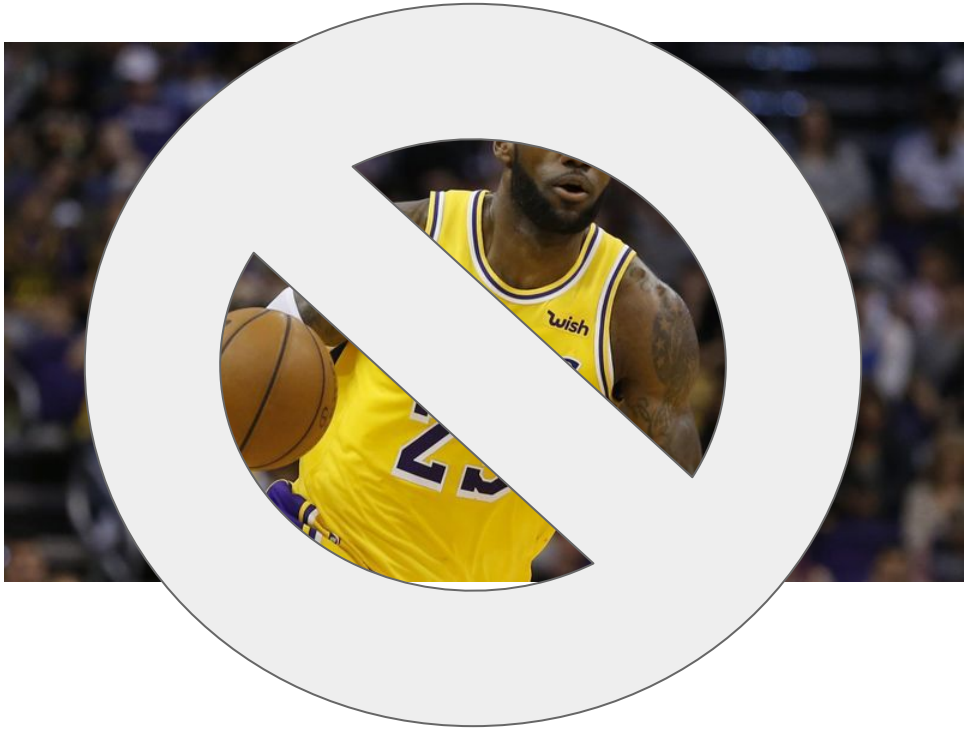
Effect of inhaled corticosteroid use on bone growth in children with asthma

By:

Daniela arias, Shana brawer, darielle connor, anthony guan, and sijia wang


wish

Clinical Scenario

It is known that systemic steroids can slow bone growth. Your 8 year old asthma patient's mother is concerned that perhaps the daily inhaled steroids (given via a metered dose inhaler or MDI) could have the same effect. What can you tell her?

Clinical/PICO Question

Does daily use of inhaled corticosteroids slow bone growth in children with mild-to-moderate persistent asthma?

PICO Search Terms

P- Children with mild-to-moderate persistent asthma

I- Daily inhaled corticosteroid

C-

O- Effect on bone growth

P	I	C	O
Children with asthma	Inhaled corticosteroids		Slowed bone growth
Prepubertal children with asthma	Inhaled Fluticasone		Linear growth
School-age children with asthma	Inhaled Budesonide		Effect on bone growth
Child with mild-to-moderate persistent asthma	Inhaled mometasone furoate		Decreased final height
	Inhaled nedocromil sodium		

Search Strategy Summary

Terms Used:

- "Children asthma inhaled corticosteroids bone growth"

Databases Searched:

Pubmed - 154 articles (Best Match), 143 articles (Most Recent)

Cochrane - 1 Cochrane review, 22 trials

Trip Database - 633 articles by quality filter

- Cochrane
  - Search criteria gave **34** results which were not specifically applicable to our clinical question.
- Trip Database
  - Search criteria gave **633** results, which were narrowed down to **4** after filters - one of which was selected.
- PubMed
  - Search criteria gave **154** results, which were narrowed down to **82** after filters. We skimmed through the first **25 - 30** "Best Match" abstracts to find the ones we liked.

