

## THE EFFECT OF RHEUMATOID ARTHRITIS AND STEROID THERAPY ON BONE DENSITY IN POSTMENOPAUSAL WOMEN

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**Objective.** To assess bone mineral density (BMD) in postmenopausal women with rheumatoid arthritis (RA) and the relative effects of disease activity, disability, and past and current use of corticosteroids.

**Methods.** One hundred ninety-five postmenopausal patients with RA were compared with 597 postmenopausal control subjects. Bone density was measured at the lumbar spine and the proximal femur using dual x-ray absorptiometry. Patients were divided into 3 groups according to corticosteroid use, i.e., never users (61%), current users (21%), and ex-users (18%).

**Results.** Compared with controls, the never users had no difference in BMD at the lumbar spine, but a 6.9% reduction at the femur (95% confidence interval [95% CI] 3.4-10.3%). In current users (mean daily prednisolone dosage 6.9 mg), BMD was reduced by 6.5% at the spine (95% CI 0-13.0%) and by 7.4% at the hip (95% CI 1.2-13.6%) compared with never users, after adjustment for age, weight, duration of meno-

pause, and functional disability. Mean BMD was similar in the ex-user and never user groups. Results were confirmed in 54 patients who had whole-body BMD measurements. There were inverse correlations between BMD and Health Assessment Questionnaire scores (femoral BMD  $r = -0.23$ ,  $P < 0.01$ ; whole-body BMD  $r = -0.40$ ,  $P < 0.01$ ) and between BMD and cumulative steroid dose (femoral BMD  $r = -0.32$ ,  $P < 0.01$ ; whole-body BMD  $r = -0.72$ ,  $P < 0.01$ ).

**Conclusion.** Osteoporosis in postmenopausal women with RA is more evident at the hip than the spine, and the most important determinants of bone loss are disability and cumulative corticosteroid dose. Low-dose steroids cannot be used with complacency, but recovery after discontinuation of use may be possible.

In efforts to identify individuals who are at high risk for osteoporosis, patients with rheumatoid arthritis (RA) have been cited as a group with increased risk of rapid bone loss, which can result in debilitating fracture. However, the results of studies to date have been conflicting, partly due to small numbers of patients and differing techniques. Most studies have shown a trend toward lower bone mass in RA groups (1-10), although at least 2 studies of the axial skeleton have failed to corroborate these findings (11,12). The factors leading to osteoporosis in RA may include active disease and immobility. Although corticosteroids have a well-documented deleterious effect on bone turnover (13-15), their effect in RA has been more controversial, with some authors suggesting that low-dose steroid therapy is not harmful to the skeleton (8,9).

The present study focused on postmenopausal women with RA, a group considered to be at further

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risk of accentuated bone loss. Using dual x-ray absorptiometry (DXA), we compared bone density at the lumbar spine and proximal femur in these women versus controls and evaluated the relative influences of disease activity, disability, and steroid therapy. In addition, we measured whole-body skeletal mass in a subgroup of 54 patients.

## PATIENTS AND METHODS

Three hundred thirty-four patients with RA according to the American College of Rheumatology (formerly, the American Rheumatism Association) criteria (16), ranging in age from 45 to 65 years, were identified from clinic registers in rheumatology centers at 4 major London hospitals. Patients were invited to participate in a study of osteoporosis in RA and were considered eligible if it was confirmed that they were postmenopausal (>1 year since last menstrual period, or follicle-stimulating hormone level >15 units/liter). Exclusion criteria included previous use of hormone replacement therapy (HRT) for >6 months and concurrent illnesses that might affect bone mass. Two hundred fifteen patients (64%) were interviewed, of whom 19 were excluded. One-hundred ninety-six patients were included, and a further 12 patients were recruited directly from a fifth center, through advertising in the clinic.

Assessments of disease activity and other patient characteristics were made by the same observer (GMH) at all 5 centers and included the Ritchie articular index (17), the Health Assessment Questionnaire (HAQ) (18), early morning stiffness, pain score (10-cm visual analog scale), erythrocyte sedimentation rate, and details on disease duration. Prior and current steroid therapy was documented according to medical records, steroid treatment cards, and patient recollection. Intraarticular steroid injections were not included. A 2-week course of intramuscular adrenocorticotropic hormone treatment was estimated to be equivalent to prednisolone at 10 mg daily for 3 months. Cumulative steroid dose was calculated from the mean daily dosage multiplied by the mean number of months the therapy was received.

