Journal of Investigative Medicine 56(8):1011–1018, 2008

ORIGINAL ARTICLE

Effects of Low-Dose Corticosteroids on the Bone Mineral Density of Patients With Rheumatoid Arthritis: A Meta-Analysis

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■ ABSTRACT

Background: The effects of long-term high-dose corticosteroids on bone mineral density (BMD) are clear, but the effects of low-dose corticosteroids in patients with rheumatoid arthritis (RA) remain controversial. The aim of this study was to assess the effects of low-dose corticosteroids on BMD in patients with RA.

Methods: The authors surveyed randomized controlled studies that examined the effects of low-dose corticosteroids on BMD in patients with RA using MEDLINE and the Cochrane Controlled Trials Register and by performing manual searches. Data were collected on BMD (end-of-period or change-from-baseline) after longest recorded treatment durations. Meta-analysis was performed using a random effects model; outcomes are presented as standardized mean differences (SMDs).

Results: Seven studies were included in this meta-analysis, which included 7 studies on lumbar BMD meta-analysis and 6 studies on femur BMD meta-analysis. Corticosteroids resulted in a moderate worsening in lumbar BMD compared with controls (SMD = −0.483; 95% confidence interval [CI], −0.815 to −0.151, $P = 0.004$), whereas the femoral BMD differences were not siginificant (SMD = −0.224; 95% CI, −0.663 to 0.215, $P = 0.318$). Subgroup analysis of BMD data performed on a change-from-baseline basis showed that corticosteroids had a clear effect on both lumbar and femoral BMDs (SMD = −0.354; 95% CI, −0.620 to −0.088, $P = 0.009$; SMD = −0.488; 95% CI, −0.911 to −0.065, $P = 0.024$, respectively).

Conclusions: This meta-analysis shows BMD loss after low-dose corticosteroid treatment in patients with RA. These findings have practical implications for the long-term management of patients with RA on low-dose corticosteroids.

Key Words: corticosteroid, bone mineral density, rheumatoid arthritis

■ INTRODUCTION

Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by chronic inflammation of the synovial joints, which leads to disability and loss of quality of life.[1] Polyarthritis causes juxta-articular bone loss of affected joints and often is accompanied by considerable generalized loss of bone mass in patients with RA.[2] The etiology of generalized bone loss in RA is multifactorial and involves inflammation, circulating cytokines, and general factors, such as a low level of physical activity, vitamin D status, and physical impairment.[3,4] Corticosteroids suppress the signs and symptoms of inflammation in RA and reduce the rate of joint destruction but are a risk factor of osteoporosis.[5] However, the relative contributions made by corticosteroids and the disease process to bone loss have not been determined.

The effects of long-term high-dose corticosteroids on bone mineral density (BMD) have been well established, but those of low-dose corticosteroids (≤10 mg/d prednisolone) in patients with RA are controversial. Moreover, corticosteroid treatment may reduce disease activity and increase patient mobility, which might offset its negative direct effect on bone.[6] However, it is still debated as to whether treatment with low-dose corticosteroid results in bone loss. Several studies have described the effects of low-dose corticosteroids on bone, but results vary and, in some cases, are conflicting,[7–13] which might be due to small sample sizes and low statistical power.

Meta-analysis is a statistical procedure for combining the results of several studies to produce a single estimate of a major effect with enhanced precision.[14] The major advantage of meta-analysis is that it increases the sample size, which possibly reduces the likelihood that random error will produce false-positive or false-negative associations.[14] Thus, the aim of the present study was to investigate, using a meta-analysis approach, the

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TABLE 1. Characteristics of Individual Studies Included in Meta-Analysis

Study	Country	Age*		Female (%)		CRP (mg/L)		Prednisolone† Dosage (mg/d)	No.		Follow-up Period	BMD	BMD Unit
		RA	C	RA	vC	RA	C		RA	C			
Svensson et al.,[11] 2005	Sweden	51 (14)	59 (13)	NA	NA	22	22	7.5	116	126	2 yr	Lumbar, femur neck	g/cm^2
Capell and Madhok,[8] 2003	United Kingdom	55	56	NA	NA	17	25	7	84	83	2 yr	Lumbar, femur neck	g/cm^2
Laan et al.,[10] 1993	Netherlands	NA	NA	NA	NA	NA	NA	7.5‡	20	19	20 wk	Lumbar, femur neck	mg/mL
Everdingen et al.,[12] 2003	Netherlands	60 (14)	64 (12)	57.5	70.7	11	20	10	32	32	3 yr	Lumbar, femur neck	T score
van Schaardenburg et al.,[13] 1995	Netherlands	69	70	71	43	NA	NA	8‡	27	20	1 yr	Lumbar, femur neck	BMC
Choy et al.,[7] 2005	United Kingdom	59 (10)	56 (13)	75	81.3	29.3§	34.2§	Intramuscular Depo-Medrol 120 mg/mo	32	29	2 yr	Lumbar, femur neck	T score
Hansen et al.,[9] 1999	Denmark	60	63.5	76.1	76.4	31.0	34.8	6	42	34	1 yr	Lumbar	g/cm^2