Articles Used:

- Based on most recent research, sample size, type of study, and applicability to our research question
  - **PubMed - 4 articles**
  - **Cochrane - 1 article**

Appraised Articles

1. **Inhaled corticosteroids in children with persistent asthma: effects on growth.**
   Zhang L, Prietsch SO, Ducharme FM.
   Cochrane Database Syst Rev. 2014 Jul 17;(7):CD009471. doi: 10.1002/14651858.CD009471.pub2. Review.
2. **Linear growth and bone maturation are unaffected by 1 year of therapy with inhaled flunisolide hydrofluoroalkane in prepubescent children with mild persistent asthma: a randomized, double-blind, placebo-controlled trial.**
   Bensch GW, Greos LS, Gawchik S, Kpamegan E, Newman KB.
   Ann Allergy Asthma Immunol. 2011 Oct;107(4):323-9. doi: 10.1016/j.anai.2011.07.017. Epub 2011 Sep 3.
3. **Long-term effects of budesonide or nedocromil in children with asthma.** Childhood Asthma Management Program Research Group, Szefler S, Weiss S, Tonascia J, Adkinson NF, Bender B, Cherniack R, Donithan M, Kelly HW, Reisman J, Shapiro GG, Sternberg AL, Strunk R, Taggart V, Van Natta M, Wise R, Wu M, Zeiger R.
   N Engl J Med. 2000 Oct 12;343(15):1054-63.
4. **Effect of inhaled glucocorticoids in childhood on adult height.**
   Kelly HW1, Sternberg AL, Lescher R, Fuhlbrigge AL, Williams P, Zeiger RS, Raissy HH, Van Natta ML, Tonascia J, Strunk RC; CAMP Research Group.
5. **Influence of inhaled corticosteroids on pubertal growth and final height in asthmatic children.**
   De Leonibus C, Attanasi M, Roze Z, Martin B, Marcovecchio ML, Di Pillo S, Chiarelli F, Mohn A.

Article #1:

Inhaled corticosteroids in children with persistent asthma: effects on growth.

Criteria:

- **Randomized controlled trials comparing daily use of ICS for at least 2-3 months vs. a placebo or NSAID in children with persistent asthma.**
  - ICS alone versus placebo.
  - ICS alone versus non-steroidal drugs, such as long-acting beta2-agonists (LABA) and leukotriene receptor antagonists (LTRA).
  - ICS associated with non-steroidal drugs versus same dose of non-steroidal drugs.

Methods:

- In 2014 the authors did a systematic search of databases including CENTRAL, MEDLINE, EMBASE, CINAHL, AMED, and PsychINFO.
- Looked at respiratory journals and meeting abstracts. Along with ClinicalTrials and manufacturers databases to look at unpublished studies.

Inhaled corticosteroids in children with persistent asthma: effects on growth.

Methods (cont.):

- Two review authors evaluated titles and abstracts, then full text articles obtained if study fit inclusion criteria.
- Standard data extraction and assessment of risk of bias in included studies
- 451 citations were screened, and 39 papers were identified as relevant → 13 articles excluded for not being a RCT, or no placebo/NSAID used as control, or growth outcomes not recorded.
- Of the remaining 26 articles 24 were eligible for review, and then 1 trial was included after checking the references of other primary articles/reviews.
- Thus **25 trials** were analyzed involving **8471** children with mild to moderate persistent asthma, of whom 5128 were treated with ICS and 3343 with placebo or non-steroidal drugs.

Inhaled corticosteroids in children with persistent asthma: effects on growth.

