# Abnormal Levels of Serum Dehydroepiandrosterone, Estrone, and Estradiol in Men with Rheumatoid Arthritis: High Correlation Between Serum Estradiol and Current Degree of Inflammation

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*ABSTRACT*. ***Objective***. Men with rheumatoid arthritis (RA) have a higher than normal frequency of low testosterone levels, but not much is known about other sex hormones. We investigated serum levels of estradiol, estrone, and the adrenal androgen dehydroepiandrosterone (DHEAS) in men with RA and evaluated the association of various disease variables with these sex hormones.

***Methods***. Inflammatory activity, measured as disease activity score including 28 joints (Disease Activity Score 28), and degree of disability, measured with the Health Assessment Questionnaire, were estimated in 101 men with RA. Presence of erosions, rheumatoid factor (RF), smoking habits, and body mass index were recorded. DHEAS (not measured in patients taking glucocorticoids), estradiol, and estrone were measured in patients and in healthy controls.

***Results***. DHEAS and estrone concentrations were lower and estradiol was higher in patients compared with healthy controls. DHEAS differed between RF positive and RF negative patients. Estrone did not correlate with any disease variable, whereas estradiol correlated strongly and positively with all measured indices of inflammation.

***Conclusion***. Men with RA had aberrations in all sex hormones analyzed, although only estradiol consistently correlated with inflammation. The high levels of estradiol may have positive implications for bone health. The low levels of estrone and DHEAS may depend on a shift in the adrenal steroidogenesis towards the glucocorticoid pathway, whereas increased conversion of estrone to estradiol seemed to be the cause of the high estradiol levels. (J Rheumatol 2003;30:2338–43)

*Key Indexing Terms:*
MEN ESTRONE ESTRADIOL
DEHYDROEPIANDROSTERONE RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is a disease associated with alterations in sex hormones[1]. There are several reports about subnormal concentrations of testosterone in men with RA[2–6], whereas estrogens are less well studied. Also, women with RA have low androgen concentrations, while there seem to be no aberrations in estrogens[7,8]. No study has yet been able to clarify if the reductions in androgens in RA are a cause or a consequence of the disease.

Both androgens and estrogens affect the immune system. Androgens suppress humoral- and cellular-mediated immune responses, while the effects of estrogens are dose-dependent; in physiological doses estrogens enhance the humoral- and suppress cellular-mediated responses[9]. Clinically, these immunomodulating effects may explain some of the sex differences in the onset and course of RA. The incidence of RA in men increases in ages above 60 years when bioavailable testosterone decreases, and the peak incidence in women is between 50 and 60 years, i.e., in the years following the menopause[10]. Further, the beneficial effect of pregnancy on RA is well known[11], and premenopausal women have milder disease compared with postmenopausal women[10].

In a previous study we reported bone mineral density (BMD) in men with RA and its correlation with disease-specific variables and sex hormones[12]. We found no correlation between BMD and indices of inflammation or with sex hormones. This prompted us to study sex hormones other than testosterone in men with RA, to determine whether they were related to variables of disease activity. Here we describe serum concentrations of estrogens and of the main adrenal androgen, dehydroepiandrosterone sulfate (DHEAS), in men with RA and in healthy controls.

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## MATERIALS AND METHODS

*Patients*. One hundred and one male patients with RA according to the American College of Rheumatology (ACR) criteria[13] were consecutively enrolled into the study. The patients were all attending the rheumatology clinic at Huddinge University Hospital. The testosterone status of these patients has been described[6]. Characteristics of the patients are shown in Table 1. Sixty-four patients were not treated with glucocorticoids (GC). Only 4 of these patients had been treated previously with GC, and the shortest interval between withdrawal of GC and inclusion in the study was 4.5 months. Twenty-three patients were not taking disease modifying antirheumatic drugs (DMARD) as they were assessed at disease start or before a new DMARD was introduced. Seven of these patients were treated with GC. The local ethics committee approved the study protocol, and informed consent was obtained from all patients.

*Controls*. One hundred and twenty-nine healthy, medicine-free men served as controls for analysis of DHEAS and estrone (E1). Most of the controls under 50 years were healthy men from hospital staff, while older men were recruited from the departments of surgery. They were admitted to the hospital for minor elective surgery. This control population has been built up during the last 10 years. Analyses were performed with the same methods as in the present study.