*Mean (SD).
†Fixed dose.
‡Mean dose.
§Erythrocyte sedimentation rate.
BMC indicates bone mineral content; C, control; CRP, C-reactive protein; NA, not available.

effects of low-dose corticosteroids on BMD in patients with RA.

■ METHODS

Identification of Eligible Studies and Data Extraction

We performed an exhaustive search on studies that examined the effect of corticosteroids on BMD in patients with RA. Literature searches were made using MEDLINE and the Cochrane Controlled Trials Register to identify available articles (the most recent article was published on December 2007). The following key words and subject terms were used in the searches: *corticosteroid*, *glucocorticoid*, *prednisolone*, *bone mineral density*, and *rheumatoid arthritis*. All references in the studies were reviewed to identify additional works not indexed by electronic databases, and all randomized controlled studies that compared corticosteroid with a placebo in patients with RA were considered eligible if they reported outcomes as BMD after treatment commencement. Studies were excluded when a placebo group was absent, or the follow-up period was shorter than 12 weeks, the published report did not contain adequate data for inclusion, or when the study concerned was cross-sectional. The cutoff of low-dose corticosteroid was prednisolone of 10 mg/d or lesser. We quantified the methodological qualities of primary studies using Jadad scores (maximum score, 5; high-quality trials score, 3 or greater; see Table 2 for criteria and for results).[15]

The following information was extracted from each study: first author, year of publication, country in which the study was conducted, dose of corticosteroid, length of follow-up, skeletal sites evaluated for BMD, and mean and SD of BMD (end-of-period or change from-baseline) at longest treatment duration. Change from baseline was reported as percent change. When there was no SD data from primary study, we imputed the SD using the mean proportional SD of the other studies for missing SD and conducted sensitivity analyses on imputed values.

Evaluation of Publication Bias

Funnel plots were used to detect publication bias. However, because funnel plots require a range of studies of different sizes and subjective judgments, we evaluated publication bias using Egger linear regression test.[16] Egger test measures funnel plot asymmetry using a natural logarithm scale of odds ratios.To assess the publication bias effect of missing studies, we also used the "trim and fill" method, which estimates the outcome and number of missing studies that would be necessary to correct the publication bias.[17] This method provides an adjusted

TABLE 2. Methodological Quality of Each Study

	Methodological Quality (Jadad Criteria[15])								
Study	***1a***	***1b***	***1c***	***2a***	***2b***	***2c***	***3***	***Total***	***ITT***
Svensson et al.,[11] 2005	1	1	0	0	0	0	1	3	X
Capell and Madhok,[8] 2003	1	1	0	0	0	0	1	3	O
Laan et al.,[10] 1993	1	0	0	1	0	0	0	2	X
van Everdingen et al.,[12] 2003	1	1	0	0	0	0	0	2	X
van Schaardenburg et al.,[13] 1995	1	0	0	0	0	0	0	1	O
Choy et al.,[7] 2005	1	0	0	1	0	0	1	3	X
Hansen et al.,[9] 1999	1	1	0	0	0	0	1	3	O

ITT indicates intention-to-treat analysis; 1a, Was the study described as randomized? (score 1 if yes); 1b and 1c, Was the method of randomization described and appropriate to conceal allocation? (score 1 if appropriated and −1 if not appropriate); 2a, Was the study described as double-blinded? (score 1 if yes); 2b and 2c, Was the method of double blinding described and appropriate to maintain double blinding? (score 1 if appropriate and −1 if not appropriate); 3, Was there a description of how withdrawals and dropouts were handed? (score 1 if yes).

estimation of effect size based on incorporating these theoretical missing studies into meta-analyses.

