Assessment of The Effect of Inhaled Corticosteroids on Bone Mineral Content in Asthmatic Children

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Abstract:

The use of inhaled corticosteroids (ICS) as a prophylaxis is now recommended in international guidelines for all patients using an inhaled bronchodilator more than once a day. We evaluated the effect of long term ICS therapy on bone mineral content of the lumbar spine, and the potential risk of impaired bone density in prepubertal children.

The study was performed on two groups. Group I included 40 asthmatic children (mean age 8.3±0.5 years) on ICS in the form of beclomethasone dipropionate, 200 to 600 μg/day (mean dosage 392±53.5 μg/day) for at least 6 months (mean 1.3±0.5 years). Group II included 40 mild asthmatic children (mean age 8.2±0.6 years). They are not receiving regular corticosteroids whether inhaled or systemic, but were treated only with inhaled β₂-stimulants whenever needed.

The bone mineral density (BMD) was measured by dual energy X-ray absorptiometry (DEXA) densitometer. Measurements for the two groups were performed at the lumbar spine (L₂-L₄). Laboratory measurements included serum calcium, phosphorus and bone specific alkaline phosphatase.

The study showed significantly higher BMD measurements in group II (mean 0.597±0.101 g/cm²) than group I (mean the 0.522±0.122 g/cm²) (P<0.05). There were no statistically significant differences between level of serum calcium, phosphorus or bone specific alkaline phosphatase in both groups.

A significant positive correlation was found between BMD and both weight and height of the children in both groups (r= 0.766, r= 0.859 in group I and 0.789, 0.825 in group II). Our findings indicated that long term use of ICS slightly reduced the gain in bone mass in mild to moderately severe asthmatic prepubertal children. We recommended the use of lowest effective dose of ICS, the use of ICS with least oral bioavailability and follow up bone density of the lumbar spine at 6 months intervals.

Introduction:

Bronchial asthma is the most common illness of childhood affecting about 4 to 5 per cent of children.¹ With the new advances in understanding the pathophysiology of asthma, as an inflammatory disease even in patients with mild intermittent illness,²,³ the use of inhaled anti-inflammatory drugs as a prophylaxis is now recommended in international guidelines for all patients using an inhaled bronchodilator more than once a day with inhaled corticosteroids being the therapy of choice.⁴,⁵

Inhaled corticosteroid (ICS) therapy is effective in patients with asthma, because a drug with high topical potency is deposited directly in the airways.⁶ Patients with asthma may require these drugs for many years, so safety is of paramount importance. Of primary concern is the long term effect of inhaled corticosteroids on bone growth.⁷ The systemic use of corticosteroids has been shown to cause osteoporosis.⁸ Studies on bone metabolism in adults treated with inhaled corticosteroids showed reduced total bone mass,⁹ reduced bone mineral density (BMD)¹⁰ and reduced serum osteocalcin and serum alkaline phosphatase values.¹¹ All these studies showed significantly greater losses of trabecular bone, which is the predominant type of bone in the vertebral bodies, than of cortical bone.

Dual energy X-ray absorptiometry (DEXA) of the lumbar spine has been recently available, which allows a rapid, accurate and highly reproducible assessment of the spinal mineral content with a very low radiation exposure.¹²

Data related to the effects of inhaled steroids on bone in asthmatic children are very contradictory. The available studies are heterogeneous for age range of the patients, doses of steroids, concomitant therapy with courses of oral steroids and methods of bone mass measurements. Furthermore, these studies have included children in different pubertal stages, which is misleading because of the effects of sex hormones on bone balance.¹³-¹⁵

The aim of this study is to evaluate the effect of long term ICS therapy on bone mineral content of the lumbar spine, evaluated by dual energy X-ray absorptiometry and the potential risk of impaired bone density in asthmatic prepubertal children.
Subjects and Methods:
The study included 80 children who have been seen in the outpatient Pediatric and Orthopedic clinics in Al-Hayat Hospital, Jeddah, K.S.A. between March 1997 and December 1998. These children were classified in two groups:

**Group I:** 40 children (25 males and 15 females) in the prepubertal age group (Tanner’s scale I){17} with mild to moderate asthma as established by the current National Heart, Lung and Blood Institute guidelines for severity.{4} Their age ranges between 6 to 10 years. This age range was selected to avoid the influence of different pubertal stages on bone mineralization. These children have been on daily beclomethasone dipropionate (BDP) at a dosage of 200-600 μg/day for 6 months to 2 years.

The BDP aerosol was delivered by a metered-dose inhaler. All patients used a 145 ml. Spacer device with one way inhalation valve, attached to their inhaler. Parents and children were given precise instructions on the use of spacer. No patient has been treated with systemic corticosteroids for more than 3 days in the previous 6 months preceding enrollment into the study.

**Group II:** (control group) comprised 40 sex and age matched mild asthmatic children (24 males and 16 females) not treated with corticosteroids, only requiring inhaled β2-stimulants. None had received systemic corticosteroids in the past 6 months.

No one of the two groups had other relevant disease or had reported recent bone fractures, metabolic bone disease or malnutrition.