Thirty-nine men, age range 23–70 years, served as new controls for analysis of estradiol (E2) together with 10 frozen sera from the former group. One-third of these were from a control population in another study with arthritis as an exclusion criterion; the rest were hospital staff, mostly physicians. In a small proportion of these men E1 and DHEAS were also analyzed. The blood samples in this group were analyzed blindly and contemporaneously with the serum samples from the current RA patients.

Because values for DHEAS, E1, and E2 in comparable age groups were almost identical in the historical and the new control groups, we combined the groups.

*Assessments*. Disease activity was measured by the composite index Disease Activity Score in 28 joints (DAS28)[14]. This index includes number of swollen joints, number of tender joints, patient global assessment of disease activity measured on a visual analog scale, range 0–100 mm, and erythrocyte sedimentation rate (ESR), with a score ranging from 0 to 10. The patients also completed the Swedish version of the Stanford Health Assessment Questionnaire (HAQ), a self-reporting instrument measuring disability[15]. This disability index comprises 20 questions, divided into 8 subcategories, each consisting of 2 to 3 activities of daily living. The response to each question ranged from 0 (no difficulty) to 3 (unable to perform). The created score for the disability index ranges from 0 to 3.0, where a higher score indicates a higher degree of disability[16].

*Table 1*. Patient characteristics of 101 men with RA.

| | No. | Median | Range |
|---|---|---|---|
| Age, yrs | | 59.0 | 24–69 |
| Disease duration, yrs | | 4.0 | 0–43 |
| RF positive | 79 | | |
| Erosions on radiographs | 70 | | |
| DAS28 | | 4.55 | 0.97–8.29 |
| ESR | | 26 | 4–140 |
| CRP, mg/l | | 18 | 6–137 |
| HAQ score | | 0.875 | 0–2.25 |
| Patients taking prednisolone | 37 | | |
| Patients taking DMARD* | 78 | | |
| Current smoking | 37 | | |
| BMI | | 25.1 | 18.4–35.1 |

*Methotrexate 35 (in combination with another DMARD, 16), sulfasalazine 24 (5), aurothiomalate 20 (5), cyclosporine 8 (5), chloroquine 4 (3), penicillamine 2 (0), auranofin 4 (1), and podophyllin 2 (1). DAS 28: Disease Activity Score in 28 joints.

Radiological examinations were performed on hands, wrists, and forefeet in the year preceding inclusion in the study.

*Biochemical analysis*. Venous blood was sampled in the morning, between 8:00 and 10:00 AM, for measurement of serum concentrations of DHEAS (not in patients receiving GC), E1, E2, ESR, C-reactive protein (CRP), and rheumatoid factor (RF).

Serum concentrations of DHEAS were determined by competitive chemiluminescence immunoassay using a commercial kit (Immulite® DHEA-SO4; Diagnostic Products Corp., Los Angeles, CA, USA). Serum concentrations of E2 were determined by radioimmunoassay using a commercial kit (ESTR-US-CT; CIS Bio International, Gif-sur-Yvette, France); and serum concentrations of E1 were determined after extraction with diethyl ether by an in-house radioimmunoassay[17] method with minor modifications.

Detection limits and within- and between-assay coefficients of variation for DHEAS were 0.79 µmol/l, 8% and 12%; for E2, 5 pmol/l, 3% and 6%; and for E1, 30 pmol/l, 7% and 10%, respectively.

The presence and titer of RF was determined using the classical Waaler-Rose hemagglutination method. The assay was calibrated against the international reference RF preparation WHO 64/1.

*Statistical analysis*. Analysis was performed using Statistica for Windows (version 4.2). All analyses were performed with nonparametric tests as DHEAS, E2, and E1 are non-normally distributed. Differences between groups were calculated with Mann-Whitney U test, and correlations were performed with Spearman rank order correlation test. Multiple regression analysis was performed with E2 as the dependent variable. E2 values were transformed by logarithm to obtain normal distribution.

## RESULTS

The patient population studied was heterogeneous with respect to age, duration of disease, and degrees of current inflammation and disability (Table 1). It illustrates a hospital-based population consisting of both patients with recent onset of RA and patients with severe disease.