Bone mineral density (BMD) was measured using DXA with either of 2 scanners (Hologic QDR1000/W apparatus). The Hologic phantom was measured 10 times on each scanner; precision at the spine was 0.9% at both sites, and the difference in results between scanners was 0.07%. BMD, expressed as gm/cm<sup>2</sup>, was measured at the lumbar spine (L1-L4) and the left proximal femur (total, femoral neck, and Ward's triangle). The contralateral femur was evaluated in patients who had undergone hip arthroplasty. Femoral measurements were not made in the 6 patients who had had bilateral hip replacements. In the event of a lumbar compression fracture as seen on plain lateral radiographs, the BMD of that individual vertebra was excluded from analysis. In addition, 54 patients were analyzed for whole-body BMD using the same Hologic QDR1000/W scanner. Skull values, which contributed between 8% and 29% of total BMD, were excluded from analysis, giving total BMD of the axial and appendicular skeleton. Thirteen black West Indian patients

had a mean BMD that was 7% higher than that of white patients and were excluded from further analysis.

The control group was drawn from the general population and consisted of 1,003 white women age 45-65 years identified from the age/sex register of an 11,000-patient general practice in eastern London. Seventy-eight percent of these women agreed to participate in a screening program for bone and joint disease, and the 597 women who were postmenopausal and had never taken HRT were included.

To examine the effects of steroids, the RA cohort was divided into 3 groups: 119 patients who had never taken oral or parenteral steroids (never users), 35 patients who had been prescribed steroids in the past but were no longer taking them (ex-users), and 41 patients who were currently taking steroids (current users).

BMD results were compared by Student's *t*-test, and continuous variables by Pearson's correlation coefficient. The effects of potential confounding features were examined using analysis of covariance with SPSS software for the personal computer. For further intergroup analyses, logarithmic transformation of variables was performed if nonlinearity was suspected.

## RESULTS

The characteristics of the 195 patients and 597 controls are detailed in Table 1. Compared with never users, disease duration in the current steroid user group was an average of 3.5 years longer ( $P = 0.05$ ). Current users tended to have more active disease, although there was not a statistically significant difference for any single parameter. There was a negative correlation between duration of menopause and BMD (lumbar spine  $r = -0.24$ ,  $P < 0.01$ ; femur  $r = -0.28$ ,  $P < 0.01$ ) and a positive correlation between weight and BMD (lumbar spine  $r = 0.34$ ,  $P < 0.001$ ; femur  $r = 0.42$ ,  $P < 0.001$ ). There was no correlation between BMD and age.

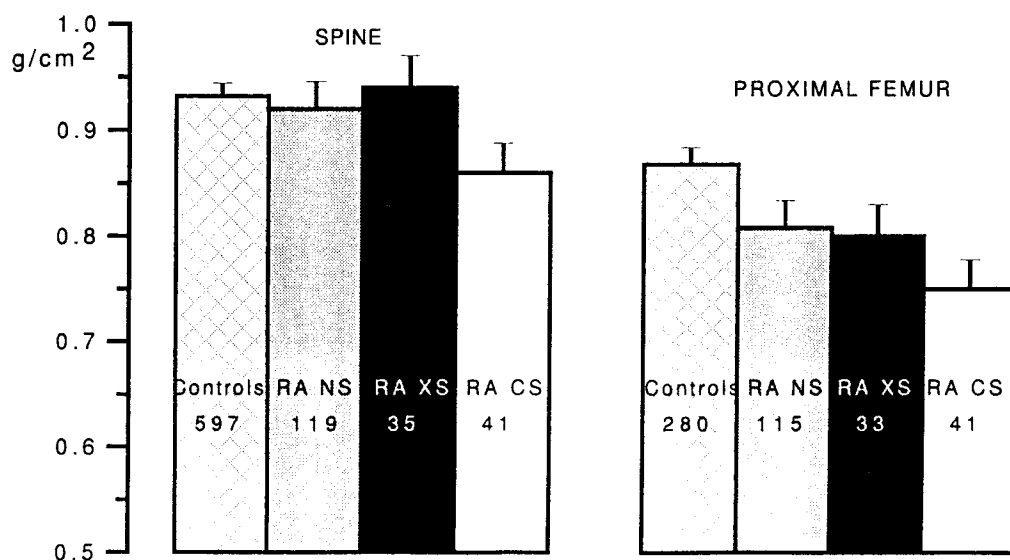
Figure 1 shows BMD of the lumbar spine and the femur in the RA groups and the controls. BMD of the spine did not differ between controls and never users (mean 0.93 gm/cm<sup>2</sup> versus 0.92 gm/cm<sup>2</sup>), but at the proximal femur the never user group had a 6.9% reduction in BMD (95% confidence interval [95% CI] 3.4-10.3%) (femoral neck 0.75 versus 0.71 gm/cm<sup>2</sup> [ $P = 0.02$ ], Ward's triangle 0.56 versus 0.51 gm/cm<sup>2</sup> [ $P = 0.02$ ]). After adjustment for weight and duration of menopause, this difference remained highly significant. Current users had reductions in BMD of 7.5% at the spine (95% CI 1.8-13.2%) and 13.8% at the hip (95% CI 8.6-19.0%) compared with controls. After adjustment for disease duration, weight, menopausal years, and HAQ score, there were significant differences between the never users and the current users in

