



Mini-Symposium - Inhaled Corticosteroids Safety Panel

Inhaled corticosteroids Effects on growth and bone health

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ABSTRACT

Background: Both slowed growth in children and reduced bone mineral density (BMD) are systemic effects of corticosteroids, and there is concern about the degree to which these systemic effects affect growth and BMD.

Objective: To engage in a data-driven discussion of the effects of inhaled corticosteroids (ICSs) on growth in children and BMD.

Methods: Articles were selected based on their relevance to this review.

Results: Studies of ICSs in children in which growth was a secondary outcome have revealed slowed growth associated with low doses of budesonide, fluticasone propionate, and beclomethasone dipropionate. In the study of budesonide, the effect was permanent, and in the study of fluticasone propionate, the effect was long-lasting, but it is unclear whether the effect was permanent. However, the results of studies in which growth was the primary outcome were mixed. Slowed growth was detected in a study of beclomethasone dipropionate; however, slowed growth was not detected in a study of ciclesonide or flunisolide. A decrease in BMD acquisition in children was associated with high doses but not low to medium doses of ICSs. In adults, there was a dose-related effect of ICSs on BMD. Both higher daily dose and larger cumulative dose were associated with increased bone density loss.

Conclusion: Because of the systemic effects on growth and bone health, children should be monitored for growth using stadiometry every 3 to 6 months and BMD should be monitored yearly in patients being treated with high doses of ICSs.

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Introduction

Slowed growth and reduction in bone mineral density (BMD) are known adverse effects of systemic exposure to corticosteroids. Studies have found systemic effects of oral corticosteroids on growth,^{1–3} BMD,⁴ and risk of fracture.⁵ Systemic exposure is reduced when corticosteroids are inhaled instead of taken orally or parenterally. However, although asthma treatment and management guidelines recommend inhaled corticosteroids (ICSs) as the preferred first-line therapy for asthma,^{6,7} uncertainty remains

among some clinicians about the extent of systemic effects among ICSs. In this article, we discuss the data on ICS systemic effects on growth and bone health.

The effects of ICSs on growth in children and bone health have been extensively reviewed in the past, and several recent reviews^{8–11} summarize this area very well. However, some clinicians who do not treat patients with asthma on a regular basis, for example, practitioners in primary care or pediatrics, are uncertain of the balance between ICS efficacy and safety. This article is one in a series of articles in a minisymposium entitled Inhaled Corticosteroids in Asthma: The Balance Between Safety and Efficacy, which was developed to help guide clinicians through identified knowledge and practice gaps concerning the balance of ICS efficacy and safety, the effects of ICS delivery and devices, and the importance of patient education and effective communication. As such, the goal of this article is not to comprehensively review all growth and bone health studies but to highlight key articles for clinicians who might not be familiar with the literature. This article focuses on key, well-designed studies of particular populations of interest. In particular,

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this review focuses on well-designed growth studies funded by the National Institutes of Health (NIH) and pharmaceutical industry after issuance of guidance by the US Food and Drug Administration (FDA).

Systemic availability varies among ICSs and depends on an ICS's pharmacokinetics, formulation, and delivery.¹¹ These effects are discussed in more detail in 2 other articles in this minisymposium (Inhaled Corticosteroids: Ocular Safety and The HPA Axis and Inhalation Devices, Delivery Systems, and Patient Technique). Factors such as receptor-binding affinity, lipid conjugation, protein binding, and clearance from systemic circulation contribute to systemic adverse effects.¹¹ In addition, drug formulation can affect the proportion of the ICS dose that is delivered to the lungs and systemic availability. In particular, in pressurized metered-dose inhalers (pMDIs), hydrofluoroalkane solution formulations deliver a higher fraction of smaller particles to the distal airways and distribute the drug more evenly throughout the lungs compared with chlorofluorocarbon formulations.¹² The type of device can also affect systemic availability. Evidence suggests that compared with dry powder inhalers (DPIs), pMDIs may enhance lung deposition while reducing systemic bioavailability via the gastrointestinal tract.^{13,14} Note that the major source of systemic bioavailability of ICSs is the lung and not the gastrointestinal tract.¹⁵ In addition, ICS bioavailability is affected by the choice of spacers and masks.^{16,17} Nebulizers also affect bioavailability, as shown in one of the few growth studies in which an ICS was delivered by nebulizer.¹⁸

Growth in Children

A frequently expressed concern of ICSs is the systemic effects on growth in children. Growth is considered the most sensitive indicator of systemic corticosteroid activity by the FDA—more sensitive than the hypothalamic-pituitary-adrenal axis.¹⁹ However, detecting effects on growth is confounded by growth rates that vary throughout childhood. Our focus is on high-quality, well-designed studies with treatment durations of approximately 1 year or longer. These include NIH-funded studies that evaluated growth as a secondary outcome and pharmaceutical-funded studies in which growth is the primary outcome to examine the risks of ICSs and compare the relative systemic activities of different ICS.