As GC suppresses DHEAS, this hormone was analyzed only in patients not treated with GC. DHEAS levels in the combined patient and control group were highly and negatively correlated with age ($r_s = –0.74$, $p < 0.001$). Therefore the 2 groups, patients and controls, were divided into decades for statistical analysis. DHEAS values were lower in the patients compared with the controls in all 4 age groups, but the difference was not significant in the youngest age group, which had a very low number of patients, n = 4 (Table 2). There was no difference in mean DHEAS levels between patients with early RA and patients with disease duration of one year or more. Median DHEAS was significantly lower in RF negative patients, 1.75 µmol/l compared to RF positive, 2.6 µmol/l (Table 3). The 2 patient groups, RF negative and RF positive, did not differ in any disease-specific variable other than DHEAS. DHEAS correlated with several markers of inflammation in RF negative patients, but with none in RF positive patients (data not shown).

E2 did not correlate with age in the patient or the control group, but had a significant but weak correlation with age in the combined group ($r_s = +0.23$, $p < 0.01$). The number of controls was too low to use age groups for analysis. We therefore included all available patients and controls for

*Table 2.* Serum concentrations of DHEAS in male patients with RA without glucocorticoids and controls in different age groups.

| | Patients | Controls |
|---|---|---|
| 20–39 yrs, n | 4 | 57 |
| Mean age, yrs | 32.0 | 29.7 |
| DHEAS, µmol/l | 5.5 (3.5–5.9) | 7.2 (5.3–8.1) |
| 40–49 yrs, n | 13 | 22 |
| Mean age, yrs | 44.6 | 44.3 |
| DHEAS, µmol/l | 3.7 (2.4–4.9)** | 5.6 (4.3–6.5) |
| 50–59 yrs, n | 18 | 29 |
| Mean age, yrs | 55.7 | 55.0 |
| DHEAS, µmol/l | 2.5 (1.5–3.5)* | 3.7 (3.0–4.9) |
| 60–69 yrs, n | 27 | 21 |
| Mean age, yrs | 65.5 | 64.1 |
| DHEAS, µmol/l | 1.75 (0.9–2.9)* | 2.5 (1.8–4.1) |

DHEAS values are given as medians and interquartile ranges. Significant differences between patients and controls are denoted * $p < 0.05$ and ** $p < 0.01$.

analysis in spite of a mean difference of 5.2 years between patients and controls, and found E2 values to be significantly higher in the patients (Table 4). Excluding parts of the population in order to obtain age-matched groups gave almost identical results and p values < 0.001.

Measures of inflammation, both clinical and laboratory, very strongly correlated with E2: the highest correlation coefficient was +0.49 for ESR and E2 (Table 3 and Figure 1). The HAQ, a measure of disability reflecting both inflammation and structural damage, was also correlated with E2, although the strength of the correlation was lower

*Table 4.* Serum concentrations of estradiol in male patients with RA and controls.

| | All Patients | Patients without Glucocorticoids | Controls |
|---|---|---|---|
| N | 101 | 64 | 49 |
| Mean age, yrs | 57.3 | 56.3 | 52.1 |
| Estradiol, pmol/l | 93 (77–128)**** | 91.5 (71.5–121.5)*** | 73.5 (56–95) |

Estradiol values are given as medians and interquartile ranges. Significant differences between patients and controls are denoted *** $p < 0.001$ and **** $p < 0.0001$.

(Table 3). The strong correlation between inflammation and E2 was convincing even looking at individual patients. Only 2 patients had serum E2 concentrations below the reference interval in our laboratory (50–150 pmol/l). These 2 patients had low-grade inflammation, with ESR 5 and 9 mm/h and DAS28 1.54 and 2.75, respectively (DAS28 below 2.6 is considered to be RA disease in remission). In contrast, 15 patients had E2 concentrations above the upper limit and their mean ESR, CRP, and DAS28 were 63, 71, and 5.65, respectively. There was no difference in the levels of E2 in patients with and without treatment with GC (Table 4). We also performed a multiple regression analysis with E2 as the dependent variable and treatment with GC, E1, and ESR as independent variables. The correlation between E2 and ESR was still significant ($p < 0.0001$). The $R^2$ value (proportion of explained variance) in this model was 0.46.