Evaluation of the Statistical Association

Bone mineral densities were expressed in grams per square centimeter, milligrams per milliliter, bone mineral content, or as T score in the studies. Standardized mean differences (SMDs) were used when different scales were integrated to measure the same concept. We used SMDs in this meta-analysis because different scales were used to measure the same outcome. Standardized mean differences were calculated by dividing the difference between the corticosteroid and control groups by baseline variance. This measure compares treatment and placebo arms in terms of standardized scores. A treatment that is 1 unit better than the placebo is 1 SD better, based on variations in original bone density. A large effect is equivalent to 1 unit; a moderate effect, 0.5; and a small effect, 0.3 units.[18]

Separate analyses were performed for BMD at each skeletal site, which included the lumbar spine or femur neck. We assessed within- and between-study variations and heterogeneities using Cochran Q statistic.[19] The heterogeneity test assessed the null hypothesis that all studies evaluated the same effect. If the significant Q statistic ($P < 0.10$) indicated heterogeneity across studies, then the random effects model should be used for meta-analysis, which assumes that different studies may estimate different underlying effects and which considers both intrastudy and interstudy variations.[20] In the present study, we used the random effects model because heterogeneity was present in most analyses.

We quantified the effect of heterogeneity using $I^2 = 100\% \times (Q - \mathrm{df}) / Q$.[21] The I^2 measures the degree of inconsistency between studies and determines whether the percentage total variation across studies is due to heterogeneity rather than chance. I^2 ranges between 0% and 100%; I^2 values of 25%, 50%, and 75% are referred to as low, moderate, and high estimates, respectively.

Our aim was to include in the meta-analysis as many studies as reasonably possible, given the limited number of published studies, and we used end point data or change data to maximize data availability. We also performed sensitivity analyses by limiting studies to the following: (1) prednisolone use, (2) end-of-period data, (3) change-from-baseline data, (4) follow-up period,

TABLE 3. Meta-Analysis of the Effect of Low-Dose Corticosteroid Use on Lumbar BMD in RA

			Test of Association			*Test of Heterogeneity*		
Site	***Group***	***No. Studies***	***Standard Difference in Means***	***95% CI***	***P***	***Q***	***P***	***I^2***
Lumbar	Overall	7	−0.483	−0.815 to −0.151	0.004	22.8	0.001	73.7
	Overall*	9	−0.620	−0.941 to −0.299	NA	39.2	NA	NA
	Prednisolone	6	−0.520	−0.905 to −0.134	0.008	22.7	<0.001	77.9
	End-of-period	3	−0.653	−1.376 to −0.070	0.076	21.8	<0.001	90.8
	Change-from-baseline	4	−0.354	−0.620 to −0.088	0.009	0.77	0.855	0
	Short follow-up†	3	−0.402	−0.982 to 0.177	0.173	0.69	0.707	0
	Long follow-up‡	4	−0.545	−1.014 to −2.281	0.023	22.1	<0.001	86.4
	Calcium supplement	2	−0.894	−1.552 to −0.237	0.008	17.9	<0.001	94.4
	No calcium supplement	5	−0.310	−0.746 to 0.125	0.163	1.97	0.741	0

*Two estimated studies were added by adjusting using the trim and fill method.
†≤1 year.
‡>1 year.
NA indicates not available.

