Increased DHEAS Levels in Patients with Rheumatoid Arthritis After Treatment with Tumor Necrosis Factor Antagonists: Evidence for Improved Adrenal Function

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ABSTRACT. ***Objective.*** To determine if major reduction of inflammation with longterm tumor necrosis factor (TNF) antagonist treatment has any influence on the adrenal and gonadal axes in patients with rheumatoid arthritis (RA).

Methods. Forty-eight patients with RA were treated with infliximab or etanercept for 2 years. Disease activity, clinical response, and physical function were evaluated and serum levels of high sensitivity C-reactive protein and interleukin 6 were analyzed before start of treatment and after 1 and 2 years. At the same timepoints adrenocorticotropic hormone (ACTH), cortisol, and dehydroepiandrosterone sulfate (DHEAS) were analyzed; luteinizing hormone (LH), estradiol, and testosterone were analyzed as well in 18 male patients.

Results. DHEAS increased ($p < 0.05$) after 1 and 2 years of treatment with TNF antagonists. No change in serum levels of ACTH, cortisol, LH, estradiol, or testosterone was recorded during the 2 years. The increased levels of DHEAS correlated with improved physical function measured by Health Assessment Questionnaire ($p < 0.01$). There was no correlation between hormone levels and clinical response or inflammatory markers. A longitudinal stability in individual hormone levels was found between baseline and 2 years, most markedly for DHEAS levels ($r_s = 0.90$, $p < 0.01$). A female subgroup characterized by low levels of DHEAS had a lower age at disease onset.

Conclusion. The increased DHEAS levels may indicate an improved adrenal function during 2 years' treatment with TNF antagonists. Improved physical function, correlated to increased DHEAS levels, may be an effect of better adrenal function during powerful antiinflammatory treatment. The stability in individual hormone levels suggests a stable hormonal homeostasis, independent of inflammatory activity. (First Release May 1 2007; J Rheumatol 2007;34:1451–8)

Key Indexing Terms:
RHEUMATOID ARTHRITIS ADRENAL INFLIXIMAB ETANERCEPT DHEAS

Rheumatoid arthritis (RA) is a chronic inflammatory disease, primarily affecting the joints with signs of local inflammation and subsequent joint destruction, but also with systemic manifestations. The etiology is unknown, but in established disease activated macrophages in the inflamed synovial tissue produce proinflammatory cytokines, such as interleukin 1 (IL-1) and tumor necrosis factor-α (TNF-α), resulting in proliferation of synoviocytes and production of inflammatory mediators and proinflammatory cytokines in a paracrine way[1].

In healthy individuals, proinflammatory cytokines are reported to influence both the hypothalamic-pituitary-adrenal (HPA) axis and the hypothalamic-pituitary-gonadal (HPG) axis. IL-1 and IL-6 influence the adrenal axis at all levels, from stimulation of corticotropin-releasing factor in the hypothalamus, to secretion of adrenocorticotropic hormone (ACTH) from the pituitary gland and stimulation of production of cortisol and dehydroepiandrosterone sulfate (DHEAS) from the adrenal cortex[2,3]. This is appropriate during acute stress, such as a traumatic injury and sepsis. On the other hand, TNF has been described to have a stimulating effect on the central parts of the axis, but an inhibitory effect on the adrenal[4]. A parallel suppressive effect on the steroidogenesis in the testis has been described[5].

In RA, the response of the HPA axis to inflammatory and stress stimuli has been reported to be inappropriate and may thus not be strong enough to combat the inflammation[6,7]. Low DHEAS and cortisol concentrations have been described in premenopausal women with RA[8-10] and low DHEAS levels in

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male patients with RA[11]. In HLA identical siblings, DHEAS levels have been reported to be lower in the RA sibling compared with the sibling without RA[12]. Further, low DHEAS and cortisol levels have been found to precede disease onset in a subgroup of premenopausal women[13]. In addition to aberrations in the HPA axis in RA, dysfunction of the HPG axis has been reported in men preceding the disease[14], and low testosterone levels have been described in men with established disease[15].