Studies With Growth as a Secondary Outcome

Three NIH-funded studies with growth as a secondary outcome—Childhood Asthma Management Program (CAMP), Prevention of Early Asthma in Kids (PEAK), and Treating Children to Prevent Exacerbations of Asthma (TREXA)—revealed suppressed growth with low doses of budesonide via DPI, chlorofluorocarbon-propelled fluticasone propionate via pMDI with valved spacer and facemask, and hydrofluoroalkane-propelled extrafine-particle beclomethasone dipropionate via pMDI, respectively.^{20–22} In the CAMP trial, the effect on growth was permanent. In the PEAK trial, the growth effect was long-lasting (2 years after discontinuation) in certain subgroups, but children were not followed up to final adult height to determine permanency. All 3 trials were randomized, double-blind, placebo-controlled trials with large sample sizes and used low doses of ICSs. Treatment durations were 4 to 6 years for the CAMP study, 2 years for the PEAK study, and 44 weeks for the TREXA study. Note that the TREXA study, with a study duration of 44 weeks, was an exception to FDA guidance that study durations should be at least 1 year.¹⁹ All 3 studies were designed with efficacy as the primary outcome and growth as a secondary outcome. PEAK enrolled preschool infants and toddlers, whereas the other 2 studies enrolled school-aged children, and certain drivers of

growth, such as nutrition, may be more important in the former population.

In the CAMP study, 1,041 children in the United States aged 5 to 12 years with mild to moderate asthma were treated twice daily with 200 μ g of budesonide via DPI (Turbuhaler), 8 mg of nedocromil via pMDI, or placebo (via Turbuhaler or pMDI) for 4 to 6 years.²⁰ The study found a decrease in the change in standing height attributable to long-term ICS treatment, but the effect was transient (Fig 1). Compared with children who received placebo, children who received budesonide grew 1.1 cm less during the study ($P = .005$). Children in the budesonide treatment group had reduced growth velocity in the first year, but in later years growth velocity increased to levels comparable to those of the placebo group. However, this resumed growth velocity could reflect an adherence issue effect in which patients were adherent in the first year but not as adherent in subsequent years, and thus in later years there was less systemic exposure of the ICSs.^{23,24} The decrease in growth velocity resulted in a permanent effect on adult height, in which there was a 1.2-cm difference (95% CI, 0.5–1.9 cm) in height 13 years after randomization when the mean age of patients was 25 years.²⁵

Comparable results occurred in the PEAK study. In this multicenter study conducted in the United States, 285 children 2 and 3 years old at high risk for asthma were treated twice daily with 88 μ g of chlorofluorocarbon-propelled fluticasone propionate or placebo via pMDI with an AeroChamber valved spacer and facemask for 2 years followed by a 1-year observation period without study medication.²¹ The AeroChamber with the facemask delivers twice the amount of fluticasone propionate to the lung in young children than with the Babyhaler,¹⁷ which had been used in previous studies and has shown no effects of chlorofluorocarbon-propelled fluticasone propionate pMDI on growth in 1- to 3-year-olds.²⁶ Treatment with fluticasone propionate was associated with a 1.1-cm reduction in growth at the end of 24 months of treatment compared with treatment with placebo ($P < .001$). However, during the 1-year observation phase, growth velocity was greater in the fluticasone propionate group than in the placebo group, and by the end of the 1-year observation phase the difference in height between groups had decreased to 0.7 cm ($P < .008$). That is, slowed growth was temporary. Two years after the 2-year treatment period ended, there was no significant difference between the fluticasone propionate and placebo groups in change in height from baseline (difference between fluticasone propionate and placebo groups, -0.2 cm; 95% CI, -1.1 to 0.6 cm).²⁷ However, a post hoc subgroup analysis suggested that the fluticasone propionate effect of slowed growth persisted 2 years after treatment ended in children who were 2 years old and weighed less than 15 kg at baseline (Fig 2). That is, ICSs suppressed growth while being taken, and one subgroup of smaller and younger patients did not catch up after ICS treatment was discontinued like the other subgroups did. However, these results should be interpreted with caution given that this was a post hoc analysis with small sample sizes and observations did not go beyond 2 years after treatment ended. Given these limitations, investigating this result further with a study designed to test the effects of age and weight on ICS use and growth in very young children is warranted.