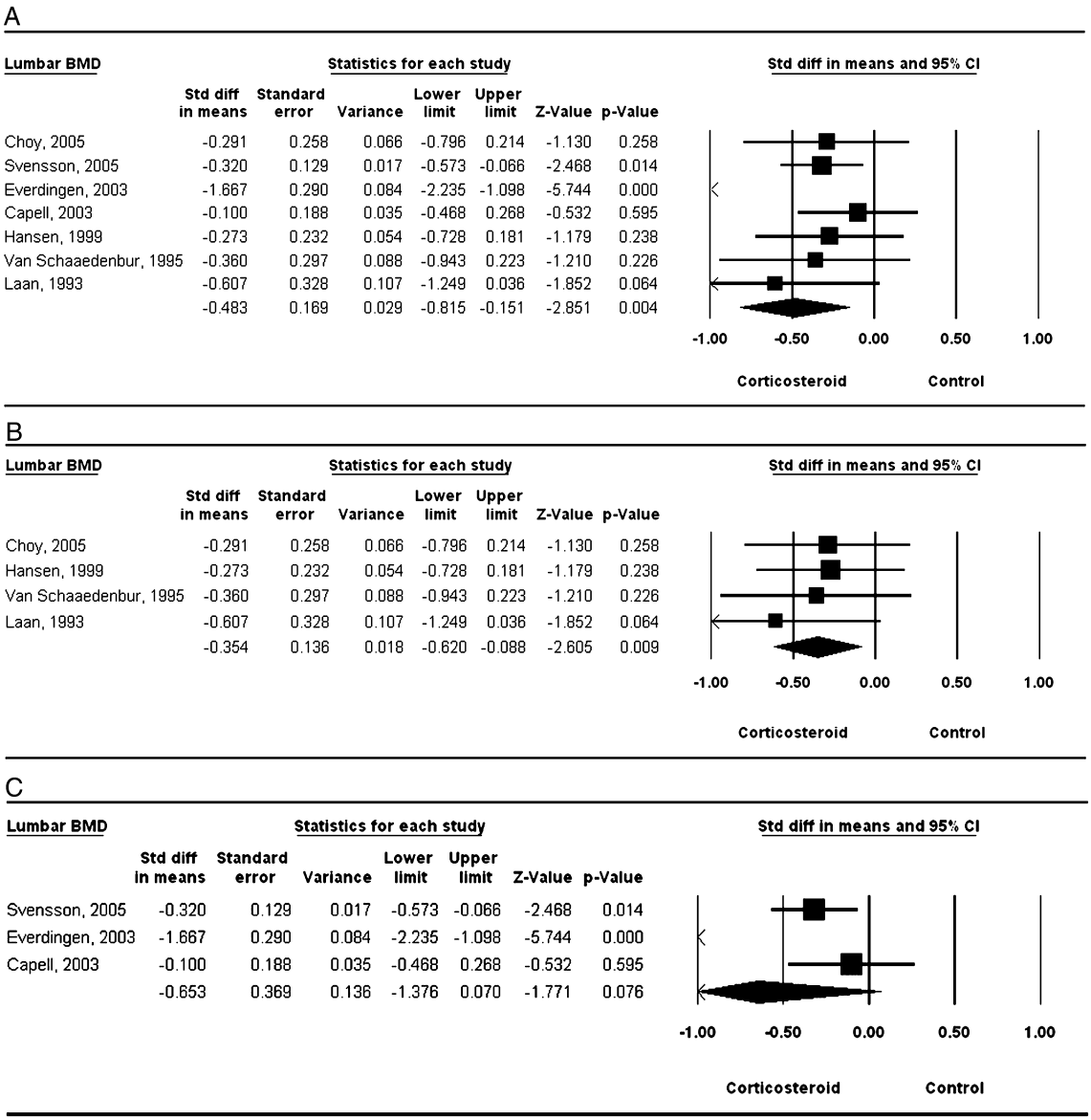

FIGURE 1. Standard difference in means and 95% CI of individual studies and pooled data for the association between corticosteroid use and lumbar BMD in patients with RA, in overall (A) and in the change-from-baseline (B) and end-of-period groups (C).

(5) calcium supplement, and (6) studies that reported SDs. Statistical manipulations were undertaken using a Comprehensive Meta-Analysis computer program (Biosta, Englewood, NJ).

■ RESULTS

Studies Included in the Meta-Analysis

Thirty-five studies were identified by electronic or manual search, and 13 were selected for full text review based on title/abstract.[7–13,22–26] However, 6 of the 11 were excluded; 4 were nonrandomized studies,[10,22–24] and the other 2 had no BMD data.[25,26] Thus, 7 studies met the inclusion criteria.[7–13] These 7 studies involved a total of 353 patients and 343 controls, and all reported the effects of low-dose corticosteroids on BMD in patients with RA. All studies were performed in European countries. The characteristic features of the studies included in the meta-analysis are given in Table 1. In all the studies, patients received daily low-dose oral prednisolone, except in 1 study, in which they received monthly intramuscular Depo-Medrol (equipotent to 5 mg prednisone daily).[7] The mean prednisolone dose administered in studies ranged from 6 to 10 mg, follow-up periods ranged from 20 weeks to 3 years, and the median Jadad score was 3 (range, 1–3) (Table 2). Six of the studies document

TABLE 4. Meta-Analysis of the Effect of Low-Dose Corticosteroid Use on Femur Neck BMD in RA

			Test of Association			*Test of Heterogeneity*		
Site	*Group*	*No. Studies*	*Standard Difference in Means*	*95% CI*	*P*	*Q*	*P*	I^2
Femur neck	Overall	6	−0.224	−0.663 to 0.215	0.318	29.2	<0.001	82.9
	Prednisolone	5	−0.099	−0.540 to −0.343	0.662	20.5	<0.001	80.5
	End-of-period	3	−0.010	−0.667 to 0.646	0.976	19.2	<0.001	89.5
	Change-from-baseline	3	−0.488	−0.911 to −0.065	0.024	3.226	0.199	38.0
	Short follow-up*	2	−0.258	−1.117 to −0.602	0.557	0.09	0.762	0
	Long follow-up†	4	−0.211	−0.778 to 0.357	0.466	28.7	<0.001	89.5
	Calcium supplement	2	0.280	−0.011 to 0.571	0.060	1.15	0.282	13.5
	No calcium supplement	4	−0.578	−0.857 to −0.299	<0.001	3.80	0.284	21.0

*≤1 year.
†>1 year.