**Table 1.** Characteristics of the healthy postmenopausal control subjects and of the rheumatoid arthritis (RA) patients grouped according to steroid use\*

Variable	Controls (n = 597)	RA patients		
		Never used steroids (n = 119)	Ex-steroid-users (n = 35)	Current steroid-users (n = 41)
Age (years)	56.6 ± 5.3	56.1 ± 4.9	54.9 ± 5.5	57.3 ± 5.1
Duration of menopause (years)	8.9 ± 5.6	8.3 ± 6.2	5.6 ± 5.1	9.1 ± 5.9
Weight (kg)	67.2 ± 11.5	65.7 ± 11.9	61.2 ± 10.1	64.7 ± 12.5
Disease duration (years)	–	11.2 ± 8.1	12.9 ± 10.1	14.7 ± 12.5†
HAQ score (0–3 scale)	–	1.3 ± 0.8	1.7 ± 0.9	1.6 ± 0.9
RAI (0–76 scale)	–	10.3 ± 8.5	12.0 ± 8.9	11.9 ± 10.3
Morning stiffness (minutes)	–	39.7 ± 45.6	43.0 ± 51.8	44.1 ± 39.8
ESR (mm/hour)	–	32.5 ± 23.0	29.2 ± 23.4	40.8 ± 26.2
Daily prednisolone dosage (mg)	–	0	8.8 ± 5.4	6.9 ± 2.9
Cumulative steroids (mg-months)	–	0	163 ± 228	520 ± 687
BMD, lumbar spine (gm/cm <sup>2</sup> )	0.93 ± 0.15	0.92 ± 0.16	0.94 ± 0.15	0.86 ± 0.17
BMD, proximal femur (gm/cm <sup>2</sup> )	0.87 ± 0.13	0.81 ± 0.15	0.80 ± 0.13	0.75 ± 0.14
BMD, whole body (gm/cm <sup>2</sup> ) (n = 54)	–	0.88 ± 0.10	0.88 ± 0.06	0.82 ± 0.09

\* Values are the mean ± SD. HAQ = Health Assessment Questionnaire; RAI = Ritchie articular index; ESR = erythrocyte sedimentation rate; BMD = bone mineral density.

† *P* = 0.05 versus the group of patients who never used steroids.



**Figure 1.** Bone mineral density of the spine and the hip in postmenopausal controls and in postmenopausal rheumatoid arthritis (RA) patients grouped according to steroid use (NS = never used steroids; XS = ex-users of steroids; CS = current users of steroids). Values are the mean and the 95% confidence interval; n values are shown within the bars.