If proinflammatory cytokines have major effects on dysregulated HPA and HPG axes in RA, a normalizing effect could be expected when a central cytokine such as TNF is inhibited. Specific TNF antagonists reported to decrease serum levels of IL-6 and IL-1ß as well as synovial expression of TNF[16] provide a way to test this hypothesis. TNF antagonists such as infliximab and etanercept are today the most efficient therapy in RA, with a rapid reduction of inflammation[17] and joint destruction[18]. To investigate the role of cytokines for the HPA and HPG axes in RA, treatments with TNF antagonists for 12 and 16 weeks, respectively, were conducted and an increase in the ratio of serum cortisol to serum ACTH has been reported[19,20]. However, longer periods of treatment are probably needed for normalization of these axes[15,21].

Our objectives were to analyze the HPA and HPG axes in RA patients longitudinally for 2 years during treatment with TNF antagonists, and to investigate whether patients responding well to TNF antagonists had hormone levels different from patients who still had active inflammation after 2 years.

MATERIALS AND METHODS

Patients and treatment. In the analysis of the HPA axis we included 36 patients with RA according to the American College of Rheumatology criteria[22], treated with either infliximab or etanercept during at least 2 years (April 1999 to April 2004). Baseline characteristics of the 36 patients are presented in Table 1. Etanercept (n = 12) 25 mg was given subcutaneously twice weekly and infusions of infliximab (n = 24) 3 mg/kg were given intravenously every eighth week after a 3-dose induction phase with infusions at 0, 2, and 6 weeks. Treatment with a TNF antagonist was initiated because of high disease activity despite treatment with disease modifying antirheumatic drugs (DMARD). The median number of previous DMARD was 5. Thirty-three patients were treated with a concomitant DMARD at baseline [methotrexate 29 patients, dose 5–30 mg/wk, median 15 mg/wk; azathioprine 3 patients; reumacon (podophyllotoxine derivative) 1 patient with minor changes in treatment and doses during the 2 years. Twenty-nine patients were treated with daily or as-needed nonsteroidal antiinflammatory drugs (NSAID) or COX-2 inhibitors at baseline. Altogether there were 30 women and 6 men with a median age of 54 years (range 29–80) and median disease duration 9 years (3–28).

In the analysis of the HPG axis 18 male patients with RA were included (Table 1). They had a median age of 59 years (range 44–74) and median disease duration 5 years (range 1–61). At baseline the 12 patients treated with concomitant oral glucocorticoids had a mean prednisolone dose of 6.6 ± SD 1.9 mg. The number of patients with prednisolone treatment at 1 and 2 years was 9 and 6, respectively. The mean dose of prednisolone was 3.4 ± SD 3.0 mg at 1 year and 2.0 ± SD 2.2 mg at 2 years. Seventeen patients were treated with concomitant DMARD at baseline (methotrexate 15 patients, dose of 5–30 mg/week, median 15 mg/week; azathioprine 1 patient) with minor changes in treatment and doses during the 2 years. Seventeen patients were treated with daily or as-needed NSAID or COX-2 inhibitors at baseline.

The local ethics committee had approved the study protocol, and informed consent was obtained from all patients.

Clinical assessments. Clinical evaluation was performed at baseline and after 1 and 2 years' treatment with TNF antagonists. Disease activity was measured by the Disease Activity Score (DAS) composite index calculated on 28 joints (DAS28)[23], which includes swollen joint count, tender joint count, and the patient's global assessment of general health measured on a visual analog scale (0–100 mm). At 1 and 2 years the EULAR response criteria were recorded for all patients[24]. Good responders were those with a DAS28 improvement of at least 1.2 and an endpoint value < 3.2. Moderate responders were patients with either an improvement of at least 1.2, independent of the attending DAS28 value, or an improvement of at least 0.6 in combination with an endpoint DAS28 < 5.1. A patient was considered to be in remission if DAS28 was < 2.6[25].

Functional disability was assessed using the Swedish version of the Stanford Health Assessment Questionnaire (HAQ)[26]. The HAQ score ranges from 0 to 3, where a higher score indicates a higher degree of disability.

Analytical methods. At baseline, before initiation of TNF antagonists, and after 1 and 2 years, blood samples were drawn mainly between 8:00 AM and 1:00 PM for analysis of erythrocyte sedimentation rate (ESR), and serum and plasma were stored at –70°C.