Similar to the CAMP and PEAK studies, the TREXA study also found slowed growth with ICSs. The TREXA study evaluated the effects of hydrofluoroalkane-propelled, extrafine-particle beclomethasone dipropionate as a daily control, as an intermittent rescue, or as both daily control and intermittent rescue (combined group) vs placebo.²² In the TREXA study, 843 children aged 5 to 18 years with mild persistent asthma were treated for 44 weeks at 1 of 5 clinical centers in the United States. Growth was 1.1 cm less in both the beclomethasone dipropionate daily control group and the combined group compared with the placebo group ($P < .001$). However, growth in the beclomethasone dipropionate intermittent rescue group was not significantly different from placebo (0.3-cm

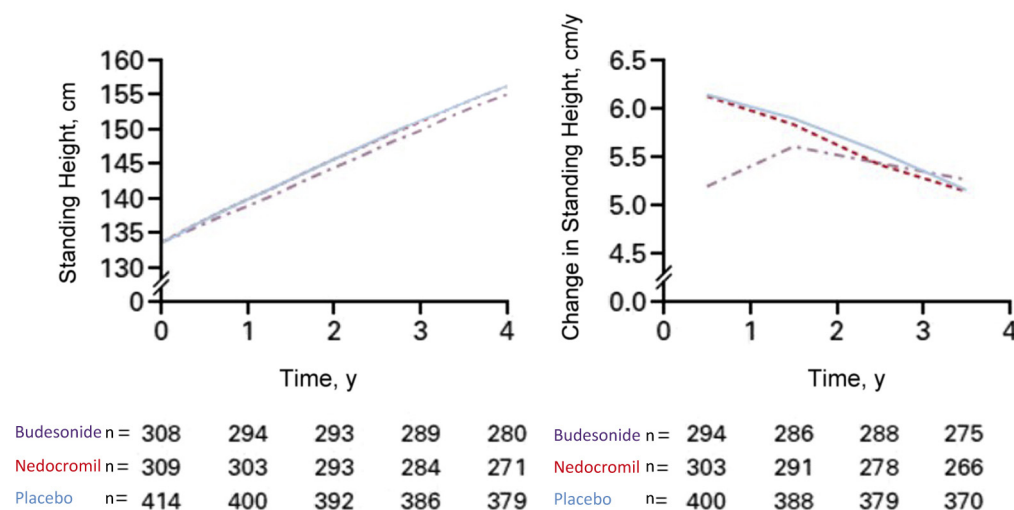


Figure 1. Standing height and change in standing height in the Camp Asthma Management Program Research Group study. Adapted from *The New England Journal of Medicine*, The Childhood Asthma Management Program Research Group, Long-term effects of budesonide or nedocromil in children with asthma, Volume 343, Pages 1054–1063.²⁰ Copyright © 2000 Massachusetts Medical Society, and used with permission.

reduction in growth, $P = .26$), showing that the growth effect of ICSs was lost with intermittent use. This finding leads to the question of whether the growth effect is caused by total amount throughout the year or persistent medication. To date, this is unclear. Note that in terms of effectiveness (time to first exacerbation), the intermittent rescue group was intermediate between the daily control group and the placebo group and was not statistically significantly different from the placebo group.

Studies With Growth as the Primary Outcome

The FDA has published industry guidance that specifies patient population, study design, and analyses needed to conduct growth studies.¹⁹ These are the guidelines that pharmaceutical companies use to assess growth as a primary outcome. The FDA requires that the patient population be prepubertal because rapid growth takes place during puberty. This rapid growth, the variability of when puberty begins, when the growth spurt happens, and how and when the growth spurt ends can confound results. Patients also should have mild, persistent asthma because more severe asthma can slow growth and may require systemic corticosteroids that also can slow growth. In addition, treatment and control groups should have comparable baseline demographics. Study design should incorporate a treatment period of at least 1 year, an untreated control group, baseline growth velocity data for at least 16 weeks, and a follow-up period of at least 8 weeks. Measures should include repeat stadiometer measurements, cortisol measurements, and pulmonary function tests. The primary end point is evaluated by regression analysis of growth velocity, whereas secondary end points should include a shift analysis in growth velocity percentile, an analysis of growth velocity percentiles, and growth velocity during follow-up.