E1, in controls, was not correlated with age in the age

*Table 3.* Correlations between hormone levels and different clinical variables in the patient group. Intercorrelations between hormones are included. For DHEAS only patients not taking glucocorticoids are analyzed. Data from our previous study on testosterone[6] are included for comparison. All hormone analyses are performed contemporaneously.

| | Bioavailable Testosterone | DHEAS | Estradiol | Estrone |
|---|---|---|---|---|
| Age | $p < 0.0001$, R = –0.44 | $p < 0.001$, R = –0.52 | NS | NS |
| Duration of RA | NS | NS | NS | NS |
| Erosive disease | NS | NS | NS | NS |
| RF | NS | $p < 0.05$ | NS | NS |
| DAS 28 | NS | NS | $p < 0.0001$, R = 0.38 | NS |
| VAS global | NS | NS | $p < 0.05$ | NS |
| Swollen joint count | NS | NS | $p < 0.001$ | NS |
| Tender joint count | NS | NS | NS (p = 0.08) | NS |
| ESR | NS | NS | $p < 0.00001$, R = 0.49 | NS |
| CRP | NS | NS | $p < 0.00001$, R = 0.44 | NS |
| HAQ | $p < 0.01$, R =–0.24 | NS | $p < 0.05$, R = 0.25 | NS |
| Smoking, pack-years | $p < 0.05$, R = –0.23 | NS | NS | NS |
| BMI | NS | NS | NS | NS |
| Treatment with glucocorticoids | NS | Not analyzed | NS | $p < 0.05$ |
| Bioavailable testosterone | | $r_s = 0.5$, $p < 0.0001$* | $r_s = 0.20$, $p < 0.05$ | Rs = 0.27, $p < 0.05$ |
| DHEAS | | | NS | $r_s = 0.29$, $p < 0.05$ |
| Estradiol | | | | $r_s = 0.39$, $p < 0.001$ |

Regression coefficients (R) are shown for continuous data if the correlations are significant. *Non-SHBG-bound testosterone and DHEAS are both negatively correlated with age. Controlling for age the significance is lost.

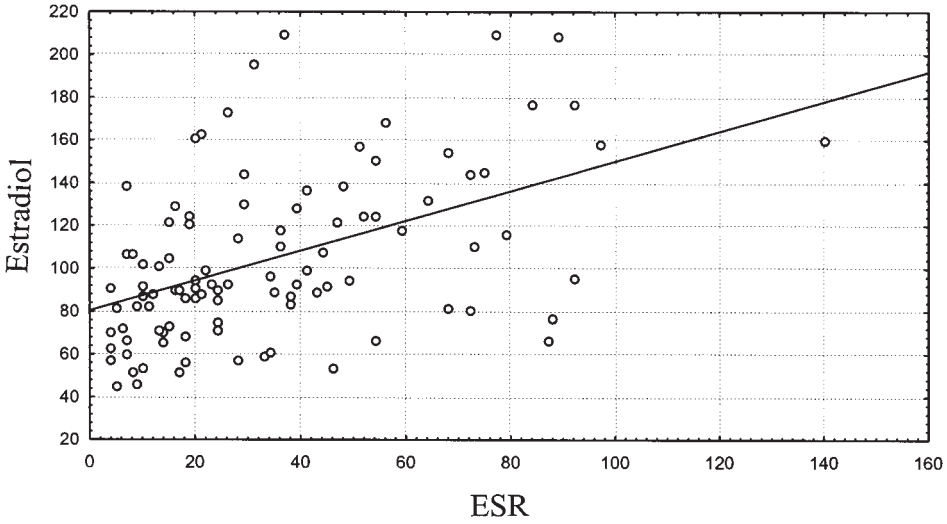


*Figure 1*. Interrelationship between estradiol and ESR for men with RA. Estradiol values are pmol/l and ESR values are mm/h.

group 40–69 years ($r_s$ = –0.01, p = 0.94). In the ages below 40 years some young controls had very high levels, leading to a statistically significant correlation with age in that group ($r_s$ = –0.38, p < 0.05); we therefore analyzed this age group separately. E1 was significantly lower in patients in both age groups in spite of the very low number of young patients (Table 5). E1 did not correlate significantly with any of the clinical or laboratory variables analyzed (Table 3). Patients treated with GC had lower E1 levels than patients without GC, median value 124.5 versus 150 pmol/l (p < 0.001). Confining the calculations to patients without GC, the levels of E1 were still substantially lower in patients (p < 0.001).