Serum concentrations of cortisol, testosterone, estradiol-17ß, and luteinizing hormone (LH) were determined by time-resolved fluorescence immunoassay (TRFIA) using commercial kits (Autodelfia®, Wallac OY, Turku, Finland). Plasma concentrations of ACTH and serum concentrations of DHEAS were determined by chemiluminescence immunoassays (Advantage®; Nichols Products, San Juan Capistrano, CA, USA). Serum concentrations of IL-6 were determined by ELISA (Quantakine®; R&D Systems, Minneapolis, MN, USA). Serum concentrations of C-reactive protein (CRP) were determined by a high sensitivity immunonephelometric assay using a commercial kit (Dade Behring GmbH, Marburg, Germany). Serum albumin was determined by the routine method of the Department of Clinical Chemistry, Karolinska University Hospital at Solna, Sweden.

Table 1. Baseline characteristics of the RA patients, organized by hypothalamic-pituitary-adrenal (HPA) axis and hypothalamic-pituitary-gonadal (HPG) axis.

Characteristic	HPA Axis, n = 36	HPG Axis, n = 18
Age, yrs, median (range)	54 (29–80)	59 (44–74)
Female/male, n	30/6	0/18
Rheumatoid factor positive/negative, n	27/9	17/1
Disease duration, yrs, median (range)	9 (3–28)	5 (1–61)
Prednisolone, mean dose ± SD, mg	0	6.6 ± 1.9
Infliximab/etanercept, n	24/12	16/2
Previous disease modifying antirheumatic drugs, median (range)	5 (2–10)	5 (2–10)

Detection limits and within- and between-assay coefficients of variation were as follows: for cortisol 15 nmol/l, 5.0% and 5.0%; testosterone 0.3 nmol/l, 2.1% and 6.1%; estradiol-17ß 50 pmol/l, 5.0% and 8.0%; LH 0.05 U/l, 2.0% and 2.0%; ACTH 0.2 pmol/l, 4.0% and 4.0%; DHEAS 0.03 μmol/l, 5.4% and 9.1%; IL-6 0.7 ng/l, 4.2% and 6.4%; and CRP 0.16 mg/l, 3.4% and 2.1%, respectively.

Statistical analysis. Nonparametric tests were used for non normally distributed variables. For analysis of variables over time Friedman's test was used. Correlation analyses were performed with Spearman's rank correlation test. Analyses between groups were by Mann-Whitney test. The significance level was set at $p < 0.05$.

RESULTS

Clinical response, markers of inflammation, and physical function. The clinical response results, inflammation markers, and physical function results for all 48 patients (36 without concomitant glucocorticoid treatment and 12 male patients with concomitant glucocorticoid treatment) are shown in Table 2.

Hypothalamus-pituitary-adrenal axis. For technical reasons, ACTH was analyzed only in patients treated with infliximab. DHEAS increased significantly after 1 and 2 years, with no correlation with albumin (Table 3). ACTH and cortisol did not change (Table 3), nor did the individual molar ratios of DHEAS to cortisol ($p > 0.05$), DHEAS to ACTH ($p > 0.05$), or cortisol to ACTH ($p > 0.05$).

There was no significant correlation between DHEAS and age in any group. As a supplementary control, the correlation between age and baseline DHEAS levels of female RA patients aged 49–71 years (mean 57.6 yrs, N = 23), $r_s = 0.41$ ($p = 0.052$), was compared with that of age-matched clinical controls from a reference dataset (age 49–70 yrs, mean 57.5 yrs), $r_s = -0.56$ ($p < 0.01$). Individually, 4 of 30 female patients had DHEAS levels below the lower reference value for the respective age interval.

Longitudinally, individual DHEAS levels at baseline were correlated with DHEAS levels at 1 year ($r_s = 0.93$, $p < 0.01$) and with DHEAS levels at 2 years ($r_s = 0.90$, $p < 0.01$; Figure 1). As DHEAS is age-dependent, we also analyzed this correlation in different age intervals and for male and female patients separately, with the same high correlation.

