TRAINEE SECTION

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Prevalence of Osteopenia and Osteoporosis in Patients with Moderate to Severe Asthma in Western Canada

Abstract

Purpose: Steroids, inhaled and systemic, are used to treat airway inflammation in patients with asthma; however, steroids are recognized to cause a number of side effects, including osteoporosis. We evaluated the prevalence of osteopenia/osteoporosis in patients with moderate-severe asthma managed through the Edmonton Regional Severe Asthma Centre.

Methods: We performed a retrospective chart review and analyzed 57 charts on patients with moderate-severe asthma followed through the specialty clinic, and recorded their bone mineral density (BMD). Steroid use was reviewed and the frequency of osteopenia/osteoporosis was compared in patients requiring continuous systemic steroids (Group 1, n=15), intermittent systemic steroids (Group 2, n=15) or inhaled steroids only (Group 3, n=27).

Results: The mean age (mean±SD) was 50±14.8 years. Cumulative systemic steroid dose of prednisone equivalent was higher in Group 1 (12.5 mg/day) than Group 2 (3.2 mg/day) (p=0.002). The frequency of osteopenia / osteoporosis was not significantly different between patients in Group 1 (67%) and Group 2 (53%, p=0.46) but was significantly greater in patients from Group 1 in comparison with Group 3 (33%, p=0.038).

Conclusion: Patients with moderate-severe asthma have a high prevalence of reduced bone density. Many patients treated with intermittent systemic steroids for exacerbations, or who were stable on inhaled steroids, had either osteopenia or osteoporosis before the age of 50. National and international osteoporosis guidelines should emphasize earlier screening for asthma patients; and increase awareness of the detrimental effects of short-term systemic steroids and inhaled steroids on BMD, especially when started at an early age and in northern climates.

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Current treatment recommendations for patients with asthma emphasize control of underlying airway inflammation with glucocorticoid therapy [1]. Inhaled steroids are sometimes inadequate to control asthma symptoms and systemic steroids are used. Although we have long-term clinical experience with glucocorticoids, they are not altogether benign and have multiple side effects including mood changes, insomnia, hyperglycemia, weight gain, adrenal suppression, and, rarely, avascular necrosis of the hip. Systemic steroids are also a recognized cause of secondary osteopenia / osteoporosis when used to treat many chronic diseases, such as asthma, chronic obstructive pulmonary disease, rheumatologic, autoimmune, and inflammatory conditions [2], and increase the risk of fractures [3]. Inhaled steroids may also affect bone mineral density (BMD), because a proportion of the dose enters systemically through direct absorption in the lungs and a proportion is swallowed [4-7]. The fraction in the lungs is the main source of systemic absorption; while the fraction that is swallowed is subject to varying extents of first-pass metabolism through the liver, depending on the specific drug [8]. As expected, diminished BMDs are more common in patients who use systemic steroids, as opposed to those only on local steroids [9].

The adverse effects of steroids on bone are dose related [10] and cumulative - and this can begin at a very young age. Children and adolescents with asthma are often treated with short courses of systemic steroids for exacerbations in addition to inhaled steroids. Adolescent growth velocity may be slower in asthma patients on inhaled steroids [11], and final adult height may be reduced [12]. Peak bone mass, which predicts future osteoporosis, is reduced in young patients treated with systemic steroids [13].

Cumulative steroid dose received by an individual patient, for asthma and / or chronic rhinosinusitis or other indications, may not be considered when prescriptions for inhaled, intranasal, and systemic steroid courses are written [14]. Additionally, asthma management strategies focus much more on upward titration of steroid therapy [1]. Currently there are no guidelines explicitly recommending screening for osteoporosis in asthma patients controlled with local inhaled and intranasal steroids; hence, gradual loss of BMD can be unrecognized for many years, and appropriate treatment may not be initiated in a timely manner. Lastly, location of residence, particularly those in northern climates, may be more affected and have higher rates of decline as opposed to those who live in regions where there is more sunlight year round [15].

The objective of this study was to evaluate the prevalence and pattern of osteopenia / osteoporosis in individuals with moderate to severe asthma who are treated through the Ed-

monton Regional Severe Asthma Centre, in conjunction with their primary care team. This regional centre manages patients who live in very northern climates in Western Canada. We compared the BMD of asthma patients treated with continuous systemic steroids, intermittent systemic steroids, and inhaled steroids alone.