**Measurement of Growth:**
Standing height was measured.{18} Measurements were made with stadiometer without shoes, with the patient standing with heels and back in contact with a vertical measuring column. Gentle, but firm, pressure upward was applied beneath the mastoid process to help the child stretch. Three height measurements were recorded at the same visit. Weight was also measured by an electronic scale. Three measurements were recorded. Height and weight were measured by the same equipment and by the same person for all children. All patients were between 10th and 90th percentile for their age.

**Bone Mineral Density Measurements:**
The measurements were performed in all patients by dual energy X-ray absorptiometry densitometer (DEXA) [Norland XR 26Dexa] machine which uses an X-ray tube as the radiation source.

Measurements were performed at the lumbar spine (L2-L4) in an anteroposterior projection.{19} During the measurements, the child was supine and physiological lumbar scoliosis was flattened by flexion of the hips and knees and calves resting on cushions. The entrance radiation dose to the child is less than 4 mRem (which is about one tenth of the exposure for a standard chest X-ray).{12} The scanning time was 3-5 minutes. The results were expressed in g/cm2.

**Laboratory Measurements:**
Serum calcium and phosphorus were measured by calorimetric assay.{20} Bone specific alkaline phosphatase activity was measured enzymatically.{21} All samples were run in duplicate and tested in a patch.

**Data Analysis:**
Comparisons between groups were made using unpaired student's t-test. BMD inter- and intra-group correlations were evaluated by analysis of variance. Correlation coefficient analysis was used to evaluate the correlation between BMD and height and weight. A probability of P< 0.05 was considered significant.

**Results:**
All children of Group I have completed a minimum of six month of BDP therapy. These children received the BDP in doses varied between 200-600 μg/day (mean 392±53.5 μg/day). The duration of ICS therapy ranged from 6 month to two years (mean 1.3 years ± 0.5). There were no significant statistical differences between the two groups in age, height, weight, or duration of the disease. (table I)

Table II represents the results of laboratory measurements of serum calcium, phosphorus and bone specific alkaline phosphatase. No statistically significant differences were found between the laboratory values in both groups.

The bone mineral density (BMD), measured by DEXA technique, ranged between 0.494 to 0.625 g/cm2 in Group I with a mean of 0.522g/cm2 (SD = 0.122). In Group II; BMD average values ranged between 0.521 to 0.712 g/cm2 with a mean of 0.597g/cm2 (SD = 0.101). BMD values were significantly higher in group II as compared to group I (P< 0.05). A significant correlation was found between BMD and both weight and height of children in both groups. (r = 0.766, r = 0.859 in group I and 0.789, 0.825 in group II).
Table I: Physical and clinical characteristics of the study population.

<table>
<thead>
<tr>
<th></th>
<th>Group I (n = 40)</th>
<th>Group II (n = 40)</th>
<th>P</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>(Inhaled BDP)</td>
<td>(Control)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>8.3 ± 0.5</td>
<td>8.2 ± 0.6</td>
<td>Non significant</td>
</tr>
<tr>
<td>Sex: Male</td>
<td>25</td>
<td>15</td>
<td>Non significant</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td></td>
<td>16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height (cm)</td>
<td>122 ± 5</td>
<td>124 ± 6</td>
<td>Non significant</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>28.2 ± 0.6</td>
<td>29.1 ± 0.7</td>
<td>Non significant</td>
</tr>
<tr>
<td>Duration of asthma (years)</td>
<td>46 ± 0.4</td>
<td>42 ± 0.6</td>
<td>Non significant</td>
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Values are expressed as mean ± SD, BDP: Beclomethasone dipropionate.

Table II: Laboratory profile of the study population.

<table>
<thead>
<tr>
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<th>Group I (n = 40)</th>
<th>Group II (n = 40)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum calcium (mg/dl)</td>
<td>9.7 ± 0.65</td>
<td>9.8 ± 0.7</td>
<td>Non significant (P&gt;0.05)</td>
</tr>
<tr>
<td>Serum phosphorus (mg/dl)</td>
<td>4.1 ± 0.71</td>
<td>4.5 ± 0.6</td>
<td>Non significant (P&gt;0.05)</td>
</tr>
<tr>
<td>Bone specific alkaline phosphatase (IU)</td>
<td>175 ± 28</td>
<td>171 ± 33</td>
<td>Non significant (P&gt;0.05)</td>
</tr>
</tbody>
</table>

Discussion:

The osteoporotic effect of systemic steroids on bone metabolism is due to: [1]. A direct inhibition of the osteoblastic function including synthesis of collagen, recruitment of osteoblastic progenitor cells, and a net decrease in bone formation. [2]. Decreased intestinal absorption of calcium with inhibition of synthesis of calcium binding protein and release of calcium from mitochondria. [3]. Increased rate of bone resorption attributed to secondary hyperparathyroidism.[8]

It is known that during steroid therapy, bone loss occurs mainly at sites in the skeleton where there is a high concentration of trabecular bone that is in fact more metabolically active than cortical bone. The mid-lumbar spine, therefore, is the ideal site for monitoring the osteopenic effect of glucocorticoid administration.[22] For this reason, DEXA technique has been used in this study as it is the newest method currently available for the in-vivo quantitation of BMD and it has been shown to be a precise and accurate non-invasive method which is well adapted to children.[23]

The study showed a slight reduction of BMD in the group of prepubertal children with moderate asthma on BDP treatment than the group of asthmatic children not receiving BDP. Furthermore, there was significant correlation between the BMD and weight and height of studied children.