The hypothalamus-pituitary-gonadal axis. Treatment with TNF antagonists induced no significant changes in serum levels of LH, testosterone, or estradiol, irrespective of concomitant prednisolone treatment (Table 4). The level of LH was lower in glucocorticoid-negative patients than in glucocorticoid-positive patients at all timepoints ($p < 0.05$). There were no other significant differences between the groups. Nine of 18 male patients had baseline testosterone values below the limit for relatively low total serum testosterone, 15 nmol/l.

Similar to the adrenal axis, there was a high correlation between the individual values at baseline versus the corresponding values after 1 and 2 years for LH ($r_s = 0.47$, $p = 0.05$ and $r_s = 0.75$, $p < 0.001$), testosterone ($r_s = 0.76$, $p < 0.001$ and $r_s = 0.70$, $p < 0.01$; Figure 2), and estradiol ($r_s = 0.81$, $p < 0.0001$ and $r_s = 0.74$ $p < 0.001$).

Table 2. Disease activity, markers of inflammation, and physical function at baseline and after 1 and 2 years' treatment with TNF antagonists in 48 patients. Friedman's test used for analysis of variables over time.

Characteristic	Baseline	1 Year	2 Years	p
DAS28, median (range)	6.18 (4.39–7.72)	3.42 (1.46–5.81)	3.30 (1.47–5.32)	< 0.001
Moderate response, %		92	94	
Good response, %		47	39	
Remission, %		22	14	
ESR, mm, median (range)	47 (8–100)	24 (4–94)	22 (3–98)	< 0.001
High-sensitivity CRP, g/l, median (range)	23 (2.9–69)	4.3 (0.5–48)	3.3 (0.2–19)	< 0.001
IL-6, ng/l, median (range)	22 (2.1–138)	6.6 (0.9–59)	3.4 (0.8–43)	< 0.001
Health Assessment Questionnaire score, median (range)	1.38 (0.12–2.75)	0.88 (0–2.25)	0.75 (0–2.38)	< 0.001

Table 3. Hypothalamic-pituitary-adrenal axis values at baseline and after 1 and 2 years of treatment with TNF antagonists. ACTH was analyzed only in infliximab treated patients due to technical reasons. Values are medians (ranges).

HPA Values	Baseline	1 Year	2 Years
ACTH, pmol/l	4.2 (2.0–7.9), n = 21	3.7 (1.2–11), n = 23	4.5 (1.7–7.9), n = 12
Cortisol, nmol/l	255 (145–693), n = 6	304 (111–646), n = 36	290 (106–666), n = 34
DHEAS, μmol/l	2.2 (0.6–8.6), n = 36	2.6 (0.4–7.7), n = 36	2.7 (0.3–6.8)*, n = 34
Albumin, g/l	38 (28–45), n = 36	41 (34–45), n = 36	41 (33–50)*, n = 34

* $p < 0.05$, Friedman's test.

