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Adrenocorticotropin, Glucocorticoid, and Androgen Secretion in Patients with New Onset Synovitis/Rheumatoid Arthritis: Relations with Indices of Inflammation*

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ABSTRACT

To determine whether alterations in adrenocortical function occur early in the development of inflammatory joint disease, we examined patients with new onset synovitis (<1 yr) prior to treatment with corticosteroids or other disease-modifying antirheumatic drugs. Thirty-two patients with new onset synovitis, including 15 fitting criteria for rheumatoid arthritis (RA), taking no medications, were referred for study by local rheumatologists; 32 age- and sex-matched healthy individuals were recruited as controls. Patients and controls had blood drawn under identical conditions between 0900 and 1100 h. Plasma ACTH, cortisol, dehydroepiandrosterone (DHEA), DHEA sulfate, free and total testosterone, erythrocyte sedimentation rate, C-reactive protein, and rheumatoid factor were measured. Compared with controls, patients had higher inflammatory indices (erythrocyte sedimentation rate, C-reactive protein) and lower basal morning levels of free testosterone (lower in males age ≥45 yr), but similar levels of ACTH, cortisol, DHEA, DHEA sulfate, and total testosterone. In addition, the positive correlations between ACTH-cortisol, ACTH-DHEA, and cortisol-DHEA, observed in the normal controls, were weakened or abolished in the patients (both total and RA subset). No positive relations between inflammatory indices and ACTH or cortisol were noted, yet an inverse correlation between these indices and DHEA and testosterone was observed. Moreover, a steeper age-associated decline in DHEA was observed in our cross-sectional sample of patients with new onset synovitis. We conclude that patients with synovitis (including those fitting criteria for RA) have adrenocortical hormone alterations within a year of disease onset. Paradoxically, these patients have no positive relation between indices of inflammation and ACTH or cortisol, but rather serum androgen levels are inversely correlated with these indices. In addition, the relations between ACTH, the classic stimulus of cortisol and adrenal androgens, and these hormones are weakened or abolished, whereas the negative relation between age and *zona reticularis* function is steeper than that of controls. (*J Clin Endocrinol Metab* **85:** 1461–1466, 2000)

RHEUMATOID ARTHRITIS (RA) is a chronic inflammatory joint disease of unknown etiology. It is characterized by painful and swollen joints and is often associated with markers of inflammation, such as an elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), which correlate with plasma interleukin (IL)-6 levels (1). Animal studies support the view that neuroendocrine factors may influence the development of chronic inflammatory disease. Defects in the hypothalamic-pituitary-adrenal (HPA) axis in Lewis rats predispose them to experimental chronic inflammatory joint diseases, as well as a wide spectrum of autoimmune or hyperimmune responses, depending on the nature of the inducing agent (2, 3).

Several lines of evidence suggest that hormones play a role in the pathogenesis of RA (4, 5). This disease is up to four times more common in women than in men, but this difference varies with the age of onset; the peak incidence of RA in women is during menopause, whereas RA incidence among elderly men approaches that of elderly women (6). RA activity decreases in pregnancy and rebounds in the postpartum period (7, 8). The rise of cortisol, progesterone, and estrogen during pregnancy parallels a decrease in RA activity, whereas the sudden decrease of these hormones has been suggested to contribute to the increased RA activity in the postpartum period (9). Androgens, however, seem to suppress both cell- and humoral-mediated immune functions and may play a role in the low prevalence of RA in young men (10).

Studies of pituitary, adrenal, and androgenic hormones in RA are frequently difficult to interpret and contradictory. Often patients are treated with corticosteroids or other disease-modifying antirheumatic drugs for an extended period of time, extensively disturbing the hormonal milieu. The presence of nonsteroidal inflammatory agents (NSAIDs) may acutely inhibit the HPA axis (11, 12). The presence of chronic inflammation itself may also obscure the initial hormonal abnormalities. It is, therefore, important to obtain hormone data on patients as early as possible.