Results:

- Regular use of ICS at low or medium daily doses is associated with a mean reduction of 0.48 cm/y in linear growth velocity and a 0.61-cm change from baseline in height during a one-year treatment period in children with mild to moderate persistent asthma.
- ICS-induced growth suppression seems to be maximal during the first year of therapy and less pronounced in subsequent years of treatment.

Limitations:

- The authors may have overlooked certain articles/trials, such as if growth data was not described in the title or abstract when they were screening.
- No trials included children with severe persistent asthma
- Most studies (15) were only 1-yr duration
- Half of the studies had a 20% drop out rate, and over half of the studies were funded by pharmaceutical companies
- Authors also performed a risk of bias on certain domains for each study and a sensitivity analyses showed that these potential biases did not significantly affect the results of this review.

Article #2:

Linear growth and bone maturation are unaffected by 1 year of therapy with inhaled flunisolide hydrofluoroalkane in prepubescent children with mild persistent asthma: a randomized, double-blind, placebo-controlled trial.

Study Design:

- Randomized
- Double-blind
- Parallel-group
- Fixed-dose study

Inclusion Criteria:

- Prepubescent children range in age between 4 and 9.5 years
- With mild asthma
- Not recently using steroids

Linear growth and bone maturation are unaffected by 1 year of therapy with inhaled flunisolide hydrofluoroalkane in prepubescent children with mild persistent asthma: a randomized, double-blind, placebo-controlled trial.

Procedures:

- Subject amount: 249
- 2-week run-in period:
  - Baseline characteristics
- Randomized assigned into 2 group:
  - Tx group: given 2 puffs flunisolide HFA (corticosteroids) twice daily (85 ug/puff)
  - Control group: 2 puffs placebo twice daily
- Study duration: 52 weeks
- Data collection:
  - Return visit: week 4, 8, 12, 20, 28, 36, 44, and 52
  - **Height**: assessed by stadiometer/each visit
  - **Radiograph** of the left hand and wrist: taken at week 52
  - **Safety** monitoring: PE, BW, UA were assessed/each visit
- A subject was removed from the study on a 4th asthma exacerbation

Linear growth and bone maturation are unaffected by 1 year of therapy with inhaled flunisolide hydrofluoroalkane in prepubescent children with mild persistent asthma: a randomized, double-blind, placebo-controlled trial.

Results: (over 52 weeks**)**

- Linear growth:
  - For only prepubescent subjects, **Mean growth velocity** with flunisolide HFA (5.85 ± 1,70 cm) was similar to placebo (6.12 ± 1.15 cm), (P = .250)
  - For only prepubescent subjects, **Mean change in height** with flunisolide HFA was similar to placebo (P = .333)
- Bone maturation:
  - The **mean change in bone age** at the end of the treatment period was similar for subjects who received flunisolide HFA (6.70 ± 1.85 yrs) and placebo (6.72 ± 1.99 yrs).
- Safety:
  - Flunisolide HFA was **well tolerated**
    - Dysphonia: 3.4% in the treatment group; no subject in the placebo group
    - Asthma exacerbation: 11.9% in the treatment group; 28.7% in the placebo group

Linear growth and bone maturation are unaffected by 1 year of therapy with inhaled flunisolide hydrofluoroalkane in prepubescent children with mild persistent asthma: a randomized, double-blind, placebo-controlled trial.

Limitations:

- Methodological Limitations:
  - Sample size: not large enough to find significant relationships and represent distribution of the population
  - Lack of available and/or reliable data: due to small sample size
  - Instruments used to collect the data: Measurement error of the stadiometer

- Limitations of the Researcher:
  - Two researchers are employed by the supporting laboratory: may have biases toward data and results that only support their hypotheses

Article #3:

Long-term effects of budesonide or nedocromil in children with asthma.