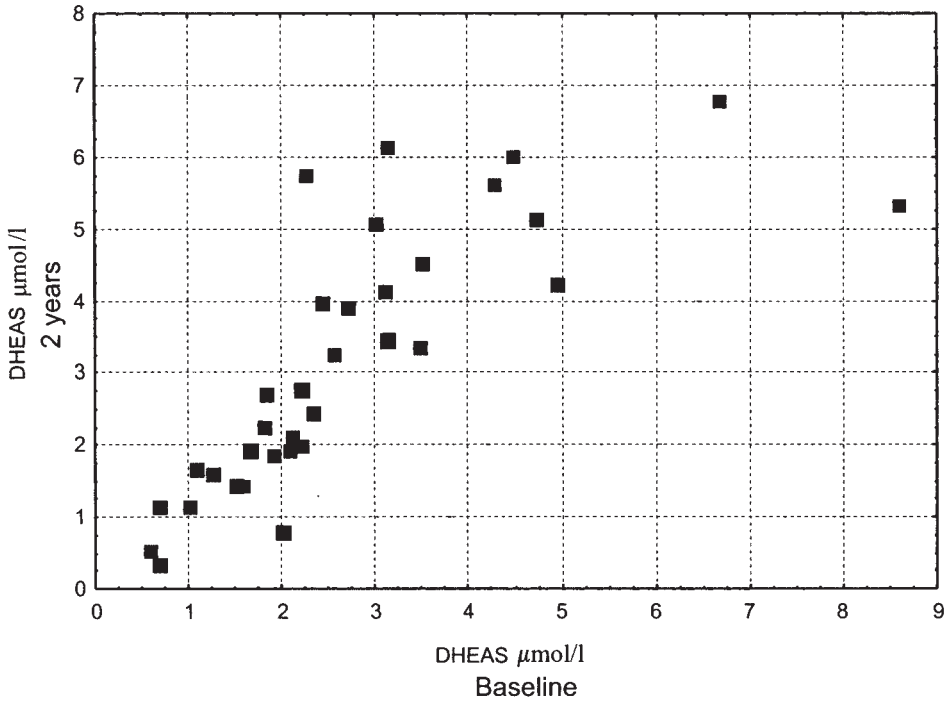

Figure 1. High individual concordance in DHEAS levels in 2 years in RA patients treated with a TNF antagonist.

Table 4. Hypothalamic-pituitary-gonadal axis values in male patients with RA with (GC+) and without (GC–) concomitant prednisolone treatment. Values are medians (ranges). No significant changes.

HPG Values	GC+ Baseline	GC+ 1 Year	GC+ 2 Years	GC– Baseline	GC– 1 Year	GC– 2 Years
Luteinizing hormone, 2–10 U/l	7.0 (3.0–12), n = 12	6.8 (2.1–27), n = 11	6.0 (2.0–12), n = 11	3.6 (2.0–5.4), n = 6	3.8 (2.6–11.5), n = 6	3.3 (2.4–6.4), n = 6
Testosterone, 10–30 nmol/l	16.6 (8.7–28), n = 12	17.0 (5.5–47), n = 11	15.6 (7.5–39), n = 11	14.0 (8.5–29), n = 6	11.8 (3.4–34), n = 6	14.1 (11.2–40), n = 6
Estradiol, < 130 pmol/l	101 (56–119), n = 12	107 (55–167), n = 11	79 (54–172), n = 11	98 (57–159), n = 6	90 (65–218), n = 6	90 (67–145), n = 6

Correlations between hormone levels and disease activity, inflammation, and physical function. DAS28 and biochemical markers of inflammation (IL-6, high sensitivity CRP, and ESR) did not correlate with hormone levels at any timepoint.

We further analyzed if the individual clinical response to TNF antagonists over 2 years was correlated with changes in hormone levels. There was no difference in changes in hormone levels during the study period between good and moderate responders and nonresponders or patients in remission. Neither patient's sex nor age affected changes in hormone levels.

Concerning hormone levels and physical function, patients with higher DHEAS at 1 and 2 years had a significantly lower HAQ score (r_s = –0.44 and r_s = –0.46, respectively, both p = 0.008).

Correlations between hormone levels and age at disease onset. In female patients with low baseline age and sex adjusted DHEAS levels, median age at disease onset was 27 years (21–30) compared with 47 years (21–65) in patients with normal DHEAS levels (p = 0.0028; Figure 3).

DISCUSSION

In our study of longterm treatment with TNF antagonists in patients with RA the major finding was an increased DHEAS level, indicating ameliorated adrenal function, which correlated with an improved physical function.

In earlier reports of RA patients concerning the effects of treatment with TNF antagonists on the HPA axis a decreased ratio of serum cortisol to serum ACTH was recorded during 12 weeks of treatment with infliximab[20,27]. In that study, however, and in a 16 week study of adalimumab treatment DHEAS levels were unchanged[27]. In comparison with the present study this difference may depend on varying effects of different TNF antagonists, or more likely, on varying study