**Table 2.** Characteristics of the RA patient groups by cumulative steroid dose\*

Variable	Never used steroids (n = 119)	Low cumulative dose (n = 20)	High cumulative dose (n = 21)
Age (years)	56.1 ± 4.9	56.4 ± 5.3	58.1 ± 4.8
Duration of menopause (years)	8.3 ± 6.2	7.8 ± 6.2	10.3 ± 5.5
Weight (kg)	65.7 ± 11.9	63.6 ± 13.3	65.8 ± 11.9
Disease duration (years)	11.2 ± 8.1	11.1 ± 10.1	18.1 ± 13.9†
HAQ score (0–3 scale)	1.3 ± 0.8	1.5 ± 0.8	1.6 ± 1.0
RAI (0–76 scale)	10.3 ± 8.5	9.6 ± 7.1	13.9 ± 12.4
Morning stiffness (minutes)	39.7 ± 45.6	35.3 ± 29.0	53.9 ± 47.4
ESR (mm/hour)	32.5 ± 23.0	42.4 ± 27.5	39.4 ± 25.8
Daily prednisolone dosage (mg)	0	6.0 ± 2.4	7.7 ± 3.2
Cumulative steroids (mg-months)	0	142 ± 80	881 ± 811
BMD, lumbar spine (gm/cm <sup>2</sup> )	0.92 ± 0.16	0.88 ± 0.18	0.84 ± 0.17
BMD, proximal femur (gm/cm <sup>2</sup> )	0.81 ± 0.15	0.76 ± 0.11	0.74 ± 0.17

\* Values are the mean ± SD. See Table 1 for definitions.

†  $P < 0.05$  versus the group of patients who never used steroids.

BMD at the lumbar spine (6.5%; 95% CI 0–13.0%) and the femur (7.4%; 95% CI 1.2–13.6%). The cumulative steroid dose exerted a negative effect on BMD at the femur ( $r = -0.32$ ,  $P < 0.01$ ), and less so at the lumbar spine ( $r = -0.13$ ,  $P$  not significant).

In light of these results, the steroid-treated patients were analyzed further, with current users divided according to the median cumulative dose of prednisolone: 21 patients had received >350 mg-months (equivalent to, for example, 10 mg daily for 35 months) and 20 patients had received <350 mg-months (Table 2). The former (high-dose) group was slightly older, and had had RA for longer, compared with the never users. BMD at the lumbar spine was 4.3% lower (95% CI -13.5–4.8%) and BMD at the femur was 6.2% lower (95% CI -13.0–0.6%) in the low-dose steroid group compared with never users, but the differences were not significant (Figure 2).

There were 35 ex-steroid users who were comparable with the never users in terms of duration and activity of disease. After adjustment for duration of menopause and for weight, there was no difference in BMD between the 2 groups. Interestingly, ex-users and current low-dose users had similar cumulative

steroid doses (163 mg-months versus 142 mg-months) and were comparable in terms of disease duration and activity. After adjustment for years of menopause, weight, and HAQ score, the current low-dose users had lower BMD at the lumbar spine (6.4%; 95% CI -16.3–3.5%) and the femur (5.0%; 95% CI -13.1–3.1%) than the ex-users, although the confidence intervals included unity.

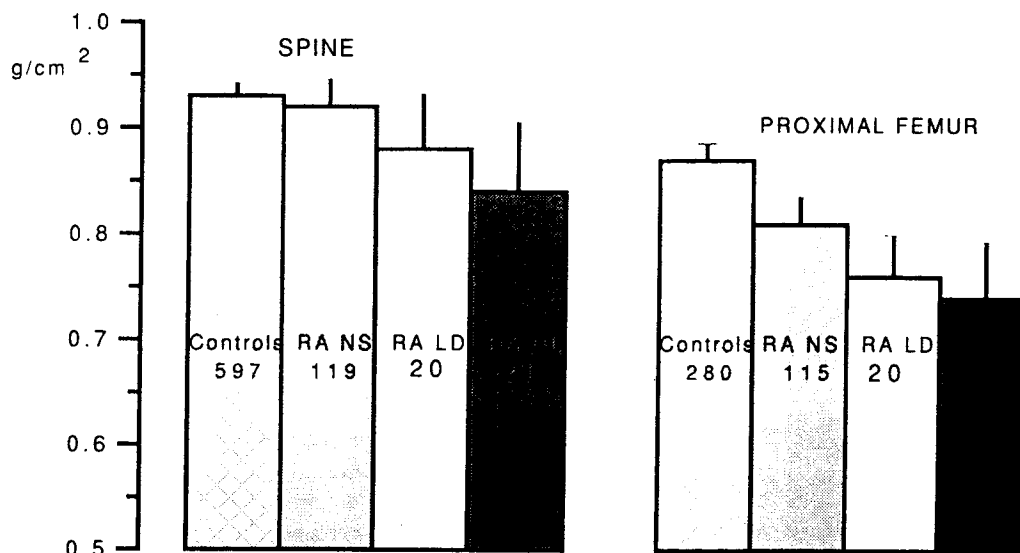
Whole-body BMD was determined in 54 consecutive patients, including 39 never users, 6 ex-users, and 9 current users of steroids. After adjustment for years of menopause and for weight, whole-body BMD in the current users was 6.8% lower (95% CI -14.4–0.8%) than in the never users. Again, BMD in the ex-users was similar to that in the never users (0.88 versus 0.88 gm/cm<sup>2</sup>). There was a strong negative correlation between cumulative steroid dose and whole-body BMD ( $r = -0.72$ ,  $P < 0.01$ ). Correlations between whole-body BMD and BMD at specific sites were stronger for the proximal femur (total  $r = 0.83$ ; Ward's triangle  $r = 0.72$ ,  $P < 0.001$ ; femoral neck  $r = 0.41$ ,  $P < 0.01$ ) than for the spine ( $r = 0.37$ ,  $P < 0.01$ ).

