Inhaled steroids and bone metabolism in clinical perspective

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Inhaled corticosteroids have become the mainstay of maintenance treatment in asthma in adults, and they are also being advocated for early use in children. The systemic side effects of inhaled steroids are much less than those from systemic steroids needed for comparable asthma control. Long term use of systemic corticosteroids is known to cause osteoporosis, and the risks from inhaled therapy are currently under study. There are reports of changes in biochemical parameters of bone metabolism due to inhaled corticosteroids, suggesting depression of bone formation and increase in bone resorption. However, the significance of biochemical changes in relation to bone mass and architecture is not known. Cross-sectional studies of bone mass suggest that dosages of more than 1 mg daily in adults may be associated with a decrease in bone mineral density. Longitudinal studies are needed to confirm the findings and define more clearly the profile and risk factors of bone loss. Current data in children show that inhaled corticosteroid in the usual therapeutic dose range has no detrimental effect on long term statural growth, while effects on peak bone mass are not yet known. The magnitude of measurable adverse effects were found to be dose-dependent, hence, the use of a minimum effective dose is recommended. Patients on inhaled corticosteroid therapy should maintain optimal intake of calcium and vitamin D. Physical activity should be encouraged and oestrogen replacement therapy in postmenopausal women considered.

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Introduction

Inhaled corticosteroid therapy has become the mainstay of treatment in chronic asthma, and it is also used in some patients with chronic bronchitis and emphysema.[1-3] It is usually given in a dose range of 200 μg to 2 mg daily, while selected cases may be given higher doses.[1] There are several preparations of inhaled corticosteroids, including beclomethasone dipropionate, budesonide, flunisolide, triamcinolone acetonide, and, more recently, fluticasone propionate. Apart from inhaling via the oropharynx, as in obstructive airways diseases, corticosteroids may also be inhaled via the nasal route, for treatment of rhinitis.[4] The dosage for this purpose is usually lower, in the range of 200 to 400 μg daily.

Systemic steroids are known to cause bone loss—particularly trabecular bone loss—and the risk is likely to be dose- and duration-related.[5,6] The clinical manifestation is bone fractures—in particular vertebral and rib fractures. Compared with systemic steroids, the dose of inhaled corticosteroids is low, and systemic absorption of most preparations via the gastrointestinal tract undergoes extensive first-pass metabolism, hence, their systemic side effects are fewer.[7,8] It has been shown that inhaled steroids up to a dose of 1.5 mg daily are not associated with significant hypothalamic-pituitary-adrenal axis suppression, and above this dose, variable biochemical suppression may occur in a minority, but the overall clinical effects are viewed as insignificant.[8] A remaining area of concern is the effect on bone metabolism—a subject currently under scrutiny.

Why the concern?

Inhaled steroids are used by many asthma patients. It is currently recommended that all patients with more than very mild asthma should be given long term regular inhaled steroids.[1,2] This trend is a worldwide one, and it is only a minority of asthma patients that need chronic oral steroid therapy.

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Inhaled steroids are becoming the advocated maintenance treatment for asthma in childhood—the period of bone growth.[9] The use of inhaled steroids in most patients is continuous and probably life-long, except for those with childhood asthma who go into remission. Minor effects on bone turnover may be cumulative. There is a trend to liberalise the high dose range of inhaled corticosteroids.[10] It stands to reason that side effects may be more significant as the dose increases. Subtle negative effects may be potentiated by other factors that operate to decrease bone mass.

Studies of biochemical changes of bone metabolism

Although osteoporosis is a well-known side effect of treatment with glucocorticoids, the exact mechanisms by which they induce osteopenia are not completely understood.[5] The evidence suggests that a corticosteroid excess reduces bone formation and increases bone resorption directly, and indirectly acts on the pituitary-gonadal axis, pituitary-adrenal axis, intestinal calcium absorption, renal tubular calcium absorption, and secondary hyperparathyroidism.[5,6]

The most commonly used biochemical markers of bone turnover include urinary hydroxyproline, a product of collagen breakdown, and serum osteocalcin as a marker of bone formation, however, these are not exclusively specific indices.[11] Many studies have found biochemical evidence of increased bone resorption or decreased bone formation with the use of inhaled corticosteroids. Inhaled beclomethasone given for four weeks in a high dose (2000 μg daily) was shown to increase urinary hydroxyproline in normal subjects, while inhaled budesonide in a similar dose range had no such effect.[12] Serum osteocalcin has been found to be decreased in normal or asthmatic subjects given high-dose inhaled corticosteroids.[13-15] Another study reported an immediate suppression of serum osteocalcin by inhaled beclomethasone in a dose of 2 mg daily in healthy subjects.[12] Likewise, normal subjects given inhaled budesonide 1.2 or 2.4 mg daily for two weeks showed a decrease in serum osteocalcin.[14] A decrease in serum osteocalcin and carboxypropeptide type I procollagen was seen in asthmatic children using inhaled budesonide compared with those using sodium chromoglycate.[15]

In contrast, no significant change was observed in several markers of bone turnover (including serum osteocalcin and urinary deoxypyridinoline cross links), in patients treated with long term inhaled beclomethasone.[16,17] The discrepancy between short term and long term studies may be due to some self-adjusting effect of bone metabolism.[18] It has been found that bone loss was most pronounced in the first six months of systemic corticosteroid treatment, and thereafter slowed down.[19]

The finding of biochemical derangement does not equate with a change of bone mass. However, it does reflect that inhaled corticosteroids can affect bone metabolism, and raises the possibility of more significant sequelae. The ultimate goal is to evaluate the effect on bone mass and architecture, which are the primary determinants of osteoporosis, and its most significant consequence—bone fracture.