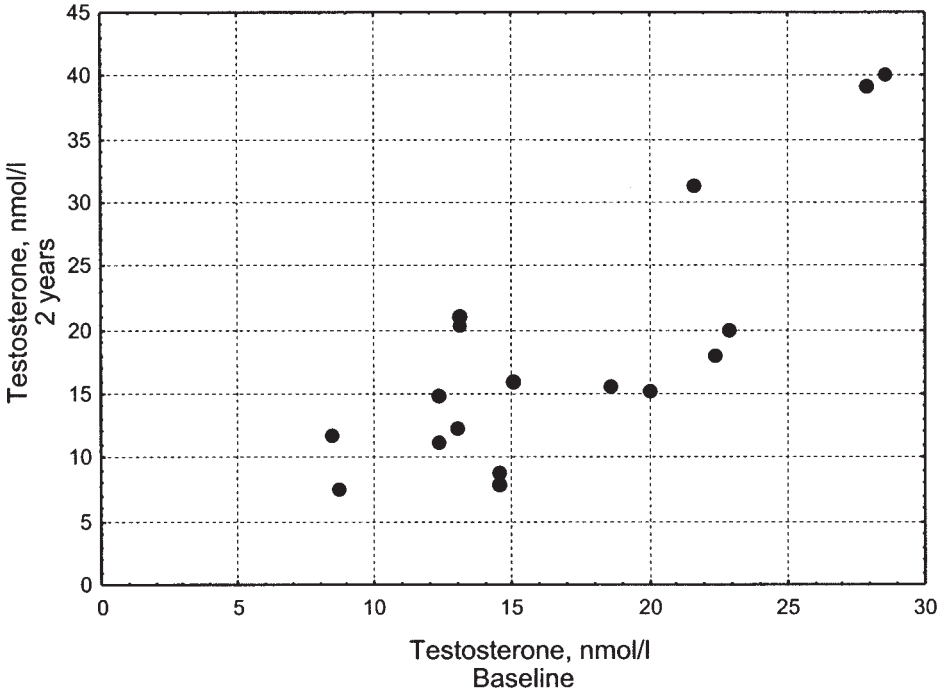

Figure 2. High individual concordance of testosterone levels in 2 years in men with RA treated with TNF antagonists.

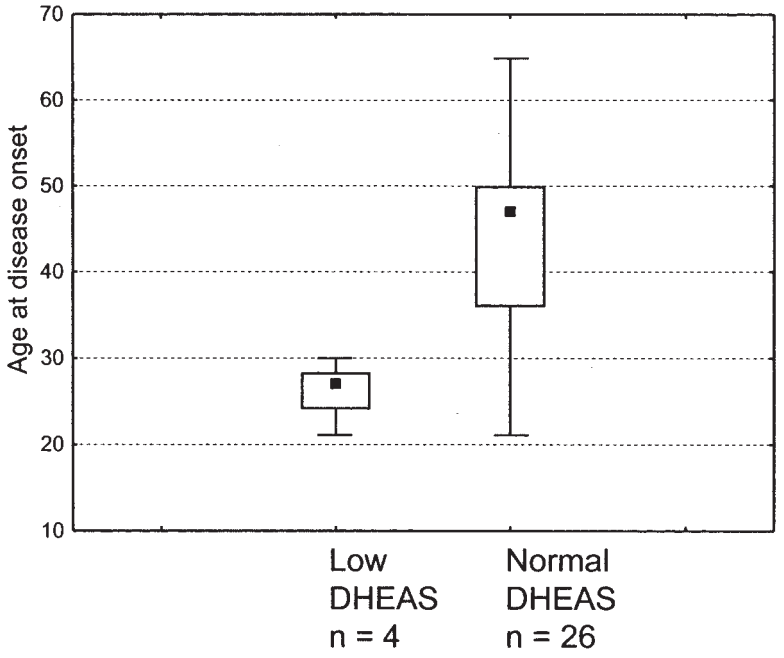

Figure 3. Age at disease onset in female patients with RA, not treated with glucocorticoids, with low (n = 4) versus normal (n = 26) age and sex adjusted DHEAS at baseline (p = 0.0028). Black symbol: median; box shows 25%–75%, minimum-maximum.

periods. As changes in DHEAS levels are slow, longterm observation periods as in our study are probably needed. We did not find any evidence for changed ratios in the HPA axis, but only limited data concerning ACTH levels were available from some of the patients due to technical reasons.

In adults DHEAS normally declines by 2% each year[28], but there was no correlation between DHEAS levels and age in our RA patients. Low DHEAS levels were reported to be associated with high disease activity in 13 premenopausal women with early RA[29] and in 68 postmenopausal women

with established RA[12] and in data from rheumatoid factor-negative men with established RA[11]. However, in healthy women no correlation was found between inflammation and DHEAS levels[30].