Methods

Study population

This study was a retrospective chart review (unfunded) performed from the database of patients, intended for general research and analysis, actively followed longitudinally through the Edmonton Regional Severe Asthma Centre. The clinic services patients from Northern Alberta, Northern British Columbia and parts of Northern Saskatchewan. This study was approved by our institutional ethics committee, and data was collected from clinical records in accordance with research ethics guidelines. All included subjects were adults who had a diagnosis of current moderate to severe asthma based on Canadian Thoracic Society (CTS) guidelines [1]. Subjects were taking a regular minimum dose of 500 mcg / day of inhaled fluticasone propionate or equivalent, which is considered a high dose by CTS asthma guidelines [1]. Patients may also have been on intranasal or systemic steroids.

Subjects with other medical conditions affecting bone metabolism, such as chronic renal disease, rheumatoid arthritis, inflammatory bowel disease, chronic liver disease, hyperparathyroidism and malabsorption, were excluded. All subjects underwent assessment and optimization of their asthma, consisting of several visits over a minimum of 6-12 months. All patients followed through the clinic underwent structured assessment and management, according to CTS asthma guidelines, to maintain clinical stability while minimizing overall steroid use.

Data collection

We examined each subject's BMD records and focused, for the purposes of data collection and analysis, on the most recent BMD assessment with dual-energy x-ray absorptiometry (DXA), currently one of the most widely available, clinically relevant and accepted tools to measure BMD [9]. Osteopenia and osteoporosis were defined by current World Health Organization guidelines by T-scores of -1 to -2.5 and less than -2.5 respectively [16] for either the hip or spine. We reviewed each subject's clinic notes, emergency department records, patient diaries and prescription records to determine the type, route, dose and duration of their steroid use. Additionally, we re-

FIGURE 1. Number of charts screened and analyzed. Patients included have moderate to severe asthma as defined by Canadian Thoracic Society asthma guidelines, and must be taking at least 500 μ g / day of inhaled fluticasone equivalent.

corded each patient's use of bisphosphonates, vitamin D and calcium and other characteristics including age, gender, smoking and body mass index (BMI).

Data analysis

Subjects were stratified into three groups, depending on their steroid use during the preceding year: continuous systemic steroids as defined by daily steroid use for at least six months in the past year to achieve asthma control (Group 1); intermittent systemic steroids as defined by treatment with at least one adequate course [1] of prednisone of 40mg / day or more for seven days but not exceeding 6 months (Group 2); or only local inhaled and intranasal steroids (Group 3). We defined intermittent systemic steroids as the use of oral or intravenous steroids at least once in the past year to control an exacerbation. The frequency of osteopenia / osteoporosis of each group were then compared. Each patient's lowest T-score (femoral neck or lumbar spine) was analysed and the mean for each group was determined. Patient's without DXA scans performed were still included in the denominator when calculating the frequency of osteoporosis or T-score, to avoid overestimation. Multivariate linear regression analysis (IBM SPSS Statistics, version 22) using the T-score as a continuous outcome was performed with independent variables of age, BMI, mean daily dose of prednisone equivalent in the past year (mg / day), and inhaled steroid

dose. Statistical significance was set as $p < 0.05$. P values for differences between groups were estimated by analysis of variance (ANOVA) for continuous variables and chi-square test for categorical variables.

Results

Patient characteristics

From a database of 139 patients, 57 charts were analysed based on inclusion criteria and exclusion criteria (Figure 1). The mean age was not different between groups and the overall mean age (mean $\pm$ SD) was 50 $\pm$ 14.8 years. Mean BMI was greater in Group 1 (32 kg/m²), than both Group 2 (25 kg/m², $p = 0.006$) and Group 3 (29 kg/m², $p = 0.019$). There were also more patients in Group 1 with childhood onset asthma compared with Group 2 ($p = 0.025$), but not Group 3 ($p = 0.15$). There were no significant differences in the ratio of males and females across groups, nor the frequency of osteoporosis between sexes ($p = 0.44$) (Table 1). There was no significant difference in the inhaled steroid dose, of fluticasone equivalent in μ g/day, across groups.