The mean E2/E1 ratios were 0.74 for cases and 0.37 for controls (p < 0.00001). E2/E1 correlated more strongly to markers of inflammation than E2 alone, e.g., the correlation coefficient between ESR and E1/E2 was 0.59 (p < 0.00001). The sum of E1 and E2 was lower in patients than in controls, median values 241 versus 286 pmol/l (p < 0.01).

There were significant positive correlations between all the studied hormones with the exception of DHEAS and estradiol (Table 3). Further, age was a confounding factor for the correlation between DHEAS and non-SHBG-bound testosterone, and the significance for this correlation was lost in multiple regression analysis.

Methotrexate, sulfasalazine, injectable gold, and cyclosporin A were used in sufficient numbers for statistical analysis. In univariate analysis methotrexate was associated with higher testosterone levels, but in multiple regression analysis the significance was lost. This was the only correlation found between the 4 DMARD and testosterone, DHEAS, E1, and E2.

## DISCUSSION

Our study shows that men with RA had low serum concentrations of DHEAS and E1 compared with healthy men, whereas E2 levels were high and correlated strongly with indices of inflammation.

The low levels of DHEAS found in our study are in agreement with an earlier report concerning men with estab-

*Table 5*. Serum concentrations of estrone in age-grouped male patients with RA and controls.

| | Patients | Patients without Glucocorticoids | Controls |
|---|---|---|---|
| 20–39 yrs, n | 4 | 4 | 39 |
| Mean age, yrs | 32.0 | 32.0 | 29.1 |
| Estrone, pmol/l | 144 (109.5–175.5)* | 144 (109.5–175.5)* | 241 (210–306) |
| 40–69 yrs, n | 86 | 51 | 79 |
| Mean age, yrs | 58.8 | 58.0 | 55.0 |
| Estrone, pmol/l | 142.5 (121–170)**** | 150 (134–182)**** | 212 (172–245) |

Estrone values are given as medians and interquartile ranges. Significant differences between patients and controls are deoted * p < 0.05 and **** p < 0.0001.

lished disease[18]. However, in 116 patients (47 men) with recent RA onset (range 0–24 mo, median 4 mo) no difference between RA patients and controls was found, after adjustment for age and sex[19]. This contrasts to our finding that men with early RA (disease duration less than one year) had low DHEAS. We have no explanation for this discrepancy. An interesting finding is that premenopausal women already have low DHEAS levels before the onset of RA[20].

The reports about correlations between DHEAS and inflammatory markers in RA have been inconsistent. Ritchie Articular Index, which was the only inflammatory marker studied earlier in men with established disease, did not correlate with levels of DHEAS[18]. Similarly, in our study, joint measures such as DAS28 and HAQ did not correlate with DHEAS, at least not in RF positive patients. This finding is in contrast to the study of Giltay, *et al,* who found a significant positive correlation between DHEAS and CRP[19].

In our study DHEAS was lower in RF negative patients than in RF positive patients. This could not be explained by differences such as age, degree of inflammation, HAQ, duration of disease, smoking, or body mass index in RF positive versus RF negative patients and has not been reported earlier. However, in RF negative but not in RF positive patients DHEAS correlated significantly with markers of inflammation.

The findings of higher E2 levels in men with RA compared with controls reported here and the strong correlations with all measured indices of inflammation have, to our knowledge, not been reported or studied earlier concerning male RA patients, nor the findings of the significantly lower E1 levels found in men with RA. Except for a minor direct testicular secretion of E2, circulating estrogens in the male are synthesized by peripheral conversion of androgens, mainly in fat tissue. Also, macrophages express aromatase mRNA and have the capacity to synthesize relevant amounts of androgens and estrogens, which may have an influence on local immunomodulation[21]. The main substrate for E1 synthesis is androstenedione, which is mainly of adrenocortical origin, while the main substrate for E2 synthesis is testosterone produced in the testis (Figure 2).