Criteria:

- Randomized control trial
- Children age 5-13 years, with mild to moderate asthma

Methods:

- 1041 children with mild to moderate asthma
- 311 randomly assigned budesonide – 208 randomly assigned matching placebo
- 312 randomly assigned nedocromil sodium - 210 randomly assigned to matching placebo

Procedures:

- Doses given as two daily doses for maximum adherence w/ education
- Albuterol used as needed. Short courses of oral prednisone were prescribed for exacerbations
- Spirometry performed 2x/year, measured both before and after use of bronchodilator. A methacholine challenge was performed annually
- Patients had a diary of asthma attacks, height and weight recorded every visit, total bone mineral density and Tanner staging assessed annually, psychological assessment done annually, allergy testing at baseline
- Bone age used to estimate final height towards end of trial

Long-term effects of budesonide or nedocromil in children with asthma.

Results:

· Mean increase in height in the budesonide group was 1.1 cm < placebo group (22.7 vs. 23.8 cm, P=0.005); difference evident mostly within the first year.

· The height increase was similar in the nedocromil and placebo groups (23.7 vs. 23.8 cm, P=0.65).

· no significant difference between treatment and placebo primary outcome, (FEV_1) after the administration of a bronchodilator.

· Patients given budesonide had lower airway responsiveness to methacholine, fewer hospitalizations (2.5 vs. 4.4 per 100 person-years), fewer urgent care visits (12 vs. 22 per 100 person-years), less need for albuterol, less use of prednisone, and a smaller percentage of additional asthma medications needed.

· As compared with placebo, nedocromil significantly reduced urgent care visits (16 vs. 22 per 100 person-years) and courses of prednisone.

Long-term effects of budesonide or nedocromil in children with asthma.

Limitations:

- Small sample size for randomized trial, larger differences may have been found with a larger trial group
- Patients still allowed to use other medication for asthma of any kind, including other systemic steroids and beta-blocking agents. These were not provided by the same company that provided the inhaled drugs for the trial
- One death from asthma occurred in the nedocromil group; the child had been receiving supplemental treatment, including inhaled corticosteroids, for several months before her death.
- One child in the placebo group required intubation for an exacerbation of asthma.
- No limitations from Pharmaceutical companies or research companies as they did not fund the trial.
- Supported by contracts with the National Heart, Lung, and Blood Institute and by General Clinical Research Center grants from the National Center for Research Resources

Article #4:

Effect of inhaled glucocorticoids in childhood on adult height.

Criteria:

- 5-13 year old
- Mild to moderate asthma

Procedures:

- 1041 children in ages of 5-13 were randomized to three different groups: placebo, 200 ug of budesonide twice daily (via dry-powder inhaler) or 8mg of nedocromil twice daily (via metered-dose inhaler) for 4 to 6 years..
- Participants were followed up for 4.5 years and height & weight were measured every 6 months.
- Participants were followed up for an additional 8 years in which height & weight were measured 1 to 2 times yearly.
- Tanner stage was also assessed yearly until participants were 18 year old or reached sexual maturity.

Effect of inhaled glucocorticoids in childhood on adult height.

.

Results:

- The adjusted mean adult height was 1.2 cm lower in the budesonide group as compared with the placebo (171.1 cm vs 172.3cm, P= 0.001)
- Adult height in the nedocromil group was similar to the placebo group (172.1 cm vs 172.3 cm, P= 0.61)
- Deficit in adult height was higher in the budesonide group for women (-1.8cm, P=0.001) than for men in the placebo group (-0.8cm, P=0.10)
- Growth velocity between the budesonide and placebo group varied during the first two years of trial for women and men, P=0.007 and P=<0.001 respectively. Noticeable difference occurred in prepubertal participants (girls and boy 5 to 11 years of age)
- Large daily dose of glucocorticoids during the first 2 years of trial was related with a lower adult height (-0.1 cm per microgram per kilogram, P= 0.007).

Limitations:

- Confounding variables limited researchers' ability to further analyze the effects of treatment duration, age at treatment and puberty status on growth velocity.
- Limited availability of original controls in the longitudinal cohort study. Use of healthy sibling instead.