The mean cumulative systemic steroid dose of prednisone equivalent was higher in Group 1 (12.5 mg/day) than Group 2 (3.2 mg/day) ($p = 0.002$). There was no difference among groups in the proportion of patients on intranasal steroid therapy.

FIGURE 2. Frequency of osteopenia / osteoporosis in moderate to severe asthma patients. Group 1 includes patients on continuous steroids (n=15), Group 2 on intermittent steroids (n=15), and Group 3 on inhaled steroids only (n=27).

Bone density

There was no difference observed in the frequency of osteopenia/osteoporosis between patients in Group 1 (67%) compared to Group 2 (53%, $p=0.46$); however, Group 1 was significantly greater than Group 3 (33%, $p=0.038$) (Figure 2). Although the frequency was higher in Group 2 than Group 3, the difference was not statistically significant ($p=0.21$).

The mean T-score (femoral neck or lumbar spine, whichever was lower for each patient) was also worse in Group 2 (-2.2, 95% CI -3.0 to -1.5), compared to Group 1 (-1.4, 95% CI -1.9 to -0.9), but not significant ($p=0.07$). Of note, ten patients in Group 1 were on treatment with bisphosphonates, six of whom had improved their BMD compared to their last scan. Of the 27 patients with reduced BMD in our study, 9 were younger than 50 years old [Table 2].

Regression analysis identified a significant negative correlation between femoral neck BMD and age, and a positive correlation with body mass index (Table 3). Although oral prednisone within the past year negatively correlated with femoral T-score, it was not significant (95% CI -0.08 to 0.01, $p=0.14$). When we analysed Group 1 alone, a significant corre-

lation was found between cumulative oral prednisone dose equivalent and predicted femoral neck T-score with a regression coefficient of -0.06 (95% CI -0.09 to -0.03, $p=0.003$).

Discussion

This study addresses the important yet underappreciated adverse effects of both locally applied and systemic steroids on bone health in asthma patients. This is particularly important for patients in northern climates who are already at higher risk for fractures [17], potentially due to a lack of sun exposure and subsequent vitamin D deficiency. In our study, the highest frequency of osteopenia and osteoporosis, 67%, was in subjects with moderate to severe asthma who required continuous systemic steroids as expected. The frequency in this group may be underestimated because all the patients with known osteoporosis, and some with osteopenia, were appropriately treated with bisphosphonates. This may account for why there was a significant difference in osteopenia / osteoporosis between Groups 1 and 3, but not between Groups 1 and 2. Another important finding was that the BMI in Group 1 was significantly greater

TABLE 1. Patient demographics

Characteristic	Group 1	Group 2	Group 3
Number reviewed - n	15	15	27
Mean age (mean±SD) years	52±10	47±14	51±17
Male - n (%)	7 (47)	7 (47)	8 (30)
Body mass index (mean±SD) kg/m ²	32±7.4	25±5.1	29±5.2
FEV1 of predicted (mean±SD) %	88.6±10%	89.5±12%	83.5±16%
Adult onset asthma - n (%)	6 (40)	12 (80)	17 (63)
Childhood onset asthma - n (%)	9 (60)	3 (20)	10 (37)
Intranasal steroids - n (%)	9 (60)	9 (60)	18 (67)
Current smoking - n (%)	1 (7)	1 (7)	1 (4)
Mean cumulative prednisone dose (mg/day)†	12.5±9.5	3.2±2.4	0
Bisphosphonate therapy - n (%)	10 (67)	5 (33)	3 (11)
Vitamin D and calcium - n (%)	15 (100)	10 (67)	12 (44)
Had BMD‡performed - n (%)	14 (93)	11 (73)	15 (56)

Mean BMI was greater in Group 1 than both Group 2 ($p=0.006$) and Group 3 ($p=0.019$). Mean oral prednisone dose was higher in Group 1 than Group 2 ($p=0.002$). Group 1 had more patients with childhood onset asthma compared to Group 2 ($p=0.025$). More patients had bisphosphonate therapy in Group 1 than Group 3 ($p<0.001$). Otherwise, there were no significant differences between any of the baseline characteristics ($p>0.05$).