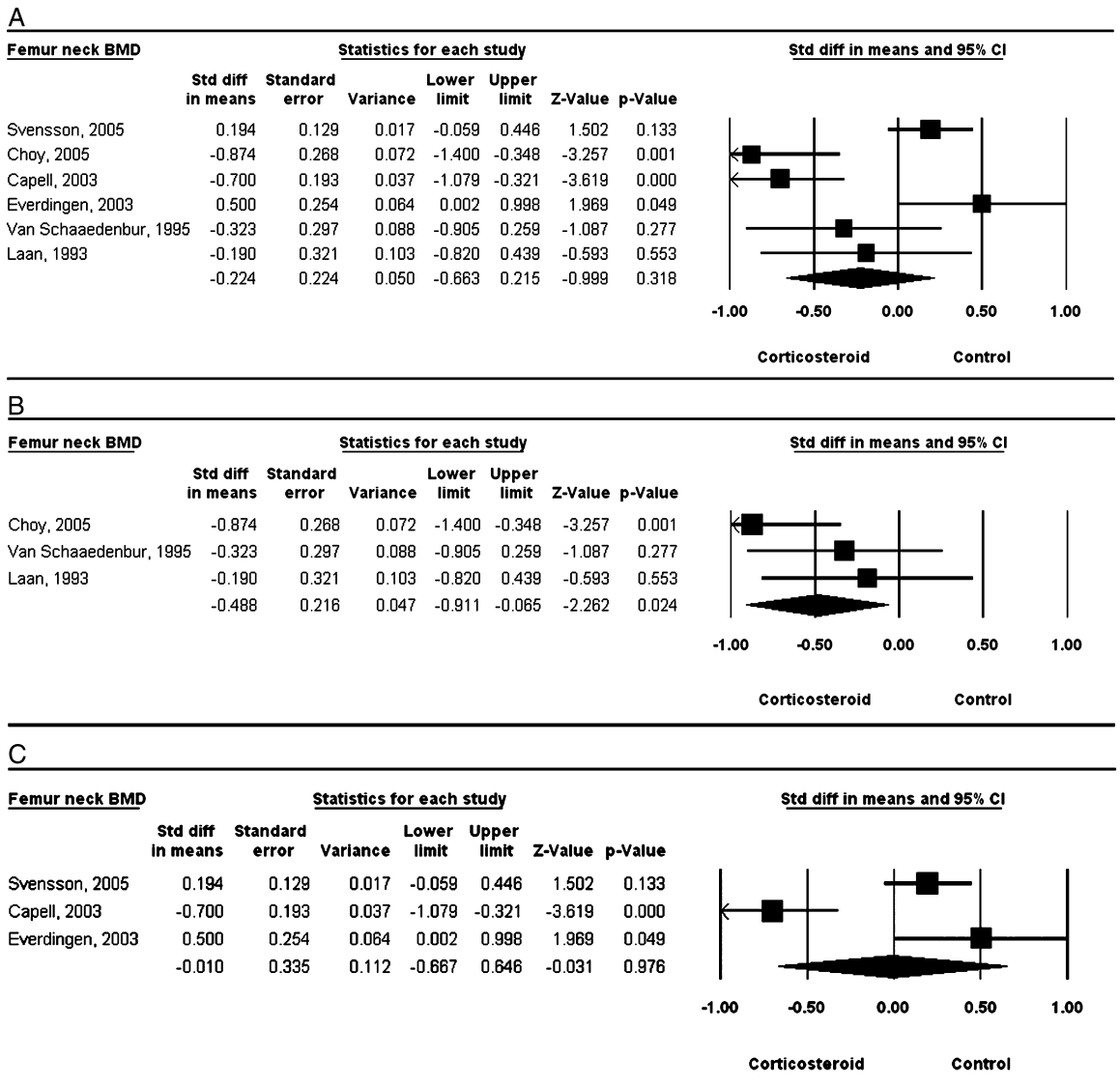

FIGURE 2. Standard difference in the means and 95% CI of individual studies and pooled data for the association between corticosteroid use and femoral BMD in patients with RA, in overall (A), change-from-baseline (B), and end-of-period groups (C).

