control group, with no significant treatment difference. This study indicates that continuous treatment with BDP 300–400 µg·day⁻¹ for 6 months does not cause significant spinal bone loss.

Thus, the majority of cross-sectional studies and the limited number of long-term, prospective studies currently available, suggest that inhaled corticosteroids have no

substantial or independent effect on bone density in adults or children with asthma. Any indication of such an effect from retrospective studies is complicated by the uncertain influence of past systemic corticosteroid therapy, confounding the interpretation of many of the studies, and different levels of disease control and physical activity, which may all have an important effect on bone density. Longer-term, prospective, well-designed and adequately controlled studies, of at least 1 yrs duration, particularly in children, are much needed to reliably assess any true effect of inhaled steroids on bone density.

In summary, a small reduction in bone density may result from the use of high doses (*i.e.*, ≥ 2 mg·day⁻¹ in adults) of inhaled corticosteroids after several years of treatment [39], perhaps particularly in genetically or medically predisposed individuals [54]. Small changes over several years may translate with continuing exposure over many years to a clinically significant change, although the evidence for this remains sparse. At present it is not clear which individuals taking high doses of inhaled corticosteroids are most susceptible to significant bone loss, apart from those also taking regular oral corticosteroid therapy, who often have reduced bone density [39]. In addition, there is currently very little information on bone structure and quality in patients with asthma, and this may be just as or more important than simple measurements of bone density in determining the risk of fractures in those requiring regular corticosteroid therapy [51, 55].

Optimal control of asthma symptoms and lung function using inhaled corticosteroids, with consequently reduced exposure to oral corticosteroids, is currently the most effective strategy for preventing significant bone loss in patients with asthma. Until more prospective data and better guidelines are available, monitoring of bone density using QCT or DEXA, in patients taking high doses of inhaled corticosteroids is probably best reserved for patients who may be predisposed to accelerated bone loss and osteoporosis (*e.g.*, patients requiring maintenance or frequent courses of oral corticosteroids, those with associated medical disorders leading to osteoporosis, those with a strong family history of osteoporosis, smokers and postmenopausal women) [56]. If bone density is low, then use of oral corticosteroids should be kept to a minimum and treatment with bisphosphonates, hormone replacement therapy or calcitriol should be considered.

Effect of corticosteroids on growth

There has been much concern over the possible effects of inhaled corticosteroids on statural growth in children and a delay in puberty has been implicated [57–59]. Children may vary in their susceptibility to corticosteroid-induced growth inhibition and a small proportion of asthmatic children could be more susceptible to this effect [59, 60]. However, studies investigating the effect of inhaled corticosteroids on growth have produced conflicting results [61]. The interpretation of these studies have been confused by a number of factors which themselves may affect growth or its measurement, including disease severity, seasonal variation in growth, pubertal status, concomitant use of oral corticosteroids and study methodology. In

addition, height measurements made over a period of <1 yr are liable to error and misinterpretation.

Asthma itself, however, like other chronic diseases, may result in poor growth and delay the onset of puberty [62, 63]. The delay in puberty may allow children with asthma to grow for a longer period, so that their final adult height is in fact normal [62, 63]. Moreover, a recent study showed that the height of asthmatic children not receiving corticosteroids correlated significantly with their pulmonary function, suggesting that asthma severity may itself have an important influence on growth [64].

Systemic corticosteroids, even at doses as low as 5 mg·day⁻¹ prednisolone [65], are known to impair growth in children and prior treatment with these may further complicate assessment of growth in children with asthma [63, 65, 66]. The direct influence of asthma on growth makes it difficult to assess the effects of corticosteroids in cross-sectional studies, although the majority of these studies have shown no effect of inhaled corticosteroids [67–76]. Longitudinal studies have also generally failed to demonstrate any significant effect of inhaled corticosteroids on statural growth in doses up to 800 μ g·day⁻¹ for up to 5 yrs of treatment [62, 77–79]. One exception, a placebo controlled, longitudinal study [10], showed a small amount of growth impairment in a group of 44 children with mild asthma treated with BDP 400 μ g·day⁻¹. However, this study was too short to make a reliable assessment of growth (7 months), the difference in growth between active and placebo treatment though significant was only 1 cm and curiously there was no catch up growth seen in the 4 month washout period which followed the treatment phase of the study. In addition, overnight urinary cortisol excretion was not reduced, suggesting a separation between the systemic effects of inhaled corticosteroids on the HPA axis and growth.