Studies of bone mass

The side effects of chronic systemic corticosteroid treatment in asthma are well documented, causing decreased bone mass and an increased fracture incidence.[20-23] The effects of inhaled corticosteroids are not as well documented. Several studies have attempted to evaluate bone mass in asthma patients taking inhaled steroids. An 8.8% decrease in total body calcium in patients on inhaled steroid therapy compared with 22 control patients (eight postmenopausal females) was noted. No such decrease was seen in 12 asthma patients not receiving steroid treatment.[19] However, the dose or duration of inhaled steroid therapy was not stated. Moreover, the control group of patients not receiving steroid treatment was much younger, although it has been reported that total body calcium has no relation to age per se. A more recent study found no increase in bone loss as measured by dual photon absorptiometry over two years in adults treated with a mean daily dose of 630 μg of beclomethasone.[24]

A subsequent study assessed three groups of asthma patients. One group did not receive steroid treatment; another was given inhaled steroids (1000 to 2000 μg daily) and intermittent booster courses of systemic steroids; the third group was given inhaled steroids and continuous oral steroids at a median dose of 7 mg prednisolone daily.[17] Bone density estimated by quantitative computed tomography was found to be significantly lower in the two groups receiving steroids compared with the control group, which comprised patients with milder asthma, not receiving any steroid treatment. No difference was found between the two steroid-treated groups.

We recently demonstrated a decrease in bone mineral density (BMD) in Chinese asthma patients treated with long term inhaled corticosteroids.[25] In a cross

sectional study of 18 premenopausal female and 12 male patients who received inhaled corticosteroid therapy at an average dose of 1100 μg daily for a mean period of 40 months, with fewer than four booster courses of systemic steroid during this time, we found a significant decrease in BMD at the hip and lumbar spine regions, compared to sex-, age- and body mass index-adjusted controls. Further analysis showed that the decrease was only seen in the female patients ($p = 0.039$, lumbar spine; $p = 0.0494$, neck of femur; $p = 0.0245$ Ward's triangle). This difference may be due to the small number of male patients or it may be a genuine phenomenon relating to greater susceptibility to osteoporosis in females, independent of menopausal status. In the female patients, there was a negative correlation between spinal and trochanteric BMD and average daily dose of inhaled steroids ($p = 0.054$ and $p = 0.047$ respectively), and a positive correlation between trochanteric BMD and body mass index ($p = 0.03$). The effect of asthma per se on bone mass could not be definitively excluded since the control group consisted of normal subjects rather than asthma patients, but it was practically impossible to find adult patients in our clinics who had similar severity of asthma who had not received any oral or inhaled steroids. It would be fallacious to use a control group of mild asthma patients as the mechanisms leading to decreased bone mass (BM) in asthma are likely to be immobility and malnutrition as a consequence of poorly controlled disease. It is important to note that our patients had a relatively low dietary calcium intake of about 500 mg daily, which could have been a predisposing factor to corticosteroid susceptibility.

The findings of others and our own suggest that long term inhaled corticosteroids of over 1000 μg daily are associated with some detrimental BM effect. Although some of the patients in both studies had received a few booster courses of systemic steroids—thus confounding the effect of inhaled steroids—these patients also represent the common scenario of moderate chronic asthma patients in clinical practice. It is likely that the results of clinical studies will always be clouded by the need for intermittent systemic steroids to control asthma exacerbations. In practice, the implications are the same—these patients are at risk for developing osteoporosis.

Inhaled steroids in children

Inhaled steroids are now accepted as the most effective maintenance treatment for moderate or severe asthma in children.[9] The suppressive effect of regular systemic steroids on growth, including skeletal growth, is well established.[26] The potential for inhaled steroids to cause similar side effects is understandably a major concern. Studies on children have employed various parameters as the index of growth—height velocity, knemometry, bone biochemical parameters, and bone densitometry. However, several issues should be emphasised when one evaluates the available data. Growth as measured by height is not the same as bone growth determined by BM, and the latter may be adversely affected without any significant change seen in height attained. Growth measured over a period may not reflect final growth attained.[27] In addition, growth failure or retardation may occur in childhood asthma, independent of any effect related to corticosteroid use.[27] Hence, any negative effect caused by inhaled steroids should be weighed against the positive effects due to the patient having better-controlled asthma.