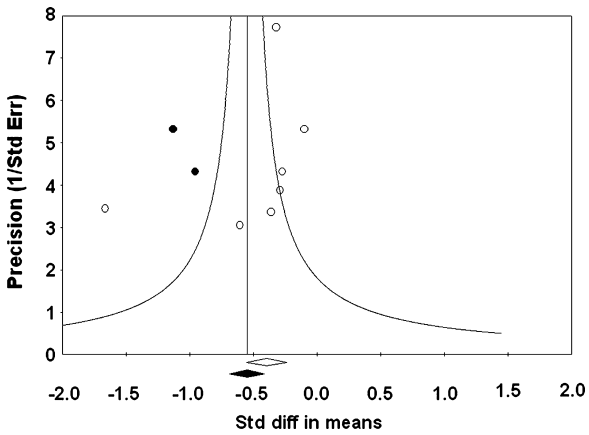

FIGURE 3. Funnel plot after performing trim and fill estimates of studies on the effect of low-dose corticosteroid on lumbar BMD. The original studies are indicated by circles, and study estimates are shown as filled black circles.

lumbar and femoral BMDs; and the remaining study, only lumbar BMD.

Meta-Analysis of the Effect of Low-Dose Corticosteroids on Lumbar BMD

All 7 studies analyzed lumbar BMD. It should be noted that a negative corticosteroid effect corresponds to a negative standardized effect size for BMD. Corticosteroids were found to have a moderate effect versus controls on lumbar BMD (SMD = −0.483; 95% confidence interval [CI], −0.815 to −0.151, $P = 0.004$), but heterogeneity was found among the studies ($I^2 = 73.7\%$, $P = 0.001$) (Table 3, Fig. 1). Meta-analysis excluding 1 study that involved monthly intramuscular Depo-Medrol or 2 studies with imputed SDs showed the same result pattern.[7,8] Subgroup analysis based on BMD change-from-base data showed that corticosteroids had a clear effect versus controls on lumbar BMD (SMD = −0.354; 95% CI, −0.620 to −0.088, $P = 0.009$), without between-study heterogeneity ($I^2 = 0\%$). Meta-analysis of studies using end-of-period data showed the same trend, but it did not reach statistical significance ($P = 0.076$) (Table 3). Meta-analyses with studies of long follow-up period (>1 year) or with calcium supplement have shown that corticosteroid has a moderate effect on lumbar BMD (Table 3).

Meta-Analysis of the Effect of Low-Dose Corticosteroids on Femoral Neck BMD

Six studies analyzed femoral neck BMD. Unlike lumbar BMD, corticosteroid was not found to have a significant effect versus controls on femoral neck BMD (SMD = −0.224; 95% CI, −0.663 to 0.215, $P = 0.318$), but between-study heterogeneity was evident ($I^2 = 82.9\%$, $P < 0.001$) (Table 4, Fig. 2). Meta-analysis by excluding 1 study that involved monthly intramuscular Depo-Medrol or 2 studies with imputed SDs showed the same pattern of results. Subgroup analysis based on BMD change-from-base data showed that corticosteroid had a clear effect versus controls on femoral neck BMDs (SMD = −0.488; 95% CI, −0.911 to −0.065, $P = 0.024$), and low between-study heterogeneity was observed ($I^2 = 38\%$, $P = 0.199$). Meta-analysis of studies based on end-of-period data showed no association between corticosteroid treatment and femoral neck BMD (Table 4). Meta-analysis with studies with calcium supplement showed that corticosteroids had a clear effect versus controls on femur neck BMD (SMD = −0.578; 95% CI, −0.857 to −0.299, $P < 0.001$), without between-study heterogeneity ($I^2 = 21\%$). Meta-analysis of studies without calcium supplement showed the same trend, but it did not reach statistical significance ($P = 00.06$) (Table 4).

Heterogeneity and Publication Bias

Between-study heterogeneity was found during most analyses except for analyses based on change-from-baseline data for lumbar and femoral BMDs. It was difficult to correlate the funnel plot, which is usually used to detect publication bias because the number of studies included in the analysis was too small. However, no evidence of publication bias was obtained (Egger regression test, $P > 0.1$). Adjusting for publication bias did not change the finding based on the meta-analyses of all studies of the lumbar BMD (Table 3, Fig. 3).

■ DISCUSSION

In patients with RA, the disease itself predisposes bone loss, and there is evidence that this loss is related to disease activity.[27] However, 1 study of early RA, in which a small subgroup of patients received prednisolone, suggested that prednisolone has a beneficial effect on bone loss.[11] The inhibitory effect of prednisolone treatment on bone formation is a concern, at least at high doses. However, at low doses, it has been suggested that this inhibitory effect may be compensated for by an ability of prednisolone to suppress disease activity and consequent inflammation-mediated bone resorption.[27]

Cross-sectional studies have shown that patients with RA tend to have lower bone mass than normal, and this has been mainly attributed to physical inactivity and corticosteroid use.[26] Moreover, it has been suggested that the favorable effects of corticosteroids on the inflammatory process and on physical activity may outweigh its negative effects on bone mass.[27] However, published data on the effects of low-dose corticosteroids on bone in patients with RA are contradictory.[7–13]