Adrenal steroid metabolism is shifted from androgenic towards glucocorticoid pathways in serious illness[9], as well as in chronic inflammatory diseases such as Crohn's disease, ulcerative colitis, systemic lupus erythematosus, and polymyalgia rheumatica[22]. This is a plausible explanation for the observed hormone levels in our study. Although our patients could not be considered critically ill, they had a chronic disease, with median disease duration of 4 years. The estrogen derived from the adrenal androgens, E1, but not the gonadal derived estrogen, E2, was depressed, which is consistent with the adrenal hormonal shift in illness. Further, GC treatment was correlated with lower levels of E1 but not E2, indicating that GC in the low doses used in this population (2.5–10 mg prednisolone) affected the adrenals but not the gonads.

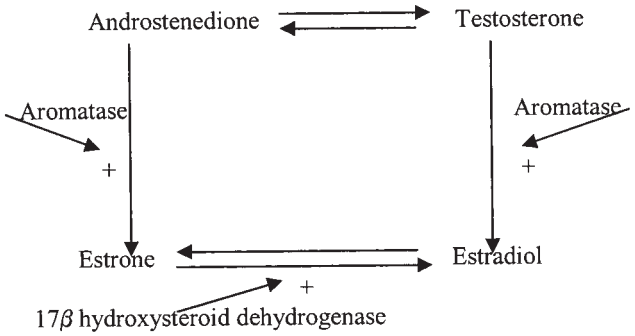


*Figure 2.* Synthesis of sex hormones. The proinflammatory cytokines tumor necrosis factor-α, IL-1, and IL-6 enhance the conversion of androgens to estrogens by stimulating aromatase activity. Further, IL-6 mediates an increase in the activity of reductive 17ß-hydroxysteroid dehydrogenase, which converts estrone to estradiol.

Not only the protracted stress seen during a chronic disease, such as RA, is associated with changes in sex hormones, but also acute inflammation such as sepsis has profound effects on androgen and estrogen levels. Thus, in male patients with sepsis testosterone decreases, whereas E1 and E2 increase[23]. In physiological stress due to myocardial infarct or unstable angina, isolated elevations of E2 have been reported in men, while male intensive care unit patients without apparent coronary disease in the same study showed increased levels of both E1 and E2[24]. The shift to the glucocorticoid pathway thus occurs in both acute diseases and stresses and in chronic inflammation. The normal or elevated levels of estrone in acute stresses differ from the finding in our study. We do not know the reason for this discrepancy; however, that the hormonal changes develop over a long period of time seems a plausible explanation. Another hypothesis is that some patients with RA may have an inherent relative adrenal insufficiency.

The cause of the increased concentrations of estrogens in critically ill men is probably enhanced aromatization of androstenedione and testosterone to E1 and E2, respectively. The aromatase activity is stimulated by the proinflammatory cytokines tumor necrosis factor-α (TNF-α), interleukin (IL)-1, and IL-6. IL-6 also mediates an enhanced conversion of E1 to E2 by stimulating 17ß-hydroxysteroid dehydrogenase[25] (Figure 2). Higher E2/E1 ratios and lower combined sums of E1 and E2 in our patients compared with controls indicate an increased conversion of E1 into E2 rather than an increased aromatisation of androgens as the origin of the elevated E2 levels.

In a previous study we reported reduced bone mass in the same cohort of men with RA[12]. We found no correlations between bone mass and inflammation. As TNF-α, IL-1, and IL-6 contribute to both reduced bone formation and enhanced bone resorption, this was an unexpected finding. Our explanation was that the study was a cross sectional

study with no information on inflammation over time. Another explanation with respect to our new findings is that the RA men with high degree of inflammation might have been protected from bone loss because of the elevated E2 concentrations. E2 is known to be beneficial not only for bone tissue in women but also for the male skeleton[26].

A very interesting issue is whether any of the hormonal aberrations found in our study precede the onset of RA. A combined insufficiency of adrenal cortisol and gonadal testosterone production has been reported in a small minority of males before the onset of RA, but not low levels of DHEAS[27]. Decreased levels of these immune suppressive hormones might play a role in the development of RA, but further research is needed to resolve this issue.

Thus men with RA have several aberrations in their sex hormones as we have shown here and in a previous study. They have low bioavailable testosterone, low DHEAS, low E1, and high E2 concentrations compared with healthy men. The high E2 but not the low E1 levels are consistent with findings in men with inflammation or physiological stress with causes other than RA. The E2 levels in men with RA were strongly correlated to the current degree of inflammation, which may have a positive implication for bone health.

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