The several placebo-controlled studies which looked at height gain in asthmatic children on inhaled steroids have reported conflicting results. One study showed no deleterious effect on growth as measured by height velocity, in over 200 asthmatic children on inhaled budesonide doses of less than 400 μg daily for three to six years compared with asthmatic children not on inhaled steroid.[28] Similarly, an open study found no growth impairment in 15 young children (mean age five years) treated with 200 μg budesonide daily for a mean period of four years.[29] A recent meta-analysis also demonstrated normal statural growth in children on a median daily dose of 400 mg of Becloforte.[30] However, several other studies have reported reduced growth velocities, although these were short term assessments conducted over several weeks or months.[31-33] It is likely that children make compensatory growth adjustments in the long term, especially as their asthma comes under control.[27] These studies also consistently showed that any short term growth suppression was dose-related. A dosage of 800 μg budesonide daily for 12 weeks was associated with a decrease in height velocity, however, the long term effects are not yet known.[31-33] The evidence suggests that long term treatment with inhaled steroids at doses of less than 800 μg daily is not associated with a diminution of final height attained, but the effect of higher doses remains to be seen.

Few studies have evaluated BM in children. Children experience an increase in BM up to late teenage or early adulthood when peak BM is attained, and only lose bone gradually thereafter.[34,35] Hence, it is important to look at the effect of inhaled steroids on the attainment of peak BM rather than a loss of BM. It is equally important to evaluate poor growth induced by

inhaled steroids, if any, against that induced by poorly-controlled asthma. A recent longitudinal study looked at the effect of beclomethasone diproprionate on bone mineral content assessed by dual energy X-ray densitometry in asthmatic children.[36] It is worthwhile to note that although Becloforte for six months at a dose of 300 to 400 μg daily did not cause bone loss, a slightly reduced gain in BM was noted with respect to a control asthmatic group not given inhaled steroids. Further follow-up studies are needed.

Inhaled steroids in the elderly

Apart from elderly chronic asthmatics, inhaled corticosteroids are also used in elderly patients suffering from chronic bronchitis and emphysema. It is an important population to study because there are many other significant risk factors at play, including age, menopausal status, smoking history, decreased mobility and malnutrition, due to respiratory incapacitation. At present, there is a dearth of data in this area.

The problem in clinical perspective

There is biochemical evidence of a negative effect on bone turnover from inhaled corticosteroids, although the significance of these changes in relation to BM is not known. Current available data suggest that long term inhaled steroids in a dose of more than 1000 μg daily lead to a decrease in trabecular BM. However, the issue is not clearly settled, since studies looking at BM are mostly cross-sectional, and therefore contaminated by confounding variables. Longitudinal studies will give a clearer picture of the profile and risk factors of bone loss in these patients. We are currently conducting a prospective longitudinal study on BMD before and after commencement of inhaled corticosteroid therapy for asthma. It is also important to study the incidence of fractures since the decrease in bone density is of a lesser magnitude than those on systemic steroids suggesting a lower risk of bone fractures, but bone density is not the only determinant of fracture risk and it has been suggested that corticosteroid-induced osteoporosis is associated with vertebral fractures at a higher BMD than involutional osteoporosis.[17,23]

From a clinical perspective, inhaled steroids in asthma have greatly helped to control the disease, and have enabled systemic steroids to be used less. Even though the adverse effects of inhaled corticosteroids on bone metabolism have not been fully elucidated, present evidence suggests the effects are much less than those caused by systemic steroids for comparable asthma control.[7] The possibility of some potential adverse effects should not deter physicians from using inhaled corticosteroids. In practical terms, inhaled steroid therapy is a useful measure for preventing the severe bone problems seen with chronic oral steroid treatment in difficult asthma.

Attention should be directed to prophylactic measures to minimise any bone loss from long term inhaled therapy, so that patients can derive the full benefit of treatment with minimal side effects. In line with preventive measures for involutional osteoporosis and steroid-induced osteoporosis, a calcium intake of 1000 to 1500 mg daily and adequate vitamin D should be recommended in patients on inhaled corticosteroids.[37] This is particularly relevant in Hong Kong since the dietary calcium intake of our patients is likely to be low, as with the general Hong Kong population.[25,38] Children on inhaled corticosteroid therapy are also likely to benefit from such measures, since it has been shown that healthy prepubertal children given calcium supplementation showed a bigger increase in BMD compared with those given placebo.[39] Exercise should be encouraged, and because better asthma control allows a child to exercise more, inhaled steroid mitigates its own adverse effect on bone metabolism. It seems reasonable that inhaled steroid use is an additional indication for oestrogen replacement therapy in postmenopausal patients, although there are as yet scanty scientific data on this aspect.[40] The role of more aggressive prophylactics, including calcitonin, diphosphonates and sodium fluoride, will need systematic evaluation. The relationship between side effects and efficacy varies between different inhaled corticosteroids, and some new preparations may have better topical-systemic activity ratios.[7,41] The use of large volume spacers and mouthwashing after inhalation decrease oropharyngeal systemic absorption.[8] Finally, systemic side effects from inhaled therapy appear to be dose-dependent, therefore it is important to remember that the inhaled steroid dose should be tailored according to variations in patient status so that the minimum effective dose is used.

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