Parameters of disease activity (Table 3) failed to correlate well with BMD in the never user group, the only significant correlation being between BMD at the femur and HAQ score ( $r = -0.23$ ,  $P < 0.01$ ). Whole-body BMD was also inversely proportional to HAQ score ( $r = -0.40$ ,  $P < 0.01$ ).

## DISCUSSION

This study demonstrates a reduction in BMD at the hip, but not the spine, in postmenopausal women with RA. Treatment with steroids results in further lowering of bone density at both sites. Although several studies have supported an association between RA and osteoporosis (1–10), small numbers of study patients and differences in study populations and methodology have led to conflicting results for sites such as the spine (11,12). Both functional disability (2,4,9,19) and disease activity (4,5,20,21) have been implicated as factors leading to osteopenia.

Als et al showed a 19% reduction in BMD of the distal radius in 42 patients (29 female) compared with controls (6), but another study, also using single-photon absorptiometry (SPA) and controlling for menopausal status, found the difference to be only 2% (22). With dual-photon absorptiometry (DPA), investigators have been able to assess the axial skeleton directly. Sambrook et al compared 40 pre- and postmenopausal patients not taking steroids with 69 con-



**Figure 2.** Bone mineral density of the spine and the hip in postmenopausal controls and in postmenopausal rheumatoid arthritis (RA) patients grouped according to steroid use (NS = never used steroids; LD = low cumulative dose; HD = high cumulative dose). Values are the mean and the 95% confidence interval; n values are shown within the bars.

controls and found significant reductions in BMD, of 6.9% and 8.9% at the lumbar spine and the femoral neck, respectively (8). Verstraeten and Dequeker controlled for menopausal status in their comparison of 36 postmenopausal patients and 43 control subjects (11), and found BMD at the lumbar spine to be surprisingly higher in the RA group. Compston et al, using computed tomography, found no difference in spinal bone content between female RA patients age >50 and controls (12). A longitudinal study of axial bone loss in RA revealed no difference between patients and controls in the rate of loss at either the spine or the hip, although there was a tendency toward more rapid femoral bone loss in the RA patients (23).

Our study focused specifically on a representative cross-section of postmenopausal women with RA. Using DXA, widely accepted as a highly precise technique, we found no difference in spinal BMD between 597 controls and 119 patients who had never taken steroids, but a significant 6.9% reduction in BMD at the proximal femur. The reason for this discrepancy between the sites is unclear. Studies have shown an increased risk of spinal fracture in RA (24-26), suggesting that lumbar spine BMD should be lower than in controls. One technical explanation may be that BMD results in some patients may be incorrectly recorded as elevated due to degenerative changes and osteophytosis (27), although there is no

compelling evidence to suggest that such changes are more prevalent in RA than in healthy individuals. Another explanation may be that there is a genuine predominance of bone loss at the hip versus the spine in RA, and the results of previous studies showing normal spinal BMD (11,12) would support this.