In present meta-analysis, low-dose corticosteroids were found to have a marked negative effect on lumbar BMD (standardized effect size, −0.483, $P = 0.004$), and

although no significant effect was found for femoral BMDs, a trend was observed (SMD = −0.224, P = 0.318). However, subgroup analysis based on change-from-base BMD data showed that corticosteroids have a clear effect on both lumbar and femoral BMDs (SMD = −0.354, P = 0.009; SMD = −0.488, P = 0.024, respectively). Our meta-analysis does not support the notion that the use of low-dose corticosteroids has a beneficial effect on bone but rather suggests that low-dose corticosteroid treatment accelerates bone loss in patients with RA. Moreover, this deleterious effect of corticosteroids on bone is unlikely to be counterbalanced by its beneficial effect on RA inflammation based on the results of this meta-analysis. Although the use of low-dose corticosteroids may retard joint damage,[11] it should be emphasized that it may lead to bone loss leading to osteoporosis and bone fracture. When low-dose corticosteroids are used for the long-term treatment of RA, prophylactic methods have to be considered to prevent osteoporosis due to corticosteroid use.

We could not perform meta-analysis on the effect of low-dose corticosteroids on hand BMD because of limited data. Two studies have been performed on hand BMD. A double-blind randomized study by Haugeberg et al.[28] showed that disease-related loss of hand bone density in RA can be decelerated by prednisolone, and another study suggested that prednisolone has a protective effect against bone loss in the hand.[10] It is unclear whether the deleterious effect of corticosteroids is counteracted by its anti-inflammatory effect in hand BMD, unlike lumbar or femoral neck BMD, because hand joints are more frequently affected by RA inflammation than other sites. Further studies are needed to clarify this point.

Present study has some shortcomings that should be considered. First, most analyses showed between-study heterogeneity. The issue of study heterogeneity is fundamental in meta-analysis. We performed subgroup analysis, but heterogeneity remained in most analyses except for analyses based on change-from-baseline data, short follow-up period, and no calcium supplement. Although we used a random effect model, which inherently allows for variations in underlying effect sizes between studies to be taken into account, we could not exclude the possibility that this heterogeneity could have biased the analysis. Second, the funnel plot of all studies for lumbar BMD was not symmetric, despite no obvious evidence of publication bias based on Egger test, and thus, the possibility of publication bias cannot be completely ruled out. However, adjustments made using the "trim and fill" method did not change our results. The trim and fill method provided 2 adjusted estimations of effect size based on incorporating these theoretical missing studies into meta-analyses. Third, combining final values and change scores in the same analysis may be of concern because different measurement scales were used, and therefore, we also performed subgroup analysis by dividing all of the studies into end-of–period and change-from-baseline groups. However, the results from meta-analysis based on combined values and change-from-baseline data were no different. Fourth, the study quality is one of the factors that may bias the meta-analysis. Although we measured the study quality in this meta-analysis, the low and middle levels of study quality should be considered as a possible limitation.

A previous meta-analysis showed that glucocorticoids given in addition to standard therapy can substantially reduce erosion progression in RA. However, the question remains whether the benefits of low-dose corticosteroids outweigh their disadvantages in RA. Thus, the benefits of low-dose corticosteroids in terms of controlling erosive joint damage have to be balanced against the potential dangers of bone loss. Further study is needed to fully address this issue.

In conclusion, this meta-analysis shows greater BMD loss after corticosteroid treatment in patients with RA. We conclude that low-dose corticosteroids for the treatment of RA may increase bone loss because, in the present study, BMD was found to be significantly reduced by low-dose corticosteroids in patients with RA. These findings have practical implication for the long-term management of patients with RA on low-dose corticosteroids.

■ REFERENCES

1. Harris ED Jr. Rheumatoid arthritis. Pathophysiology and implications for therapy. *N Engl J Med*. 1990;322: 1277–1289.
2. Peel NF, Spittlehouse AJ, Bax DE, et al. Bone mineral density of the hand in rheumatoid arthritis. *Arthritis Rheum*. 1994;37:983–991.
3. Bhalla AK, Shenstone B. Bone densitometry measurements in early inflammatory disease. *Baillieres Clin Rheumatol*. 1992;6:405–414.
4. Laan RF, Buijs WC, Verbeek AL, et al. Bone mineral density in patients with recent onset rheumatoid arthritis: influence of disease activity and functional capacity. *Ann Rheum Dis*. 1993;52:21–26.
5. Kirwan JR. The effect of glucocorticoids on joint destruction in rheumatoid arthritis. The Arthritis and Rheumatism Council Low-Dose Glucocorticoid Study Group. *N Engl J Med*. 1995;333:142–146.
6. van Everdingen AA, Jacobs JW, Siewertsz Van Reesema DR, et al. Low-dose prednisone therapy for patients with early active rheumatoid arthritis: clinical efficacy, disease-modifying properties, and side effects: a randomized,

double-blind, placebo-controlled clinical trial. *Ann Intern Med*. 2002;136:1–12.