†The mean cumulative steroid dose of oral prednisone equivalent taken per day

‡Bone mineral density

than both Group 2 and 3. Higher BMI is associated with a higher BMD [18]. This may partly explain the lack of differences in the frequency of osteoporosis / osteopenia and T-score between Groups 1 and 2. Whether the higher BMI is a result of the higher dose of steroid exposure or by chance alone is difficult to discern in the context of this retrospective study.

It is important for the clinical community to recognize that young patients with asthma are at long term risk for osteoporosis over many years with repeated exposure to intermittent systemic steroids. Over half of the patients in Group 2 had abnormal BMDs at a mean age of 47 years. One of the male subjects with childhood-onset asthma in Group 2, but no other known risk factors for osteoporosis, had a T-score of -3.0 and was only 19 years old. Asthma patients treated with systemic steroids, either intermittently or continuously, should have earlier and regular screening for osteoporosis as part of the evaluative algorithm of asthma management. Identifying osteoporosis earlier will facilitate appropriate treatment and prevent the morbidity and mortality associated with osteoporotic fractures [9].

Reduced BMD is common in patients well-controlled on locally applied steroids. 33% of the patients in Group 3 had osteopenia / osteoporosis, three of whom were younger than 50 years old. This is an underestimation, because half of the subjects in Group 3 did not have BMDs measured, but were included in the denominator. If we exclude these patients, of the remaining patients who actually had DXA scans performed, we found that 60% of the scans demonstrated osteopenia / osteoporosis. The high frequency of reduced BMDs in Group 3, despite the lack of patients who had scans, suggests that many patients in this group likely have osteopenia / osteoporosis but were simply not investigated for it. This paucity of data partially relates to the fact that no current guidelines discuss early screening for osteoporosis in patients taking only inhaled steroids. Consideration should be given to screen all asthma patients on local or systemic steroids before the age of 50. Additionally, the frequency of rhinosinusitis in our study, 63%, was equal among the groups. Rhinosinusitis is common in asthma patients [19], and is clinically worse in those with severe asthma [20]; hence, increasing overall steroid burden.

TABLE 2. Frequency of abnormal bone mineral density in asthma patients

Result	Group 1	Group 2	Group 3
Osteopenia - n (%)*	8 (53%)	4 (27%)	6 (22%)
Osteoporosis - n (%)*	2 (13%)	4 (27%)	3 (11%)
Total with T score ≤ -1 - n (%)*	10 (67%)	8 (53%)	9 (33%)
T score ≤ -1 and age ≤ 50 - n (%)*	3 (20%)	3 (20%)	3 (11%)
Femoral neck T-score – mean (CI 95%)	-0.92(-1.36 to -0.48)	-1.15 (-2.0 to -0.29)	-0.85 (-1.5 to -0.18)
Lumbar T-score - mean (CI 95%)	-0.98 (-1.7 to -0.29)	-2.01 (-3.0 to -1.0)	-1.31 (-1.9 to -0.67)
Total patients reviewed	15	15	27

*The denominator used was the total patients reviewed per group, some which did not have bone mineral densities measured.

TABLE 3. Relationships of patient characteristics and bone mineral density

T-score (n=38)	Covariate			
	Age	Body mass index	Systemic steroid dose*	Inhaled steroid dose
<u>Femoral neck</u>				
β	-0.03	0.11	-0.04	-0.0004
P value	0.01	<0.01	0.14	0.89
95% CI	-0.06 to -0.01	0.05 to 0.16	-0.08 to 0.01	-0.001 to 0.001
<u>Lumbar</u>				
β	-0.02	0.07	0.07	-0.0003
P value	0.19	0.08	0.73	0.5
95% CI	-0.06 to 0.01	-0.01 to 0.14	-0.05 to 0.08	-0.001 to 0.001
<u>Lowest BMD</u>				
β	-0.02	0.07	-0.03	-0.0001
P value	0.15	0.03	0.31	0.78
95% CI	-0.05 to 0.01	0.006 to 0.14	-0.08 to 0.03	-0.001 to 0.001

β = regression coefficients from multivariate linear regression for BMD

*Cumulative oral prednisone dose equivalent in past year

BMD = Bone mineral density

Current Canadian osteoporosis guidelines recommend screening of average-risk patients at age 65, or patients younger than 50 who were taking systemic steroids for at least 3 months at a cumulative prednisone dose of 7.5mg/day in the previous year [21]. Our study illustrates that asthma patients on locally applied and / or intermittent systemic steroids, are also at significant risk for developing BMD problems and should be risk

stratified and monitored more aggressively for osteopenia and osteoporosis.

