The Effect of Inhaled Corticosteroids on Bone Mineral Density measured by Quantitative Ultrasonography in an Older Population

ABSTRACT:

Introduction:

Prolonged use of systemic corticosteroids leads to reduced bone mineral density and osteoporosis, in turn increasing the risk of minimal trauma fractures with their associated morbidity and mortality in elderly populations. The effect of inhaled corticosteroids on bone mineral density has been debated in the medical literature.

Objectives:

We aimed to determine the unconfounded effect of inhaled corticosteroids on bone mineral density using calcaneal quantitative ultrasonography in a cohort of older Australians.

Methods:

Data was collected from the Hunter Community Study, a longitudinal cohort of Australians aged 55-85. Simple and multiple linear regression methods were used to test the cross-sectional association between inhaled corticosteroids and other psychosocial aspects and calcaneal bone mineral density at baseline. A causal diagram was used to determine the minimally sufficient number of co-variates necessary to determine the unconfounded effect of inhaled corticosteroids on bone mineral density; these included gender, body mass index, smoking, asthma, alcohol use, age, physical activity, and diet.

Results:

There were 152 (6.8%) patients on inhaled corticosteroids and 2098 (93%) controls. Simple and multiple linear regression methods showed a non-significant effect of inhaled steroids on BMD with slight decrease of BMD -0.010 g/cm^2 (95% CI-0.042-0.022, p=0.55) and -0.013 g/cm^2 (95% CI-0.062-0.036, p=0.61) respectively. Age, gender, body mass index and smoking were stronger predictors of BMD.

Conclusions:

No statistically significant relationship was established between the use of inhaled corticosteroids and reduced bone mineral density in this observational study of a cohort of older Australians.

MeSH (key words)
1 Inhaled corticosteroids
2 Osteoporosis
3 COPD
4 Asthma
5 Calcaneal ultrasound
6 Bone mineral density

Introduction:

The effect of inhaled corticosteroids (ICS) on bone mineral density and osteoporosis has been debated in the past.(1-5) Osteoporosis is increasing in Western communities at the same time as inhaled corticosteroid use is becoming more common.(6) There are many well characterised risk factors for osteoporosis including female sex, advancing age, low body mass index (BMI), smoking, premature menopause, Asian or Caucasian ethnicity, previous history of fracture, systemic glucocorticoid therapy, poor intake of calcium, low vitamin D levels, and immobilisation. (7)

The prolonged use of systemic corticosteroids leads to reduced bone mineral mass and osteoporosis. This is due, at least in part, to increased osteoclastogenesis and osteoclast activity during the early phase and decreased osteoblast activity along with apoptosis of osteoblasts during late phase of treatment with corticosteroids. (8, 9) It is not clear whether inhaled corticosteroids lead to significant systemic absorption from the lungs and therefore cause a reduction in bone mineral density and osteoporosis. Studies investigating the effect of inhaled corticosteroids on bone mineral density have shown mixed results. Some studies have shown that ICS use results in loss of bone mineral density and an increased risk of osteoporotic fractures (3, 5) but others show no such relationship. (1, 2, 4) Two meta-analyses have provided conflicting results. [10, 11] There are limited data in an elderly population where use of inhaled corticosteroids is increasing due to the burden of chronic obstructive pulmonary disease.

In this context, we hypothesised that ICS use in older patients would impact bone mineral density. We tested this hypothesis on a well characterised cohort of older Australian adults using an established method for assessing bone mineral status, calcaneal (heel) quantitative ultrasonography. Some of the results of this study have been previously reported in the form of an abstract. (12)

Material and Methods:

Cohort description:

We used an existing cohort study of older Australians aged 55-85, the Hunter Community Study (HCS) (13), to investigate any potential association. The cohort includes 3253 community dwelling people, recruited in the Newcastle region (New South Wales, Australia). Participants were randomly selected from the electoral roll and contacted between December 2004 and December 2007. Listing in electoral roll is compulsory for Australians. Invitations to enrol into the study were mailed, using a modified Dillman

recruiting strategy. (14) Initial non-responders were contacted through publicly listed telephone numbers if available. Five attempts were made before considering the person as a non-responder; the final response rate was 45%. Persons living in a residential aged-care facility or from a non-English speaking background were excluded from the cohort. All participants gave informed written consent, including consent to link their personal information to local health databases and to Medicare Australia (Medicare and Pharmaceutical Benefit Scheme) which keeps a record of subsidised medications under this scheme.

Inclusion criteria:

2250 participants out of 3253 who had medication data, including their use of inhaled steroids, and bone mineral density level at baseline were included in this study. Participants with autoimmune diseases were excluded along with participants who were on long term systemic corticosteroids for other clinical indications.

Measurements:

Two self-reported questionnaires were completed by participants which included all prescription medicines along with inhaled corticosteroids which were cross checked by HCS staff. Participants also visited a study centre where various anthropometric, physical, and clinical measures were obtained. (13)

Bone mineral density was measured using heel ultrasound with a Sahara bone sonometer (Hologic Inc, Mass, USA). This instrument uses through-transmission of ultrasound waves between the heel and the two transducers, which are faced with rubber pads. (15) This method is highly reproducible, avoids ionising radiation, and is inexpensive and portable. Bone mineral density measurements obtained by heel ultrasounds are comparable to X-ray bone densitometry. [16-19] Quantitative ultrasound measures broadband ultrasound attenuation and speed/velocity of sound across the bone which are used to calculate a quantitative ultrasound index and bone stiffness which correlate with bone mineral density. Calibration of the machine was performed every day using a standard phantom as per manufacturer’s guidelines.

Covariates:

A causal diagram was created describing the relationships between corticosteroids and bone mineral density (figure 1). This diagram was used to determine the minimally sufficient number of covariates necessary to determine the unconfounded effect of inhaled steroids on bone mineral density. These covariates include age, gender, BMI, smoking category, co-existent asthma, physical activity, diet and alcohol use. BMI was calculated using height and weight measured by HCS data collection staff. Diet was measured using the Australian Recommended Food Score (ARFS) (20) which ranges from 0 to 73, with higher scores indicating increased adherence to national dietary recommendations and guidelines. Alcohol use was also derived from the ARFS score. Physical activity was measured as mean daily step count by a pedometer which was worn for 7 consecutive days during waking hours. Simple and multiple linear regressions were used to test the association between each predictor and bone mineral density using the SAS statistical package (SAS Institute, NC, USA).

Results:

Baseline characteristics of all participants (ICS users and non ICS users) are summarised in table 1. There were 152 participants in the ICS group and 2098 participants in the control group. The median age of ICS users was 68.1 years, being slightly older than non ICS users (66.6) (p= 0.053). Mean (SD) bone mineral density of ICS users was 0.54 g/ cm^2 (0.15) which was not significantly different from non-ICS users 0.55 g/cm^2 (0.16) (p=0.56). 45% of non-ICS users and 41% of ICS users were overweight, whilst just over one third of participants in both groups were classified as obese. 54% were never-smokers. Diet scores, measured using ARFS, were almost the same in both groups (28 score), indicating similar dietary intake (p=0.54). About 20% of participants reported zero daily alcohol consumption whilst 36% and 43% of participants consumed one and two standard drinks daily respectively; this pattern was similar in ICS and non-ICS users (p=0.32). 83% of ICS users were diagnosed with asthma/COPD (self-reported) while about 10% of non ICS users had a self-reported diagnosis of asthma/COPD but were not on regular inhaled steroids. Daily exercise, measured as step counts, was similar in both groups. (p=0.11)

Crude and adjusted estimates showing the unit change in bone mineral density (g/ cm^2) with each predictor were measured (table 2). ICS use was not associated with a significantly lower bone mineral density in our cohort of older Australians. Bone mineral density in ICS users was not different when compared to non ICS users {-0.010 g/cm^2 (95% CI -0.042 to 0.022 p=0.55)} in unadjusted measurement. Bone mineral density was marginally low in the ICS group {-0.013 g/cm^2 (95% CI -0.062 to 0.036, p=0.61)} compared

to non ICS users after adjusting for all included potential confounders, with this difference not being statistically significant. As expected, females had significantly lower bone mineral density compared to men (by 0.07g/cm2, $p<0.0001$). Low BMI was associated with low bone mineral density, as demonstrated in other epidemiological studies. (21) Bone mineral density in active smokers was reduced compared to never-smokers (-0.052g/cm^2, $p=0.04$). Alcohol use was associated with lower bone mineral density, with borderline significance ($p=0.066$). History of asthma/COPD was not a risk factor for low bone mineral density ($p= 0.23$). Average dietary intake, alcohol use and daily exercise did not affect bone mineral density significantly.

Discussion:

Our cross sectional analysis of a cohort of older Australians did not show any significant effect of ICS on bone mineral density though ICS users had a slightly lower bone mineral density as compared to control group. Our results are consistent with another recent study which showed that ICS use does not lead to reduction in bone mineral density in people older than 50 years as compared to participants younger than 50 years. (22) Although our study is cross-sectional, an earlier longitudinal study done by Matsumoto et al. did not show any significant effect on bone mineral density.(1) Corticosteroid associated osteoporosis is associated with increased bone turnover markers. Hughes et al. studied the effect of high dose inhaled corticosteroids on bone mineral density and bone turnover markers at baseline and one year and found no significant effect. (23)

This is in contrast to a recent meta-analysis by Richy et al. They performed a systematic review of 11 studies which included five randomised control trials, two prospective cohort studies and four retrospective cohort and cross-sectional studies. The effect size of ICS on bone mineral density was significant (Effect size=0.271, $p<0.0001$). However, current smoking is a risk factor for osteoporosis, as was demonstrated in our study. By removing two studies which did not control for active smokers from the systematic review, the effect size was reduced and became non-significant.(24)

It is therefore possible that previous retrospective studies may have found an effect of ICS on bone mineral density and fracture risk due to residual confounding.(3, 5) Halpern et al. performed a meta-analysis which included 10 randomised control trials and 4 prospective studies. 12 out of 14 studies included patients who were on moderate to high dose of inhaled corticosteroids as per National Asthma Education and Prevention Program definition. There was no annual change in bone mineral density at lumbar, femoral neck or major trochanteric sites. (25) A recent Cochrane review by Yang et al.

which included only randomised control trials showed no increased risk of any fractures or reduction in bone mineral density. (26)

Based on 80% power and a p value of 0.05, we estimate that our sample size should have been able to detect an effect of 0.04 g/cm^2 (using the program PS Power by Dupont and Plummer). (27) Female gender, low BMI and active smoking were predictors of low bone mineral density, which is consistent with previous studies. (7)

There are some limitations to our study. We do not have fracture data in this cohort and are unable to study the relationship of ICS on fracture risk. Being a cross sectional study, we could not explore the longitudinal relationship of ICS with bone mineral density. There were few participants who provided exact number of puffs of inhaled steroids and due to this, we could not explore a dose-response curve.

Conclusion:

There was no indication of lower bone mineral density in ICS users in our cross-sectional study of community dwelling older Australians when adjusted for a number of potential confounders. Despite these reassuring results, the lowest clinically effective dose of inhaled steroids required to control airways disease should be used. Ideally these data should be confirmed in longitudinal studies with accurate measurement of potential confounders.

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Table 1: Comparison of two groups (ICS users and non-users)

		Inhaled steroid		
Predictor	Category	Non-user (n=2098)	User (n=152)	P-value for difference
Bone mineral density	mean (SD)*	0.55 (0.16)	0.54 (0.15)	0.5496
Age at first clinics	mean (SD)*	66.61 (7.58)	68.10 (7.47)	0.0527
Gender	Female	1016 (51%)	82 (58%)	0.1189
	Male	978 (49%)	60 (42%)	
BMI†	Underweight	12 (0.7%)		0.7275
	Normal	339 (19%)	26 (21%)	
	Overweight	805 (45%)	50 (41%)	
	Obese	645 (36%)	47 (38%)	
Smoking category	Never smoked	1109 (53%)	81 (54%)	0.2274
	Previous smoker	819 (39%)	54 (36%)	
	Current smoker	147 (7.1%)	16 (11%)	
Asthma/COPD	Absent	1868 (90%)	25 (17%)	<0.0001
	Present	200 (9.7%)	126 (83%)	
ARFS‡	mean (SD)*	27.81 (8.06)	28.25 (8.05)	0.5454

		Inhaled steroid		
Predictor	Category	Non-user (n=2098)	User (n=152)	P-value for difference
Alcohol (ARFS)‡	0	365 (20%)	31 (24%)	0.3169
	1	653 (36%)	50 (38%)	
	2	802 (44%)	49 (38%)	
Mean daily steps (pedometery)	mean (SD)*	6490.2 (3122.1)	5882.3 (3012.4)	0.1110

This table provides the baseline characteristic of two groups and different covariates that were used for relationship between inhaled corticosteroids and bone mineral density

*SD (standard deviation), † BMI (bone mineral density), ‡ ARFS (Australian Recommended Food Score)

Table 2: Results of multivariate regression analysis

This table showed the change in BMD with different predictors after adjustment with all confounders (Multivariate regression method).

Predictor	Category	Change in BMD Adjusted estimate (95% Confidence interval)	p-value
Inhaled steroid	Users	-0.013 (-0.062,0.036)	0.6069
	Non-users	reference	
Gender	Female	-0.070 (-0.090,-0.049)	<.0001
	Male	reference	
BMI*	Normal	0.073 (-0.080,0.226)	<.0001
	Obese	0.138 (-0.015,0.291)	
	Overweight	0.115 (-0.038,0.267)	
	Underweight	reference	
Smoking category	Current	-0.052 (-0.093,-0.011)	0.0411
	Never	-0.002 (-0.023,0.018)	
	Previous	reference	
Asthma/COPD†	Absent	0.026 (-0.008,0.061)	0.1329
	Present	reference	
ARFS‡		0.000 (-0.001,0.002)	0.4841
Alcohol (ARFS) ‡	0	-0.033 (-0.061,-0.005)	0.0663
	1	-0.012 (-0.033,0.010)	
	2	reference	
Age at first clinics		-0.001 (-0.002,0.000)	0.2036

Predictor	Category	Change in BMD Adjusted estimate (95% Confidence interval)	p-value
Mean daily steps		0.000 (-0.000,0.000)	0.4778

*BMI (body mass index); † COPD (Chronic Obstructive Pulmonary Disease); ‡ ARFS (Australian Recommended Food Score)