We chose to examine the hormonal environment in patients with persistent synovitis of less than 1-yr duration,

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who had never been treated with corticosteroids or second line agents and who stopped all NSAIDs prior to testing. We examined the plasma levels of ACTH, cortisol, dehydroepiandrosterone (DHEA), DHEA sulfate (DHEAS), and free and total testosterone in 32 such patients and 32 appropriate controls. We analyzed the hormone data for these patients in the context of clinical data such as age, ESR and CRP. We also compared these data with those obtained in parallel from 32 age- and sex-matched healthy controls.

Materials and Methods

All patients and controls were seen and examined at the Clinical Center of the NIH. All patients and controls signed an informed consent document as part of a research protocol approved by the intramural institutional review board of the National Institute of Arthritis and Musculoskeletal and Skin Diseases. All patients were referred by local rheumatologists. All of the patients had persistent joint tenderness and swelling. All were seen within 1 yr of developing synovitis, and none were on corticosteroids or disease-modifying antirheumatic drugs. Those taking NSAIDs were instructed to stop them at least 3 days before the study. Age- and sex-matched controls were recruited from the local community and examined at the NIH Clinical Center. All were healthy and on no medications.

All patients and controls had basal blood samples collected between 0900 and 1100 h. An indwelling catheter was placed approximately 1 h before phlebotomy to provide uniformity between samples. Plasma ACTH, cortisol, DHEA, DHEAS, and free and total testosterone were measured. ESR, CRP, and rheumatoid factor were also measured. Blood samples for ACTH, cortisol, and DHEA were collected every 20 min, for a total of three samples, while the subjects were seated comfortably to minimize stress-induced changes. Results were averaged for analysis.

Statistical analysis

Differences between groups were determined using a standard Student's *t* test or Mann-Whitney Rank Sum test depending upon data normality with Bonferroni correction for multiple comparisons. ACTH-cortisol, ACTH-DHEA, and cortisol-DHEA relationships were evaluated by linear regression analysis. Correlations were determined using a Spearman Rank Order Correlation. Statistical analysis was performed with SigmaStat and SigmaPlot (Jandel Scientific, San Rafael, CA).

Results

Patient profiles

The clinical characteristics of each population are shown in Table 1. Patients and controls were very closely matched to avoid bias. Of these 32 patients, 15 satisfied American College of Rheumatology criteria for RA (13). The other 17 patients were diagnosed with undifferentiated arthritis (UA) (14, 15). UA was diagnosed in patients with synovitis of recent onset who did not fulfill the established criteria for RA or the European Spondyloarthopathy Study group criteria for spondyloarthropathy, or any other specific diagnostic features (16).

Hormone studies

The mean morning basal plasma levels and SE of ACTH, cortisol, DHEA, DHEAS, and free and total testosterone in the total new onset synovitis group, all controls, the RA subset, the UA subset, and all controls are listed in Table 2a. DHEA and DHEAS were found to correlate significantly in all groups (data not shown). When the total patient group was compared with controls, no differences were found. No significant differences were found among the RA or UA subset when compared with age- and sex-matched controls either. No significant differences were noted when women were analyzed separately according to age (Table 2b). When males were analyzed according to age (Table 2c), free testosterone levels were found to be significantly decreased in males older than 45 yr of age compared with controls ($n = 4$, $P < 0.03$).

The relations between morning basal ACTH to cortisol, ACTH to DHEA, and DHEA to cortisol were plotted in the total patient group, as well as the RA subset (Fig. 1). In the control groups, positive statistically significant relations between basal ACTH and cortisol, basal ACTH and DHEA, and DHEA to cortisol were evident. In the patients, however, these relationships were weakened or abolished.

Correlations with inflammatory indices

No positive correlation was seen between the ESR and CRP and ACTH or cortisol in the total patient group. An inverse correlation was found between CRP and DHEA ($n = 31$, $r = -0.41$, $P = 0.02$) and between the ESR and free testosterone ($n = 29$, $r = -0.37$, $P = 0.048$) and total testosterone ($n = 29$, $r = -0.39$, $P = 0.038$) in the total patient group. No positive correlations were noted in the analysis of RA or UA subsets.