Valuable to this debate, are the results of a recent meta-analysis of 21 studies involving 810 children with asthma, treated with oral (nine studies) and/or inhaled corticosteroids (12 BDP studies) [80]. As expected this showed significant growth retardation associated with the use of oral corticosteroids, but no such effect with inhaled BDP. In fact, a significant moderate tendency was observed for treatment with inhaled BDP to be associated with attaining normal stature. Moreover, there was no statistical evidence for BDP to be associated with growth impairment at higher doses, with a longer duration of therapy or with more severe asthma.

It is possible that the growth inhibitory effect of inhaled corticosteroids is dose-dependent for individual patients. High dose treatment in perhaps genetically susceptible individuals could result in permanent growth impairment, whereas the growth retardation associated with low dose treatment is likely to be offset at maturation by catch-up growth [81]. In fact, two studies have investigated the effect of high doses of inhaled corticosteroids on growth. One showed no clinically important effect of long-term treatment with >800 μ g·day⁻¹ budesonide [82] and the other no growth inhibition with 1,000 μ g·day⁻¹ of flunisolide used for 1 yr [83]. There are anecdotal reports of growth deceleration in asthmatic children treated with inappropriately high doses (*i.e.*, 5–10 times the recommended dose) of inhaled corticosteroids [84]. However, these reports have been criticised for their lack of: appropriate clinical

management; controls; sound methodologies and growth measurements; and absence of statistical analyses [85].

In addition, data from three studies are now available investigating the effect of inhaled FP on statural growth in asthmatic children. In the first, height velocity standard deviation scores (HVSDS) were calculated from stadiometric height measurements in 41 children (25 male), aged 6–12 yrs (mean 8.9 yrs), with moderately severe asthma, treated with FP 100 or 200 $\mu\text{g}\cdot\text{day}^{-1}$ according to clinical need, for a mean of 1.2 yrs [86]. Growth during treatment with FP was not significantly different from age and sex matched national standards, with a mean HVSDS of 0 and a range of -2.3 to 2.8. Moreover, no significant difference in HVSDS post-treatment were noted in 30 of the children for whom pretreatment scores in the year prior to starting FP were available.

The second study, a prospective, randomized, double-blind, parallel group trial, compared the effects of FP 100 $\mu\text{g}\cdot\text{day}^{-1}$, FP 200 $\mu\text{g}\cdot\text{day}^{-1}$ and placebo on statural growth using a Holtain stadiometer over 1 yr, in 352 pre-pubescent children, aged 4–11 yrs, with mild to moderate asthma [87]. There were no statistically significant differences observed in the whole population or the actual pre-pubescent population (57 patients entered puberty during the course of the study), between either dose of FP and placebo, for mean change in height, or mean change in growth velocity. All three treatment groups in fact grew at a normal rate. In addition, plasma P1CP, a biochemical marker of bone formation, was not affected by either dose of FP.

In the third study, statural growth was measured using a Holtain stadiometer in 60 prepubertal children with mild asthma, aged 4–10 yrs, treated with FP 50 μg *b.i.d.* or sodium chromoglycate (SCG) 20 mg *q.i.d.*, prospectively over 1 yr [88]. There were no significant differences between patients who received FP or SCG in terms of height velocity adjusted for age and sex (*i.e.*, 6.0 $\text{cm}\cdot\text{yr}^{-1}$ and 6.5 $\text{cm}\cdot\text{yr}^{-1}$, respectively) or HVSDS (0.2 and 0.5 respectively). There were, however, fewer withdrawals and lung function improved to a greater extent in the FP treated patients compared with those receiving SCG.

Effect of corticosteroids on knemometry

Knemometry, which specifically and precisely measures lower leg growth rate, is thought to be a very sensitive indicator of possible systemic effects of corticosteroids. Indeed it has been shown that treatment with 2.5 $\text{mg}\cdot\text{day}^{-1}$ of prednisolone almost completely arrests lower leg growth [89]. A number of early knemometry studies, which were not ideally designed, small in size and without suitable placebo or washout phases, demonstrated some reduction in lower leg growth rate with doses of inhaled steroids (*i.e.*, BDP and budesonide), between 400 μg and 800 $\mu\text{g}\cdot\text{day}^{-1}$ [90–93].