Article #5:

Influence of inhaled corticosteroids on pubertal growth and final height in asthmatic children.

Study Design: Retrospective Cohort

Criteria:

Cohort:

Prepubertal children (aged 5-7) with persistent mild-to-moderate asthma who:

- Received a daily inhaled corticosteroid treatment (budesonide, mometasone furoate, or fluticasone propionate) for at least 8 months/year
- Were not using systemic corticosteroids for more than 2 weeks/year or nasal corticoids to treat rhinitis
- Were not going into complete remission for asthma

Control:

Children of the same age group without evidence of any:

- Chronic diseases
- Physical disabilities
- Abnormalities in pubertal development
- Malnutrition or born with low birth weight (<2500 gr)

Influence of inhaled corticosteroids on pubertal growth and final height in asthmatic children.

Methods:

Asthmatic patients:

- **245** prepubertal children with asthma (diagnosed by a single pediatric respiratory physician) were identified
- 108 patients were excluded because they did not meet the above criteria→ **137** patients included in initial analysis
- Of the 137 patients, 24 were excluded for not attaining final height → **113** asthmatic patients analyzed

Control Children:

- **160** patient charts reviewed
- 83 patients excluded because they did not meet the above criteria→ **77** patients included in initial analysis
- Of the 77 patients, 11 were excluded for not attaining final height → **66** control patients analyzed

Procedures:

Height, weight, lung function were measured from both groups at four visits:

- Visit 1: baseline prepubertal visit
- Visit 2: onset of puberty
- Visit 3: late puberty
- Visit 4: achievement of final height (FH)

Data was then converted to standard deviation scores (**SDS**). Growth was assessed as :

- peak height velocity (**PHV**),
- age at peak height velocity (**APHV**)
- pubertal height gain SDS (**PHG-SDS**)
- final height SDS (**FH-SDS)**
- **FH** gain SDS
- Parental-adjusted height **(PAH)-SDS**

→ General linear model (GLM) created

Influence of inhaled corticosteroids on pubertal growth and final height in asthmatic children.

Results:

- **FH-SDS:** *significantly lower* in asthmatic children compared to controls in both boys and girls.
- **PHG-SDS:** *significantly decreased* in asthmatic patients compared to controls.
- **PHV:** *lower* in asthmatic patients compared to controls.
- **APHV:** *similar* to control in both boys and girls.
- **PAH-SDS:** *significantly reduced* in asthmatic children compared with controls, meaning asthmatic children did not reach their genetic potential.
- **GLM:** showed that IC type, duration, and cumulative dose had a *significant effect* on FH. Patients on Fluticasone had significantly lower FH compared to children using budesonide or mometasone. Longer duration of treatment and greater cumulative dose were also significantly associated with reduced FH.

Bottom Line→ final height was significantly reduced in asthmatic patients on ICS compared to controls.

Limitations:

-Small sample size

- Retrospective design with potential for selection bias

- Lack of information on bone age and pubertal biochemical markers such as DHEAS, estrogen and testosterone, GH, and IGF-1 levels.

-Clinical based and not population based study design

-Asthma may have growth-reducing effects on its own

-International

Summary of Mini-CAT Grid

Key Findings:

1. **Zhang et. al, 2014**
   - Children with persistent asthma treated with daily ICS have:
     - A statistically significant reduction in linear growth velocity, during a one-year treatment period
     - Maximal growth suppression during the first year of treatment with no significant effect during the second year
2. **Bensch et. al, 2011**
   - Chronic treatment with flunisolide HFA did not affect growth velocity in children with mild persistent asthma.
   - Treatment with flunisolide HFA did not affect bone maturation in children with mild asthma
3. **Szefler et. al, 2000**
   - In children with mild-to-moderate asthma, neither budesonide nor nedocromil is better than placebo in terms of lung function.
   - Inhaled budesonide improves airway responsiveness and provides better control of asthma than placebo or nedocromil.
   - The side effects of budesonide are limited to a small, transient reduction in growth velocity.
4. **Kelly et. al, 2013**
   - Lower adult height was associated with higher daily dose of inhaled glucocorticoid in first two year of treatment. Decrease in growth in pubertal children treated with inhaled glucocorticoids remain until adult height.
5. **Loke et. al, 2016**
   - ICs reduced final height in asthmatic children compared to controls. Final height in asthmatic patients was 2.5 ± 2.89 cm lower in boys and 2.0 ± 2.03 cm lower in girls than controls. Final height reduction was dependent on the dose and duration of the IC use.