A study with growth as the primary outcome found slowed growth during 56 weeks of treatment with chlorofluorocarbon-propelled beclomethasone dipropionate.²⁸ In this multinational study, 360 prepubertal children aged 6.4 to 9.4 years with mild persistent asthma were treated either with 5 mg of montelukast via chewable tablet once daily, 200 μ g of chlorofluorocarbon-propelled beclomethasone dipropionate twice daily via pMDI with spacer, or placebo. Note that the beclomethasone dipropionate treatment group served as a positive control. No significant differences were found in linear growth during the 56-week treatment period between the placebo and montelukast groups (0.03-cm difference; 95% CI, -0.26 to 0.31 cm), but linear growth for the beclomethasone dipropionate treatment group was less than that for the placebo group (0.78-cm difference, $P < .001$) and the montelukast group (0.81-cm difference, $P < .001$). Growth in the beclomethasone dipropionate treatment group was slowed throughout the 56-week treatment period.

In contrast, a study of hydrofluoroalkane-propelled, extrafine-particle ciclesonide and a study of hydrofluoroalkane-propelled, extrafine-particle flunisolide did not detect any effects on growth.^{29,30} In the first study, which was a multinational,

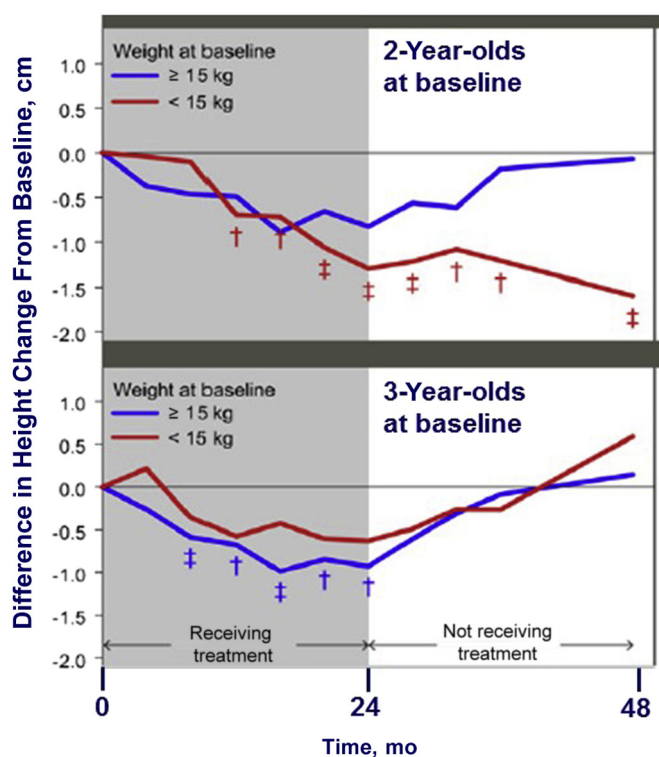


Figure 2. Difference in height change from baseline between fluticasone propionate and placebo treatment groups in a post hoc analysis in the Prevention of Early Asthma in Kids study. [†] $P < .05$; [‡] $P < .01$. Adapted from *Journal of Allergy and Clinical Immunology*, Vol 128, Guilbert et al, Growth of preschool children at high risk for asthma 2 years after discontinuation of fluticasone, Pages 956–963.e7, Copyright 2011²⁷, and used with permission.