The finding of slight reduction of BMD observed in our study, is consistent with the observation of Ruegsegger et al.[24] who found that BMD of asthmatic patients tends to be lower than the values of control. Sorva et al.[25] reported also that biochemical markers of bone metabolism in children treated with ICS for 6 months, have shown decreased serum osteocalcin and carboxypropeptide of type I procollagen levels. Another study done by Birkeback et al.[26] on twelve prepubertal boys and four prepubertal girls with mild asthma showed that treatment with ICS is associated with suppression of bone and collagen turnover. Boraldi and coworkers,[13] although they did not find any difference between BMD in their 2 groups, however they had a slightly reduced gain in bone mass in BDP group.

Our results are in contrast with most published studies which showed a lack of effect of inhaled steroids on bone formation and resorption. This was previously observed by Konig and colleagues[14] in smaller number of asthmatic children between 4 and 17 years of age receiving BDP for 25 months, by Hopp and coworkers[27] in 11 children between 6 and 16 years of age and by Kimberg and associates[28] in 30 children between 5 to 18 years of age with moderate to moderately severe asthma. Similarly, no effect on bone mineral density was observed by Agertof and Pederson[29] in 27 asthmatic children at a mean daily dose of 671 ug for 3 to 6 years and by Hopp and colleagues[30] in 15 moderate to moderately severe asthmatics aged 6-13 years.

Precise knowledge of the benefits and risks of inhaled corticosteroids at different doses is not available and dose-response curves showing the wanted and unwanted effects of ICS have not been established in children. While it is generally agreed that systemic effects are unlikely to occur at recommended doses in most of patients, there may
be a wide variation in individual susceptibility to adrenal suppression and other unwanted systemic effects.\(^7\)\(^,\)\(^3\)\(^1\) The systemic actions of ICS result from their absorption through the airways, although some drug is metabolized there and to a lesser extent from the gastrointestinal tract because some is swallowed. The amount that reaches the lungs varies with the preparation, the delivery system and the ability of the patient to coordinate the release and inspiration of the medication.\(^6\) So, we used a spacer device in this study as the delivery of glucocorticoids is less dependent on the patient’s coordination, less drug is deposited in the oropharynx and more drug (70 to 80 per cent) reaches the lungs.

Our study deals with a homogenous population of prepubertal asthmatics. This seems important because, as observed in previous studies, the use of a wide age range of the study population increases the standard deviation of the measured BMD with a large probability for committing a type II statistical error.\(^28\)

Children with chronic asthma have a tendency for a delay in the onset of puberty with a subsequent physiologic deceleration of growth velocity and bone mineralization. Adolescence is a particularly critical time for bone mineral accretion as more than half of the adult bone calcium is normally laid down during the teen years.\(^3\)\(^2\) Because the aim of our study was to evaluate the effect of treatment of asthma on bone mass, we carefully selected young prepubertal patients in order to avoid the confounding factor of sexual maturation which is the major criticism of other studies.

Asthma, like other chronic diseases can affect growth in mid-childhood. Growth may be influenced by a number of factors including seasonality, gender, age, asthma severity, age of onset of asthma and the use of systemic corticosteroids.\(^7\) In our study we did not include moderate to severely asthmatic children in whom disease-mediated growth suppression is more apparent and may be well improved by better control of asthma as observed in the study of Volovitz and his colleagues\(^16\) on 15 children aged 2 to 7 years with severe asthma treated with ICS for 3-5 years. All our patients were between 10\(^\text{th}\) and 90\(^\text{th}\) percentile for their height or weight and we found a positive correlation between BMD and body height and weight, a relation that was attributed to the growing skeletal size. This finding was observed before by Glastre and his associates\(^12\). There was no significant difference in height between BDP treated patients and non treated patients.

We failed to find any significant correlation between serum calcium, phosphorus or bone specific alkaline phosphatase and BMD. In a longitudinal study, Johnston et al.\(^3\)\(^3\) demonstrated that calcium supplementation had a positive effect on the rate of increase in bone mineral density in healthy growing children. It will be important to determine whether calcium supplementation could also be a useful preventive strategy in asthmatic children under long term treatment with ICS.

In conclusion, our findings indicate that long-term use of ICS slightly reduced the gain in bone mass in mild to moderately severe asthmatic prepubertal children. So, we recommend the use of the lowest effective dose of ICS, the use of ICS with least oral bioavailability, to maintain good nutritional status and follow bone density of the lumbar spine at 6-month intervals for at least the first two years. We think that further longitudinal research is needed to evaluate the long-term (in years) safety of ICS therapy on bone serving each child as his or her control.

References:


