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Association of Topical Corticosteroid Use and Bone Mineral Density in Patients with Atopic Dermatitis

Carsten Paulson
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Association of Topical Corticosteroid Use and Bone Mineral Density in Patients with Atopic Dermatitis

Abstract

Background

Atopic dermatitis (AD) is a common pruritic inflammatory skin disease. First-line therapy for AD involves the use of topical corticosteroids. With long-term use, these agents exert systemic effects and have been associated with adverse effects on bone health. This review assesses the current evidence for an association between topical corticosteroid use and bone mineral density in patients with atopic dermatitis.

Methods

An exhaustive search of available literature was conducted in using the MEDLINE-Ovid, Web of Science, CINAHL, and Evidence-Based Medicine Reviews Multifile databases. Keywords searched included eczema, atopic dermatitis, and bone density. Articles that assessed bone mineral density in patients with atopic dermatitis and reported bone mineral density (BMD) as a Z-score were included. The quality of relevant articles was evaluated using the GRADE Working Group guidelines.

Results

Three studies met eligibility criteria and were included in this systematic review. All were observational, cross-sectional studies. One study of 42 adults found a statistically significant decrease in bone mineral density in patients using moderate or high potency topical corticosteroids. A second study of 125 adults reported a 60% increased risk of low BMD in patients using higher doses of oral and topical corticosteroids that was not statistically significant. In the third study of 60 children, no association between corticosteroid use and BMD was observed. All studies had very low quality of evidence based on GRADE guidelines.

Conclusion

The long-term use of topical corticosteroids may be associated with decreased bone mineral density in patients with atopic dermatitis. Providers should consider calcium and vitamin D supplementation in these patients. Additional research is needed to further evaluate long-term risks.

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Degree Name
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First Advisor
Annjanette Sommers, PA-C, MS

Keywords
eczema, atopic dermatitis, bone density, topical corticosteroids

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Association of Topical Corticosteroid Use and Bone Mineral Density in Patients with Atopic Dermatitis

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A Clinical Graduate Project Submitted to the Faculty of the
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Biography

[Redacted for privacy]
Abstract

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Results
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Conclusion
The long-term use of topical corticosteroids may be associated with decreased bone mineral density in patients with atopic dermatitis. Providers should consider calcium and vitamin D supplementation in these patients. Additional research is needed to further evaluate long-term risks.

Keywords
Atopic dermatitis, bone mineral density, topical corticosteroids
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List of Abbreviations

AD                  Atopic Dermatitis
BMD                 Bone Mineral Density
DEXA                Dual-Energy X-Ray Absorptiometry
GIO                 Glucocorticoid-induced Osteoporosis
TARC                Thymus and Activation-Regulated Chemokine
TCI                 Topical Calcineurin Inhibitors
TCS                 Topical Corticosteroids
Association of Topical Corticosteroid Use and Bone Mineral Density in Patients With Atopic Dermatitis

BACKGROUND

Atopic dermatitis (AD) is a common chronic inflammatory skin disease that affects up to 20% of patients at some point in their lifetime. Most cases of AD begin in childhood before the age of five years, with spontaneous remission in about 70% of patients before adolescence. The disease is most prevalent in developed countries, affecting 2-15% of adults in these areas. In recent years, the incidence of AD appears to be greatly increasing in multiple regions worldwide, likely a result of the adaptation of a Western lifestyle.

Atopic dermatitis is characterized by dry, scaly skin that is intensely pruritic. Flexural surfaces of the extremities, the face, neck, and eyelids are the sites most commonly affected. The symptoms of AD can be severely debilitating, even causing insomnia from the severe itch. A number of criteria have been developed for the diagnosis of AD, beginning with Hanifin and Rajka in 1980, which is still the most commonly used. These criteria require 3 of 4 major criteria and 3 of 23 minor criteria be met. The criteria were refined as the U.K diagnostic criteria in 1997, which subsequently has become the most extensively validated in scientific literature. There is currently no consensus on classifying the severity of AD. However, a semi-objective set of criteria called the SCORAD Index has been developed that involves grading the severity of six objective signs: erythema, edema/papulation, oozing/crusts, excoriations, lichenification, and dryness. In addition, an objective marker of disease activity, serum thymus and activation-regulated chemokine (TARC) has been shown to significantly correlate with disease severity in AD.
Treatment of AD primarily involves topical agents. Topical moisturizers are commonly utilized to treat the associated xerosis and help restore the skin barrier. Topical corticosteroids (TCS) are the mainstay of anti-inflammatory therapy for both children and adults. TCS are commonly prescribed for both acute inflammatory disease and chronically for prevention of recurrence, usually with twice-daily application dosing. Topical calcineurin inhibitors (TCI) are a newer class of topical anti-inflammatory medication that is approved as second-line therapy for AD. TCI are especially useful for areas where the epidermis is thin, such as the face, as they do not have the risk of systemic absorption or local skin atrophy like TCS. They are also useful for reducing the need for TCS in patients with severe AD.9

The adverse effects of topical glucocorticoids are well established. The most common side effects occur locally at the site of administration and include atrophy, telangiectasia, striae, acne, and steroid rosacea. While less common, systemic effects due to TCS have also been reported, including hypothalamic-pituitary axis disruption, Cushing disease, glaucoma, hyperglycemia, and osteopathy including fracture and aseptic necrosis.10 In atopic dermatitis the epidermal barrier is impaired, causing two to ten times greater penetration of TCS than in healthy skin.11 Systemic effects of TCS are even greater in children due to their 2.5 to 3-fold higher ratio of total body surface area to body weight as compared with adults.10

Glucocorticoid-induced osteoporosis (GIO) is the most common form of secondary osteoporosis. Glucocorticoids exert inhibitory and antiproliferative effects on osteoblasts, the cells responsible for bone formation. In addition, glucocorticoids inhibit synthesis of type I collagen by osteoblasts, reducing the amount bone matrix for
mineralization. In humans, GIO happens in two stages. First, a rapid initial phase leads to a 12% loss of bone during the first few months of treatment. This is followed by a slower progressive phase that results in a 2-5% loss of bone annually. Although it is well-documented that chronic glucocorticoid use causes bone loss and increases the risk of fractures, few patients receiving treatments are screened for skeletal health.

Most studies evaluating the harmful effects of glucocorticoid administration on bone mineral density (BMD) have focused on patients taking oral glucocorticoids. However, a correlation of significantly decreased bone mineral density with long-term use of inhaled corticosteroids has also been documented. While the decrease in BMD only causes a slight increase in fracture risk, the vast number of patients prescribed inhaled corticosteroids could lead to a significant public health risk.

A recent study found a significantly increased prevalence of fracture and bone or joint injury causing limitation in patients with atopic dermatitis. Patients with AD have multiple potential risk factors for these injuries including impaired sleep, use of sedating antihistamines, chronic inflammation, and long-term use of topical corticosteroids. Few studies have measured the BMD of patients with atopic dermatitis to evaluate for an increased risk of fracture.

Can the use of topical corticosteroids in patients with atopic dermatitis be associated with a change in bone mineral density?

METHODS

An exhaustive search of available literature was conducted in May 2015 using the MEDLINE-Ovid, Web of Science, CINAHL, and Evidence-Based Medicine Reviews Multifile databases. Keywords searched included eczema, atopic dermatitis, and bone
density. The search results were narrowed to include only English-language articles.

References cited in the included articles were examined for additional relevant sources. Articles that assessed bone mineral density in patients with atopic dermatitis and reported BMD as a Z-score were included. The quality of relevant articles was evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group guidelines.21

RESULTS

The initial literature search yielded 65 articles for review. After screening abstracts and titles for eligibility, three articles were selected that met inclusion criteria. All three studies used an observational cross-sectional study design. Two of the articles examined BMD in an adult population18,19 and the third focused on a pediatric population.20 See Table I. An additional study22 that examined BMD in a pediatric population was excluded because it reported results as a change in BMD and did not include Z-scores.

Aalto-Korte et al

This cross-sectional study18 evaluated the correlation between topical and oral glucocorticoid use and bone mineral density in adult patients with atopic dermatitis, accounting for risk factors including skin barrier function, duration of AD, and total dose of topical glucocorticoids in the past 12 months. The study included 29 patients from Finland who were included in a previous investigation by the same authors examining the absorption of hydrocortisone in patients with AD.23 All of the included patients had atopic dermatitis covering at least 50% of their total skin area and had been admitted to
the hospital because of AD. There were 13 men and 16 women, of whom five were postmenopausal. All of the patients met the Hanifin and Rajka criteria for AD.  

BMD was measured with dual-energy x-ray absorptiometry (DEXA) in the lumbar spine and left femoral neck and the results were evaluated as age-adjusted Z-scores. Patients were interviewed about their use of topical corticosteroids in the past 12 months, lifetime oral and inhaled glucocorticoid use, duration of AD, and hospital admissions for AD. The median duration of dermatitis was 27 years. The included patients had been admitted to the hospital for their dermatitis a median of 2.6 times, used oral glucocorticoids a median of 1.3 times in their lifetime, and used a median of 400 grams of TCS in the previous 12 months.

The DEXA result from one of the study patients was considered unreliable because of large body habitus, so 28 of the 29 patients were evaluated for BMD. The Z-scores were greater than two standard deviations (cutoff value for osteoporosis) below the mean of a healthy control series in all but three patients. The age-matched Z-score medians did not differ significantly from the reference series of normal patients without AD. Lumbar BMD did not correlate significantly with any of the single risk factors evaluated, including use of oral glucocorticoids, potent TCS, duration of dermatitis, or percutaneous absorption of hydrocortisone during AD exacerbation. Patients were divided into two groups based on the potency of TCS they used in the previous 12 months. One group was comprised of those who had used moderate or high potency TCS, while the second was used only hydrocortisone (low potency) or no TCS. Between these groups, the authors found a significantly lower BMD in the patients using more potent TCS (median Z-score -1.0 vs. +0.1; P=0.026). The patients in moderate/high potency
TCS group were over four times as likely to have a Z-score greater than one standard deviation (cutoff for osteopenia) from the mean BMD of healthy controls as compared to the low potency group (RR=4.06, NNH=3). In addition the patients in the moderate/high potency TCS group had significantly more hospital admissions than the patients in the low potency group (median 3.5 vs. 2.2 visits; \( P=0.037 \)).

Limitations included lack of blinding of radiologists interpreting DEXA scans, relatively small sample size, and reliance on patient questionnaires for corticosteroid use. In addition, the patients included in the study had widespread AD that was likely more severe than the average patient with AD.

**Haeck et al**

This cross-sectional study\(^{19}\) assessed the prevalence of osteopenia and osteoporosis in adults with AD. The authors also examined the association between topical/oral corticosteroid use and BMD and the association between AD disease activity and BMD. The study included 125 patients with moderate to severe atopic dermatitis, 64 male and 61 female. Of the study population, median age was 35.0 years (range 24.5 to 48.0 years). The patients enrolled in the study were recruited from the Department of Dermatology of the University Medical Center Utrecht in the Netherlands. All of the patients met the Hanifin and Rajka criteria for AD.\(^{19}\)

Bone mineral density was measured at the lumbar spine and hips using DEXA. Data were compared with control values from American and European patients and expressed as T-scores and Z-scores. Radiologists interpreting the DEXA scans were privy to the patients’ diagnosis of AD, but were blinded to their amount of corticosteroid use and disease duration. Cumulative corticosteroid use over the five years prior to the study
was calculated for each patient from pharmacy records. The patients were interviewed about their total number of years of TCS use. The authors also measured the serum concentration of thymus and activation-regulated chemokine (TARC) as an objective measure of AD disease activity. Patients were also interviewed about lifestyle parameters including dairy product intake, daily sunlight exposure, alcohol consumption, coffee intake, exercise, smoking, hospital admissions, use of contraception, menopause, and family history of bone diseases.19

The data analysis revealed no significant difference in the cumulative dose of corticosteroids used in the previous 5 years in patients with low BMD (P=0.238). Low BMD was defined as a Z-score greater than one standard deviation from the mean BMD of age-matched controls. There was also no significant difference in the use of topical corticosteroids in the previous two years between patients with a low versus normal BMD (P=0.484). The authors used logistic regression analysis to determine that patients using higher doses of TCS had a 60% greater risk of having low BMD than patients using a lower dose of TCS (NNH=14) after adjusting for sex, BMI, and serum TARC level. This risk, however, was not statistically significant. The serum TARC concentration was not statistically different between patients with normal and low BMD (P=0.946), nor were the 25-hydroxyvitamin D concentrations (P=0.654) or parathyroid hormone levels (P=0.942).19

Limitations of the study include a probable overestimation of corticosteroid use from using pharmacy records, rather than actual amount taken or applied. Also the patients in the study were enrolled after being referred to a tertiary hospital and are likely not representative of the average patient with AD.
Van Velsen et al

This cross-sectional study investigated the prevalence of low BMD in children with moderate to severe AD. Low BMD was defined as a Z-score greater than 2 standard deviations from the mean of age-matched controls. The study included 60 children ages 5 to 16 years (mean age 10.5 years) with moderate to severe AD who were being treated at the outpatient pediatric/allergology dermatology department of the University Medical Center Utrecht in the Netherlands. All of the patients had been given a diagnosis of AD using the Hanifin and Rajka criteria. The inclusion criteria were SCORAD index greater than 20, more than four visits to the outpatient department in one year, history of a hospital admission for AD, current use of potent (class III) TCS, or history or current use of systemic immunosuppressive therapy (prednisone and/or cyclosporine).

Bone mineral density was measured using DEXA in the lumbar vertebrae L1 to L4. Data were expressed as Z-scores compared with age and sex-matched controls of a Caucasian population in the United States. Z-score was corrected for body height to prevent falsely low BMD in patients with small body size for their age. Radiologists interpreting DEXA scans were aware of the patients’ diagnosis of AD but were blinded to their corticosteroid use. Cumulative dose of corticosteroids (topical, inhaled, and systemic) and topical calcineurin inhibitors over the preceding five years prior to the study were calculated from pharmacy records. Patients were interviewed about their total number of years of therapy for AD. Disease activity was estimated using the SCORAD index and measurement of serum TARC.
Statistical analysis revealed that the use of topical corticosteroids was not associated with a lower lumbar spine Z-score (P=0.260). The authors further subdivided the children into three groups based on their cumulative TCS use over the previous 5 years: less than 30 grams, 30 to 50 grams, and greater than 50 grams. In these groups, higher cumulative corticosteroid use was not associated with a decreased lumbar Z-score (P=0.935). Three patients in the study were given a diagnosis of low BMD and one was given a diagnosis of osteoporosis. Of these four patients, three had used less than thirty grams of TCS over the past five years and one had used more than thirty grams (RR=0.407). A history of using oral corticosteroid was associated with a lower BMD, but the relationship was not statistically significant (P=0.825).20

Limitations included a likely overestimation of actual corticosteroid use since the authors calculated cumulative dose from pharmacy records and not actual use. In addition the study population was small and only four cases of low BMD were reported. The patients were recruited from a specialty care setting and likely had higher severity AD than the average patient with AD.

DISCUSSION

The prevalence of AD has been greatly increasing in various regions worldwide over the last two decades.4 A recent study found that eczema in adulthood seems to be a risk factor for fracture or bone and joint injury causing limitation.16 The focus of this systematic review was to determine the association of topical corticosteroid use and bone mineral density in patients with AD to evaluate if long-term TCS exposure has an adverse impact on bone health.
The results of the studies reviewed\textsuperscript{18–20} were conflicting (Table II). In addition, results were reported differently by each study, making direct comparisons difficult. The only statistically significant correlation between topical corticosteroid use and bone mineral density was observed in the oldest study included in the analysis.\textsuperscript{18} This study also had the lowest quality, with a small panel of 29 patients, lack of blinding, and reliance on patient questionnaires to assess TCS use. Higher potency TCS use seemed to have a protective effect against low BMD as compared with low potency TCS in the study that examined a pediatric population,\textsuperscript{20} a spurious finding likely due to the infrequency of low BMD in the study population. Direct comparison of pediatric and adult populations is further hindered by differing definitions of osteopenia (Z-score $\leq -1$ in adults, $\leq -2$ in children) in these studies.

Although the correlation between TCS (duration and potency) and BMD in patients with atopic dermatitis is not established at this point, clinicians may want to screen patients at a younger age for low BMD if their AD has been treated with high-potency glucocorticoids for extended durations. Moreover, supplementation with calcium and vitamin D should be considered in these patients without contraindications. A recent review\textsuperscript{24} by The Cochrane Collaboration concluded that providers starting patients on corticosteroids should consider prophylaxis with these medications to prevent bone loss.

All three of the studies assessed in this review provided very low quality evidence based on GRADE guidelines (Table I).\textsuperscript{21} All of the studies used observational, cross-sectional designs. Blinding was limited to the radiologists interpreting DEXA scans in two of the studies\textsuperscript{19,20} and was not addressed in the third,\textsuperscript{18} a potentially significant source of bias.
Each of the studies enrolled their patients from single medical centers in Europe, leading to a strong risk of selection bias in the patient populations. Additionally, the patients in all of the included studies tended to have high severity AD and were likely not representative of a general population of patients being treated for AD with TCS. This limits the generalizability of the results of these studies to broader populations.

Two of the studies assessed in this review relied on pharmacy records to calculate the total dose of corticosteroid to which patients were exposed. Since patients frequently do not apply an entire tube of topical medication before disposing of the remainder, this approach may have grossly overestimated their actual TCS exposure. The third study simply relied on patient questionnaires to assess TCS use, a technique with potentially significant recall bias.

Due to the very low quality of evidence in these studies, it is difficult to make conclusions about the effect of long-term TCS on BMD in patients with AD. Since the risk of osteopenia continues to increase over time with a larger cumulative corticosteroid dose, further investigation is needed that assesses BMD longitudinally in patients with AD. Larger patient panels are also needed to increase the statistical power of primary outcomes. Autoimmune joint diseases characterized by chronic inflammation, such as rheumatoid arthritis and seronegative spondyloarthropathies, are known to be associated with bone loss. Further research could investigate if the chronic inflammation associated with AD also adversely affects bone health. Topical calcineurin inhibitors are commonly used as second-line agents to treat the symptoms AD. Since TCI do not carry the same systemic risks as TCS, further investigations could examine the possibility of
using these agents in patients requiring long-term TCS to reduce adverse impacts on skeletal health.

CONCLUSION

The association between topical corticosteroid use and bone mineral density in patients with atopic dermatitis is unclear from the results of the studies included in this review. A statistically significant correlation between TCS use and BMD was observed in only one\textsuperscript{18} of the three studies examined. However, a second study found an increased risk of having low BMD in patients with higher use of topical and oral corticosteroids that was not statistically significant.\textsuperscript{19} A recent population-based study observed an increased risk of fracture and bone or joint injury causing limitation in adults with AD.\textsuperscript{16}

These studies, though seriously flawed, illustrate the potential of an increased risk of low BMD in patients with AD. Since AD is a common disease, the public health implications for an increased risk of fractures in patients with AD would be significant. From the current review, providers may consider a lower threshold for assessing BMD in patients with AD. In addition, supplementation with calcium and vitamin D, a safe and efficacious regimen for steroid-induced osteoporosis,\textsuperscript{24} should be considered in patients requiring long-term use of potent topical corticosteroids.
References


Table I. GRADE Evidence Profile

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...of events (4 total patients with osteopenia).
Table II. Summary of Findings

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