The mechanisms for the increased DHEAS in our results may only be speculated upon. It was not associated with sex, age, or disease duration. Serum albumin is the main strong binding protein for DHEAS, and changes in serum albumin are tightly linked to changes in circulating DHEAS[31]. However, there was no association between changes in albumin and changes in DHEAS in our study. Low levels of DHEAS in the presence of normal levels of cortisol are observed in several forms of physical stress including acute trauma and illness, chronic illness, and malnutrition and also in natural aging[32]. This probably reflects a redistribution of the steroid flux in order to maintain adequate cortisol production despite a reduced or disturbed adrenal function[33]. The increase in serum DHEAS, and in earlier reports an increased DHEAS/cortisol ratio, together with unchanged ACTH and cortisol levels following treatment with infliximab[20] may thus reflect an adrenal improvement following a powerful antiinflammatory treatment, an improved general condition, and a reduced stress due to the treatment. A normalization of the levels of proinflammatory cytokines on adrenal androgen secretion has also been reported in an *in vitro* study[4].

In our study the supposed ameliorated adrenal function reflected in an increase in DHEAS levels was associated with an improved physical function, and this is possibly also relevant to other effective antiinflammatory therapies, rather than being a specific effect of TNF antagonists. In healthy individuals a positive correlation between DHEAS and physical activity has been reported[34,35], but in 23 female RA patients no effect on DHEAS was recorded during 12 weeks of strength and endurance training[36].

Further, we observed a high individual concordance from baseline on to 1 and to 2 years for levels of LH, testosterone, and estradiol in the male patients. This suggests that the individual hormone levels of the gonadal axes are notably stable throughout the course of disease, independent of inflammatory activity. The recorded independence from inflammatory mediators in the hormonal axes during chronic inflammation was supported by the lack of association between hormone levels and clinical response to TNF antagonists, a finding not reported previously. This independence from inflammation opens the possibility that testosterone may be an appropriate adjuvant therapy in men with RA with low testosterone levels[37].

The low levels of adrenal androgens and the inadequate low levels of cortisol in RA have been suggested to be the consequences of longterm inflammation[3]. However, in women with premenopausal onset of RA low levels of DHEAS that even preceded the disease onset have been reported[13]. Our report strengthens this data further, with a significantly lower age at disease onset in women with a low DHEAS level. In this subgroup a hypoactive adrenal axis may instead contribute to the chronicity of the disease.

Longitudinal studies of the stability of adrenal and gonadal hormones over time in RA are lacking. It was recently reported that cortisol levels during the insulin tolerance test were similarly decreased, irrespective of disease duration or disease activity[38]. There are few reports of longitudinal individual stability in hormone levels in healthy individuals. Such stability was reported for testosterone during 1 year[39] and for estradiol during 2 years[40] in healthy men above age 55 years, and for DHEAS and testosterone up to 5 years in healthy women[41]. Cortisol and DHEAS levels have been suggested to be partly hereditary[42,43] from data in twin studies, and there were no differences in levels of testosterone, androstenedione, estradiol-17ß, and sex hormone binding globulin in 50 HLA-identical RA-discordant postmenopausal siblings[12]. However, DHEAS levels were significantly lower in the sibling with RA, and DHEAS may thus be regarded as the androgen that is most easily influenced by disease related factors such as inflammation.

Regarding the adrenal axis, we identified a distinct subgroup of female patients with RA with low levels of DHEAS. This group was characterized by a considerably lower age at disease onset. DHEAS levels in relation to age at disease onset have been investigated by Deighton, *et al*[44], who reported numerically lower (but not statistically significant) DHEAS levels in postmenopausal women with disease onset before menopause compared with women with postmenopausal onset. However, no age adjustment of DHEAS levels was performed, so a comparison with our data is not possible. A similar young female subgroup with low adrenal axis activity at, or even before, disease onset has been described[13]. Together with our data this may indicate that hormonal levels remain low over time in these individuals.

In summary, increased DHEAS levels in patients with RA during 2 years of treatment with TNF antagonists may indicate an ameliorated adrenal function.

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