randomized, double-blind, placebo-controlled trial, 661 prepubertal children aged 5.0 to 8.5 years with mild persistent asthma were treated daily with 40 μg of ciclesonide, 160 μg of ciclesonide, or placebo via pMDI without a spacer for 1 year followed by a 2-month follow-up period.²⁹ Growth rates during the 1-year treatment period were 5.73 cm per year (95% CI, 5.57–5.89 cm per year) for the 40 $\mu\text{g}/\text{d}$ of ciclesonide group, 5.60 cm per year (95% CI, 5.44–5.76 cm per year) for the 160 $\mu\text{g}/\text{d}$ of ciclesonide group, and 5.75 cm per year (95% CI, 5.59–5.90 cm per year) for the placebo group. Neither ciclesonide treatment group was significantly different from the placebo group. Although this study did not detect any significant effect of ciclesonide on growth and found that ciclesonide was noninferior to placebo, the drug was not approved for use in children younger than 12 years because the FDA stated that conclusions could not be drawn from this study because medication adherence could not be assured. In the second study, 218 prepubescent children aged 4 to 9.5 years with mild persistent asthma were treated twice daily with 170 μg of flunisolide-hydrofluoroalkane or placebo via pMDI with a built-in spacer for 52 weeks.³⁰ The study found no evidence that flunisolide-hydrofluoroalkane suppressed growth or bone maturation. Mean (SD) growth velocity was 6.01 (1.84) cm per 52 weeks for flunisolide-hydrofluoroalkane and 6.19 (1.30) cm per 52 weeks for placebo ($P = .42$). Bone maturation as measured by radiographic bone age was also the same for the 2 groups. Adherence rates were 86.1% for flunisolide-hydrofluoroalkane and 87.7% for placebo. These results are compelling because the study was designed to detect small effects, used a medium (not low) dose and the maximum FDA-approved (not starting) dose, used a delivery device with 68.3% lung deposition, and included an evening dose, which has a worse growth effect than a morning dose in some³¹ but not all studies.³² The results of the ciclesonide and flunisolide studies are similar to that of mometasone furoate, which had no significant effect on growth in children aged 4 to 9 years when dosed at 110 μg once daily by DPI.³²

Bone Health

ICSs also have systemic effects on bone health. Glucocorticoids cause reduced bone formation and increased bone resorption, which in turn decrease bone mass.³³ Bone mass increases during childhood, peaking between 20 and 40 years of age.³⁴ After the age of approximately 30 years, bone mass gradually decreases. Corticosteroid use can affect both the increase in bone mass in children and the rate of bone mass loss in adults. For adults, the main concerns of corticosteroid use are osteoporosis and its accompanying risks, such as a higher risk of bone fracture. The risk of ICS-induced loss of bone mass is particularly a concern in older individuals and postmenopausal women because there is a natural decrease in bone mass in these populations. For children, although growth suppression is the primary concern of ICS use, loss of bone mass is also a concern because there is the possibility of predisposing children for osteoporosis during adulthood.^{33,34}

The primary adverse effect of interest is risk of fracture, but study durations need to be long enough to detect differences in risk between treatment and control groups, given the relative infrequency of fractures. Biochemical markers of bone resorption and formation can be used to measure the systemic effects of corticosteroids, but these tend to have value only in the short term because the effect of corticosteroids on these markers attenuate after the first few weeks to months of ICS therapy.³⁴ Thus, these markers are useful for evaluating acute effects of corticosteroids but not chronic effects. BMD is an important marker because it is a sensitive measure of corticosteroid effects on bone and is the best measure in predicting fracture risk.³⁴ BMD can be assessed at various sites throughout the body, including the lumbar vertebrae,

which are clinically relevant sites for assessing BMD loss and risk of fracture.³⁴

Studies of Bone Health in Children

A study of high-dose ICSs found decreased acquisition of bone mineral in children treated with ICSs. In this study, 48 prepubertal children aged 5 to 14 years were studied for 9 to 20 months while they received either beclomethasone dipropionate via pMDI and spacer or budesonide via Turbuhaler, with doses ranging from 400 to 2000 $\mu\text{g}/\text{d}$.³⁵ These 48 children were compared with 9 children of similar age who were not receiving ICSs. Mean (SD) change in total bone mineral content from baseline was 264 (68) mg for the ICS-treated children and 330 (68) mg for the controls ($P < .02$). Furthermore, ICS dose was inversely correlated with the change in total bone mineral content.

Slowed BMD acquisition in children is thought to be a consequence of high doses because studies of low to moderate doses have found no effect on BMD. A cross-sectional study of bone density in children with asthma found no effect of low to moderate doses of beclomethasone dipropionate.³⁶ This study compared 15 children aged 6 to 13 years with moderate to moderately severe asthma taking chlorofluorocarbon-propelled beclomethasone dipropionate via pMDI to 15 age- and sex-matched controls. No statistically significant differences were found between the treatment group and the control group in terms of total bone density, spinal density, or leg density. However, sample sizes were small, and some of the children were entering puberty (Tanner stage 2).