Conclusion

Does daily use of inhaled corticosteroids slow bone growth in children with mild-to-moderate asthma?

After appraising each of the articles, we found that the strongest and most persuasive articles drew these conclusions: *[Zhang et. al, 2014, Kelly et. al, 2013, Loke et. al, 2016]*

- The studies suggests that children treated daily with ICS may grow approximately half a centimeter per year less than those not treated with these medications during the first year of treatment. However the magnitude of ICS-related growth reduction may depend on the type of drug, dose, and duration.
- Growth reduction seems to be maximal during the first year of therapy and less pronounced in subsequent years of treatment.
- Evidence provided by the Zhang et. al review allows us to conclude that daily use of ICS can cause a small reduction in height in children up to 18 years of age with persistent asthma; this effect seems minor compared with the known benefit of these medications for asthma control.

Clinical bottom line

The findings support the need to use the lowest effective dose of ICS in children with mild-to-moderate persistent asthma to limit growth reduction as much as possible. The benefit of asthma control outweighs the slight decrease in height in asthmatic children who require ICS. Asthmatic children on ICS should be monitored and seen for routine follow up visits to ensure proper administration and dose of the ICS, and should have the dose lowered whenever possible. Modifiable environmental triggers, such as allergens and smoke, should be considered and properly addressed to avoid asthmatic exacerbations. Alternatives to ICS should be considered for other respiratory issues, along with proper prescription and administration, as ICS should not be used for viral wheeze or infrequent intermittent asthma.

References

1. **Inhaled corticosteroids in children with persistent asthma: effects on growth.**
   Zhang L, Prietsch SO, Ducharme FM.
   Cochrane Database Syst Rev. 2014 Jul 17;(7):CD009471. doi: 10.1002/14651858.CD009471.pub2. Review.
2. **Linear growth and bone maturation are unaffected by 1 year of therapy with inhaled flunisolide hydrofluoroalkane in prepubescent children with mild persistent asthma: a randomized, double-blind, placebo-controlled trial.**
   Bensch GW, Greos LS, Gawchik S, Kpamegan E, Newman KB.
   Ann Allergy Asthma Immunol. 2011 Oct;107(4):323-9. doi: 10.1016/j.anai.2011.07.017. Epub 2011 Sep 3.
3. **Long-term effects of budesonide or nedocromil in children with asthma.** Childhood Asthma Management Program Research Group, Szefler S, Weiss S, Tonascia J, Adkinson NF, Bender B, Cherniack R, Donithan M, Kelly HW, Reisman J, Shapiro GG, Sternberg AL, Strunk R, Taggart V, Van Natta M, Wise R, Wu M, Zeiger R.
   N Engl J Med. 2000 Oct 12;343(15):1054-63.
4. **Effect of inhaled glucocorticoids in childhood on adult height.**
   Kelly HW1, Sternberg AL, Lescher R, Fuhlbrigge AL, Williams P, Zeiger RS, Raissy HH, Van Natta ML, Tonascia J, Strunk RC; CAMP Research Group.
5. **Influence of inhaled corticosteroids on pubertal growth and final height in asthmatic children.**
   De Leonibus C, Attanasi M, Roze Z, Martin B, Marcovecchio ML, Di Pillo S, Chiarelli F, Mohn A.