Sambrook et al (8) have also suggested that femoral BMD is relatively lower compared with the spine and, along with others (9,19), have concluded that poor mobility is an important factor. We found that the HAQ score was inversely proportional with femoral BMD and whole-body BMD but not with

**Table 3.** Correlations (r) between disease activity parameters and bone density in the group of RA patients who never used steroids\*

	Spine BMD	Hip BMD	Whole-body BMD
Disease duration	-0.004	-0.08	0.17
RAI	-0.11	-0.07	-0.26
HAQ	-0.08	-0.23†	-0.40†
ESR	-0.06	-0.17	-0.27
Morning stiffness	-0.11	-0.10	-0.14
Duration of menopause	-0.24†	-0.28†	-0.22
Age	-0.07	-0.11	-0.003
Weight	0.34‡	0.42‡	0.45†

\* See Table 1 for definitions.

†  $P < 0.01$ .

‡  $P < 0.001$ .

BMD at the lumbar spine, suggesting that functional disability has a less important effect on spinal bone mass compared with bone mass at the hip and other sites. Interestingly, a study of physical fitness in normal postmenopausal women showed fitness to be more strongly correlated with BMD at the femoral neck than with BMD at the spine (28), supporting the view that the hip may be particularly vulnerable to the effects of immobility. Whole-body BMD correlated better with femoral BMD ( $r = 0.83$ ) than with lumbar spine BMD ( $r = 0.37$ ), again implying that either lumbar spine measurements are less accurate or the spine is less vulnerable to the effects of RA. A single measurement of femoral BMD may be a reliable method of evaluating overall skeletal condition in postmenopausal women with RA.

Increased skeletal loss has been associated with more active RA (4,5,20,21), but this remains controversial mainly because of the interpretation of variables in cross-sectional data. Our measurements of various parameters of disease, including disease duration, all showed weakly negative correlations with BMD, but only the correlation with the HAQ score, reflecting disability, was significant. It is possible, however, that, analogous to recovery following steroid therapy, bone mass may improve with disease remission.

The effect of corticosteroid therapy on bone mass in RA has been a matter of controversy. Most investigators have shown a deleterious effect on the skeleton (2,3,5-7,22,29,30), but others suggest that low-dose steroids may be relatively safe (8,9,31-34). Sambrook et al (8) found that in 64 postmenopausal patients, the mean difference in BMD in steroid-treated compared with non-steroid-treated patients was 3.4% at the spine and 7.4% at the femoral neck. However, differences could be explained in part by longer disease duration and greater disease activity in the steroid users. There was no effect of cumulative dose. In another study in which axial skeleton measurements were made using DPA, it was concluded that there was no difference between the steroid-treated and non-steroid-treated groups after correction for disease duration. Paradoxically, there was a higher incidence of vertebral fractures in the steroid-treated group (11). Laan et al, using computed tomography, found reductions in vertebral BMD of more than 30% in steroid-treated patients compared with non-steroid-treated women with RA (29), and Butler et al confirmed significant reductions in forearm BMD with steroid usage (22). Reid et al found that levels of

total body calcium were significantly reduced in female patients receiving low-dose prednisolone (5).

In our cohort, current steroid usage led to significant reductions in BMD, of 7.4% at the proximal femur and 6.5% at the spine. Both low- and high-cumulative-dose groups were at risk for decreased BMD, and the data on whole-body BMD confirmed the overall osteopenic effect of steroids.

In our 35 patients who had discontinued steroid therapy, BMD at all sites was very similar to that in the patients who had never used steroids, suggesting that there may be recovery of bone mass following cessation of therapy. The cumulative dose in ex-users was similar to that in the current low-dose users, yet ex-users exhibited higher BMD, of 6.4% and 5% at the lumbar spine and the femur, respectively. These findings support the isolated reports of recovery from endogenous steroid-induced osteoporosis (35,36).

This is the first report to date of possible skeletal recovery following corticosteroid therapy; clearly, a prospective study of steroid therapy and disease activity in RA would help in corroborating these cross-sectional data.

Our findings suggest that the hip is especially vulnerable to bone loss in RA, particularly in disabled patients. Steroids exert a negative (but possibly reversible) effect on bone, cumulative dose being more important than daily dose. Clinicians must not be complacent when prescribing long-term steroids in postmenopausal women with RA.

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