7. Choy EH, Kingsley GH, Khoshaba B, et al. A two year randomised controlled trial of intramuscular depot steroids in patients with established rheumatoid arthritis who have shown an incomplete response to disease modifying antirheumatic drugs. *Ann Rheum Dis*. 2005;64:1288–1293.
8. Capell HA, Madhok R. Another DMARD option in rheumatoid arthritis? *J Rheumatol*. 2003;30:2085–2087.
9. Hansen M, Podenphant J, Florescu A, et al. A randomised trial of differentiated prednisolone treatment in active rheumatoid arthritis. Clinical benefits and skeletal side effects. *Ann Rheum Dis*. 1999;58:713–718.
10. Laan RF, van Riel PL, van de Putte LB, et al. Low-dose prednisone induces rapid reversible axial bone loss in patients with rheumatoid arthritis. A randomized, controlled study. *Ann Intern Med*. 1993;119:963–968.
11. Svensson B, Boonen A, Albertsson K, et al. Low-dose prednisolone in addition to the initial disease-modifying antirheumatic drug in patients with early active rheumatoid arthritis reduces joint destruction and increases the remission rate: a two-year randomized trial. *Arthritis Rheum*. 2005;52:3360–3370.
12. van Everdingen AA, Siewertsz van Reesema DR, Jacobs JW, et al. Low-dose glucocorticoids in early rheumatoid arthritis: discordant effects on bone mineral density and fractures? *Clin Exp Rheumatol*. 2003;21:155–160.
13. van Schaardenburg D, Valkema R, Dijkmans BA, et al. Prednisone treatment of elderly-onset rheumatoid arthritis. Disease activity and bone mass in comparison with chloroquine treatment. *Arthritis Rheum*. 1995;38:334–342.
14. Egger M, Smith GD, Phillips AN. Meta-analysis: principles and procedures. *BMJ*. 1997;315:1533–1537.
15. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials*. 1996;17:1–12.
16. Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997; 315:629–634.
17. Duval S, Tweedie R. Trim and fill: a simple funnel-plot–based method of testing and adjusting for publication bias in meta-analysis. *Biometrics*. 2000;56:455–463.
18. Corbett J, Gu CC, Rice JP, et al. Power loss for linkage analysis due to the dichotomization of trichotomous phenotypes. *Hum Hered*. 2004;57:21–27.
19. Davey Smith G, Egger M. Meta-analyses of randomised controlled trials. *Lancet*. 1997;350:1182.
20. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7:177–188.
21. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002;21:1539–1558.
22. Chung CP, Russell AS, Segami MI, et al. The effect of low-dose prednisone on bone mineral density in Peruvian rheumatoid arthritis patients. *Rheumatol Int*. 2005;25: 114–117.
23. Habib GS, Haj S. Bone mineral density in patients with early rheumatoid arthritis treated with corticosteroids. *Clin Rheumatol*. 2005;24:129–133.
24. Miyamoto S, Kageyama Y, Ozeki T, et al. Effects of glucocorticoids on bone mineral density in rheumatoid arthritis patients. A longitudinal study. *Arch Orthop Trauma Surg*. 1999;119:18–21.
25. Sambrook PN, Eisman JA, Yeates MG, et al. Osteoporosis in rheumatoid arthritis: safety of low dose corticosteroids. *Ann Rheum Dis*. 1986;45:950–953.
26. Verhoeven AC, Boers M, te Koppele JM, et al. Bone turnover, joint damage and bone mineral density in early rheumatoid arthritis treated with combination therapy including high-dose prednisolone. *Rheumatology (Oxford)*. 2001;40:1231–1237.
27. Verhoeven AC, Boers M. Limited bone loss due to corticosteroids; a systematic review of prospective studies in rheumatoid arthritis and other diseases. *J Rheumatol*. 1997;24:1495–1503.
28. Haugeberg G, Strand A, Kvien TK, et al. Reduced loss of hand bone density with prednisolone in early rheumatoid arthritis: results from a randomized placebo-controlled trial. *Arch Intern Med*. 2005;165:1293–1297.