A more compelling study is the CAMP study, which found no effect of low-dose ICSs on change on bone density among 1,041 children aged 5 to 12 years with mild to moderate asthma treated twice daily with 200 μg of budesonide via the Turbuhaler DPI, 8 mg nedocromil via pMDI, or placebo.²⁰ Mean change in bone density during the study was 0.17, 0.17, and 0.18 g/cm^2 for the budesonide, nedocromil, and placebo groups, respectively ($P = .53$ for budesonide vs placebo). Interestingly, a cohort follow-up study found sex-specific effects of both ICS and oral corticosteroids.⁴ Boys treated with ICSs had a small but significant decrease in bone mineral accretion compared with boys who did not receive ICSs, and there was also a significant dose-dependent effect of oral corticosteroids on bone mineral accretion. There was no effect of ICSs or oral corticosteroids on BMD in girls.

Studies of Bone Health in Adults

In a cross-sectional study of adults conducted in the United Kingdom, cumulative ICS dose was negatively associated with BMD.³⁷ BMD was assessed at the lumbar spine and proximal femur in 196 adults aged 20 to 40 years who had asthma and had taken ICSs for at least 6 months. Mean duration of ICS use was 6 years (range, 0.5–24 years), and the median cumulative ICS dose was 876 mg (range, 87–4380 mg). Most participants (80%) used beclomethasone dipropionate, whereas another 14% used budesonide, and the remaining 6% used fluticasone propionate. Most patients (76%) used a pMDI, and 11% of patients used a spacer device. After adjusting for the effects of age and sex, doubling the cumulative ICS dose was associated with a decrease in BMD of 0.023 g/cm^3 (95% CI, 0.005–0.041 g/cm^3 ; $P = .01$) at the lumbar spine, 0.020 g/cm^3 (95% CI, 0.002–0.038 g/cm^3 ; $P = .03$) at the femoral neck, 0.027 g/cm^3 (95% CI, 0.008–0.047 g/cm^3 ; $P = .006$) at Ward's triangle of the femur, and 0.019 g/cm^3 (95% CI, 0.002–0.035 g/cm^3 ; $P = .02$) at the trochanter. The clinical implications of this study's results are that although changes in bone density are not likely to be important in a few years, continuing exposure to high doses for many years might result in clinically important effects.

A dose-related decrease in BMD was also observed in premenopausal women in the United States.³⁸ In a 3-year prospective

study, bone density was measured in 109 premenopausal women aged 18 to 45 years who had asthma and were taking chlorofluorocarbon-propelled triamcinolone acetonide via pMDI. This study addressed many of the criticisms of previous studies by including a long treatment duration, verifying the doses of ICS taken by study participants, and controlling for the intermittent use of oral corticosteroids. By excluding menopausal women, the study also eliminated potential confounding effects of menopausal bone loss, although, of course, this also eliminated the possibility of gathering data from a subpopulation in whom ICS-induced bone loss is a particular concern. Another limitation is that the study investigated only triamcinolone acetonide, which is no longer on the market and had one of the highest oral bioavailabilities. In addition, the study used a nonapproved device to measure medication adherence. However, despite these limitations, this study remains one of the best designed studies. After adjusting for age, use of inhaled and oral corticosteroid use, and oral contraceptive use, each 100- μ g puff of triamcinolone acetonide led to a 0.00048-g/cm² decrease in bone density at the hip and a 0.00042-mg/cm² decrease at the trochanter ($P = .008$ and $P = .01$, respectively). The investigators noted that different ICSs might have different effects on BMD because of differences in formulation and delivery system, but they also noted that the decrease in BMD at the trochanter was similar to that observed in the cross-sectional study of beclomethasone dipropionate, budesonide, and fluticasone propionate described above.³⁷

Conclusions

Low doses of systemically active ICSs can suppress growth and permanently affect the adult height of children with mild or moderate persistent asthma. The effect on adult height is on the order of 1 to 1.5 cm. Although this effect on growth should not stop us from using ICSs for asthma, it should be part of shared decision making among the child, the parent, and the physician. ICSs differ in their levels of systemic activity, and some ICSs, even at the highest recommended dose, have no detectable activity on growth. Children using ICSs should be monitored frequently, approximately every 3 to 6 months, for growth using stadiometry.⁸

ICSs have systemic effects on BMD at high doses but not at low to medium doses. An ICS-induced decrease in bone density increases the risk of fracture, particularly in older adults and menopausal women, when there are already age-related and sex hormone-related decreases in bone mass. In children, the concern is for long-term effects that might increase the risk of fracture later in life. However, systemic effects on growth remain the larger concern in children. Because of the systemic effects on BMD, monitoring is recommended. BMD should be monitored yearly in all patients taking high-dose ICSs. Because vertebral compression causes height loss, monitoring height in older adults is also an effective method of detecting bone mineral loss in conjunction with monitoring BMD.

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