A recent placebo-controlled study investigated the effect of budesonide 800 $\mu\text{g}\cdot\text{day}^{-1}$ on knemometric measurements and bone markers in adolescents [94]. This demonstrated a significant reduction in lower leg growth rate, as well as PINP, ICTP and urinary pyridinoline cross-links, suggesting a possible link between lower leg growth suppression and type I and III collagen turnover in adolescents.

One of the most carefully designed knemometry studies investigated the effect of FP 200 $\mu\text{g}\cdot\text{day}^{-1}$ and 400 $\mu\text{g}\cdot\text{day}^{-1}$ and budesonide 200 $\mu\text{g}\cdot\text{day}^{-1}$ and 400 $\mu\text{g}\cdot\text{day}^{-1}$, as dry powders, and placebo on lower leg growth rate [95]. This was a single centre, randomized, double-blind, double dummy, three way crossover study with each treatment lasting 15 days, carried out in 48 children aged 6–12 yrs with mild asthma. Twenty four children received 200 $\mu\text{g}\cdot\text{day}^{-1}$ of FP or budesonide or placebo and 24 other children received 400 $\mu\text{g}\cdot\text{day}^{-1}$ FP or budesonide or placebo. A washout period of 2 weeks separated each of the three treatment periods. The results showed no significant difference between lower leg growth rate during treatment with FP 200 $\mu\text{g}\cdot\text{day}^{-1}$, budesonide 200 $\mu\text{g}\cdot\text{day}^{-1}$ or placebo. However, lower leg growth rate during treatment with budesonide 400 $\mu\text{g}\cdot\text{day}^{-1}$ was significantly lower than during placebo, although this was not so with FP 400 $\mu\text{g}\cdot\text{day}^{-1}$.

Despite their immediate attractions, however, knemometry and short-term growth studies have a number of limitations. It is becoming clear that there is no good link between short-term growth and long-term growth or final height and the possibility of "catch-up" growth after stopping therapy must also be considered [96]. Other drawbacks of short-term studies include variations in normal growth patterns (*i.e.*, seasonal patterns and "spurts"), the need for longer run-in and washout periods and the need to take measurements at the same time of day to account for possible leg-shrink phenomenon (*i.e.*, usual compression of joint cartilage with weight bearing during the course of the day) [96–98]. Knemometry, therefore, appears to be a sensitive technique for comparing the systemic activity of different inhaled steroids, but does not relate to long-term growth.

These data in children, indicate that inhaled corticosteroids, at least within their recommended dose ranges (*i.e.*, currently up to 400 $\mu\text{g}\cdot\text{day}^{-1}$ with BDP and budesonide and up to 200 $\mu\text{g}\cdot\text{day}^{-1}$ with FP), have no substantial effect on long-term growth or on biochemical markers of bone formation and resorption. This conclusion is further supported by a number of studies in children with asthma of all severities, which have demonstrated only minimal or no systemic effects or HPA axis suppression with a similar dose range of inhaled corticosteroids [1, 5, 99], as well as a recent comprehensive clinical review of safety measures in children [100]. Further long-term, prospective dose ranging studies, with carefully standardized height measurements are necessary to define the safe and optimal use of higher doses of inhaled corticosteroids in children with asthma. In the meantime it may be advisable to measure statural growth at least every 6 months in all children receiving more than 400 $\mu\text{g}\cdot\text{day}^{-1}$ of inhaled corticosteroids. This needs to be carried out by trained personnel using regularly calibrated equipment.

Impact of delivery device and different inhaled corticosteroids

Spacer devices used with metered-dose inhalers (MDIs) generally enhance lung deposition and reduce oropharyngeal deposition and systemic bioavailability [101–103]. Therefore, the use of spacer devices also need to be considered when comparing inhaled medications, as they may critically affect the safety profile of the drug [104], particularly when required long-term. The effect of spacers on

bones and growth is ultimately likely to depend on to what extent they affect overall systemic bioavailability *via* the lung and gut.

Dry powder inhalers (DPIs), *i.e.*, the Diskhaler and Turbuhaler, unlike MDIs, require deep and forceful inspiration, rather than slow, co-ordinated inspiration. This difference in technique along with the inability to use DPIs with a spacer, increase the probability of significant oropharyngeal drug deposition and systemic activity *via* the gastrointestinal tract.

In fact some bioavailability data with budesonide suggests that the Turbuhaler may produce twice the lung deposition of an MDI used without a spacer [103]. However, as the risk of systemic effects of inhaled corticosteroids is thought to be determined primarily by systemic absorption from the peripheral airways (which is not subject to first pass metabolism), as opposed to the gastrointestinal tract [104], the increased lung deposition from the Turbuhaler may be at the expense of increased systemic activity and side-effects. This suggests the dose of budesonide *via* the Turbuhaler should be halved and one clinical study in children using budesonide *via* the Turbuhaler at half the dose given by MDI and large volume spacer, revealed similar urinary cortisol excretion at doses between 200 to 800 $\mu\text{g}\cdot\text{day}^{-1}$ [105]. This potential risk with increased lung deposition may also apply to some of the new chlorofluorocarbon (CFC)-free corticosteroid aerosols which have a smaller mean particle size and may consequently increase peripheral lung deposition [106] and long-term safety data on bones and growth with these are eagerly awaited.

With regard to device data on inhaled corticosteroids and their effect on bones and growth, no studies have specifically assessed their potential differential effects. It seems likely from what has been said above, that different devices with different systemic bioavailabilities could affect bones and growth to different extents, particularly in the long term. The current review of all the key bone marker and bone density studies in patients, however, indicate no obvious device effect or differences, despite MDIs, DPIs and spacers all having been used (tables 1 and 2). Further studies specifically addressing this point are clearly needed.

Few studies have specifically assessed the differential effects of different inhaled corticosteroids on bones and growth in patients with asthma. These studies have essentially compared BDP, budesonide and FP, with very little data being available on flunisolide or triamcinolone.

With regard to bone markers, four studies have compared FP with BDP or BUD (table 2), but only one has demonstrated any difference. In the latter study therapeutically equivalent doses of FP and BDP over 6 weeks demonstrated a significant reduction in markers of bone formation (*i.e.*, osteocalcin and PICP) with BDP but not with FP [23]. For bone density, only one study has prospectively compared two inhaled corticosteroids [39]. In this study therapeutically equivalent doses of FP and BDP were compared over 2 yrs. FP had no effect on spinal or limb bone density, but BDP produced a small fall in spinal bone density, as measured by QCT, the clinical relevance of which is uncertain.

In terms of statural growth studies, none are currently available prospectively comparing two inhaled corticosteroids. Two studies, however, have directly compared different inhaled corticosteroids in their effects on short-term

growth of the lower leg as measured by knemometry [93, 95]. In one study, BDP at 400 $\mu\text{g}\cdot\text{day}^{-1}$ and 800 $\mu\text{g}\cdot\text{day}^{-1}$ was associated with a significantly greater reduction in lower leg growth velocity compared with FP 200 $\mu\text{g}\cdot\text{day}^{-1}$ [93]. In the most well-designed knemometry study [94], FP 200 $\mu\text{g}\cdot\text{day}^{-1}$ and 400 $\mu\text{g}\cdot\text{day}^{-1}$ were compared with budesonide 200 $\mu\text{g}\cdot\text{day}^{-1}$ and 400 $\mu\text{g}\cdot\text{day}^{-1}$ and placebo. Neither dose of FP had an effect on growth rate, although budesonide 400 $\mu\text{g}\cdot\text{day}^{-1}$ did significantly reduce this *versus* placebo.

Clearly the current data is limited, although there is an indication that FP at therapeutically equivalent doses (*i.e.*, half the milligram dose of other corticosteroids) [29–34, 107] may have a smaller effect on some measurements of bones and growth. Further prospective, comparator, dose ranging studies involving all the commonly used inhaled corticosteroids are necessary to satisfactorily address this question.

Conclusion

It is clear that most of the areas reviewed, particularly the relatively new ones of biochemical bone markers and bone density, require further longer-term, properly controlled, prospective investigation. However, the data as they currently stand suggest that doses of inhaled corticosteroids up to 1000 $\mu\text{g}\cdot\text{day}^{-1}$ in adults and up to 400 $\mu\text{g}\cdot\text{day}^{-1}$ in children can be considered safe and have no significant effect on bones and growth in the large majority of patients with asthma. Further data are necessary to determine any important difference in risk between different individuals, different inhaled corticosteroids and different devices.

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