Femoral neck T-score correlated well with cumulative steroid dose in our patients who were on continuous systemic steroids. We estimate a change of femoral T-score by -0.06% for every 1 mg / day of prednisone equivalent, which is similar to a previous meta-analysis which studied steroid-induced osteopo-

rosis [22]. This relationship was not found for lumbar T-score in patients in Group 1, although previously described [23], perhaps due to a lack of power. We were not able to identify a relationship between steroid use and BMD in groups 2 and 3, although we would not necessarily conclude from this that intermittent or inhaled only steroids do not affect bone density. Patients on intermittent systemic steroids may have recovery in BMD [24], and the power of our study is also limited, especially for Group 3.

Since this is a retrospective study, it is also difficult to precisely correlate relationships between asthma and osteoporosis, unless a larger prospective clinical study is done. Individuals in Group 3 may have been exposed to systemic steroids earlier in life; thus, potentially inflating the true effect of inhaled steroids alone. Assessing lifetime cumulative steroid dose accurately is challenging as recall is poor and patients may change practitioners over time. This is especially true and important for inhaled steroids, which are an independent risk factor for fractures [25, 26], but have yet to be shown to directly reduce BMD in robust randomized clinical studies [27]. In addition, the lack of BMD results in many of our reviewed patients limited the power of our statistical analysis, and also possibly led us to underestimate the actual prevalence of osteopenia / osteoporosis. This also reduced the power of the study to detect small differences between groups, particularly for comparisons involving Group 3. We recognize that patients may have other comorbidities not known to affect bone mineral density such as hypertension or dyslipidemia, but we felt they were unlikely to have had a major effect on the results, given the young mean age of the study population. As well, it is important to recognize that this is an unfunded retrospective analysis, therefore we utilized available clinical data; and as such vitamin D levels were not sampled on most patients due to cost. This study is limited by the smaller sample size; however we do think this retrospective review adds significant value to the available published literature in this area.

Relatively speaking, there is much less published literature in regards to “step-down” steroid therapy in asthma - compared to escalation of therapy, which may in part be related to the means by which many asthma treatment studies are funded. One strategy to consider is to use sputum cell counts which may greatly assist with tapering steroid dose [28,29] if clinically available / funded within the region. Another strategy is to introduce long-acting beta-agonists sooner and reduce the dose of inhaled steroids, although this may mask increasing airway inflammation [30].

This study highlights the importance of the adverse effects of both inhaled and systemic steroids and brings it to a height-

ened level of awareness. We learned that asthma patients, even those controlled by only inhaled steroids, are at risk in regards to bone health. We also realized the need for more studies and guidelines to address the issue of down-titrating asthma therapy.

Conclusion

In summary, we found a high prevalence of osteopenia / osteoporosis in subjects with moderate-severe asthma treated with steroids, locally applied or systemic. Early recognition of osteoporosis and implementation of prophylactic treatments, including consideration of steroid down-titration where feasible, is important for long-term bone health. We recommend that guidelines committees consider directed work related to earlier age of screening for osteoporosis in patients with moderate to severe asthma in Canada and elsewhere (i.e. before the age of 50), even if controlled on inhaled steroids alone. We advocate for future research and development of national (Canadian, US, other) and international guidelines to this end. Efforts should be undertaken to increase awareness of the cumulative and detrimental effects of even short courses of systemic steroids in asthma patients, especially in northern climates and if started at a young age. Although steroids remain fundamental in asthma therapy, clinicians must consider the adverse effects of steroid therapy when prescribing treatment plans. This is especially important, because patients are frequently labelled as having asthma without confirmatory pulmonary function tests [31], and their steroid dose may be infrequently stepped down [3,32]. Larger prospective clinical trials are required to more clearly delineate the pattern of bone loss in patients with asthma and to help clinicians better personalize asthma therapy.

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