No correlation between free testosterone and ESR was noted in the controls ($n = 30$, $r = -0.3$, $P = 0.1$), although an inverse correlation was noted between total testosterone and ESR ($n = 32$, $r = -0.43$, $P = 0.02$). All controls had an undetectable CRP (<0.8 mg/dL), so no correlation analysis with DHEA was possible.

Correlations with age

An age-associated cross-sectional decline in DHEA was noted in both controls and new onset synovitis patients. This

TABLE 1. Clinical characteristics

	New onset synovitis total (n = 32)	Healthy controls (n = 32)	New onset synovitis RA subset (n = 15)	Healthy controls (n = 15)	New onset synovitis UA subset (n = 17)	Healthy controls (n = 17)
Age (yr)[a]	40.5 ± 2.3	40.0 ± 2.6	44.9 ± 2.0	44.4 ± 3.7	36.5 ± 2.4	36.1 ± 2.4
% female	59% (n = 19)	59% (n = 19)	67% (n = 10)	67% (n = 10)	53% (n = 9)	53% (n = 9)
% RF positive (>20 IU/mL)	38%	0%	67%	0%	12% (n = 2)	0%
ESR (mm/h)[a]	44 ± 6.3 (n = 31)	16.3 ± 1.6	48.5 ± 7.8[3]	18.4 ± 2.7	39.8 ± 9.8 (n = 16)	14.4 ± 1.7
P value		<0.001		0.001		0.03
CRP (mg/dL)[a]	2.0 ± 0.4 (n = 31)	<0.8	2.1 ± 0.5	<0.8	1.9 ± 0.6 (n = 16)	<0.8
P value		0.015		0.03		NS

[a] Age, ESR, and CRP values shown are mean ± SE.
NS, Not significant.

TABLE 2a. All patients and subsets

	New onset synovitis (n = 32)	Healthy controls (n = 32)	New onset synovitis RA subset (n = 15)	Healthy controls (n = 15)	New onset synovitis UA subset (n = 17)	Healthy controls (n = 17)
ACTH (pg/mL)	17.3 ± 1.4	17.6 ± 2.5	17.3 ± 2.3	16.7 ± 4.0	17.3 ± 1.8	18.4 ± 3.3
Cortisol (μg/dL)	11.5 ± 0.6	9.9 ± 0.5	11.7 ± 1.0	9.2 ± 0.8	11.3 ± 0.6	10.5 ± 0.6
DHEA (ng/dL)	338.4 ± 28.8	338.6 ± 22.0	325.6 ± 45.6	285.9 ± 29.1	349.7 ± 37.5	385.0 ± 28.6
DHEAS (μg/mL)	1.2 ± 0.14 (n = 30)	1.4 ± 0.17 (n = 30)	1.2 ± 0.21	1.2 ± 0.25	1.2 ± 0.2 (n = 15)	1.6 ± 0.2 (n = 15)
Free testosterone (pg/mL)	47.1 ± 10.2 (n = 30)	63.8 ± 13.7 (n = 30)	41.7 ± 15.4 (n = 14)	43.8 ± 15.0 (n = 14)	51.8 ± 13.9 (n = 16)	81.3 ± 21.7 (n = 16)
Total testosterone (ng/dL)	167.2 ± 33.8 (n = 30)	225.0 ± 45.7 (n = 30)	166.9 ± 56.4 (n = 14)	194.0 ± 70.4 (n = 14)	167.4 ± 41.5 (n = 16)	252.1 ± 60.9 (n = 16)

Two female patients did not have DHEAS measured, and two female patients did not have free and total testosterone levels measured. Values shown are mean hormone levels ± SE. No significant differences were found when compared with controls ($P > 0.05$).

TABLE 2b. Females

	New onset synovitis females <45 (n = 12)	Healthy controls females <45 (n = 12)	New onset synovitis females ≥45 (n = 7)	Healthy controls females ≥45 (n = 7)
ACTH (pg/mL)	17.6 ± 2.4	20.6 ± 5.2	17.6 ± 3.2	12.2 ± 1.6
Cortisol (μg/dL)	11.5 ± 0.8	10.2 ± 1.0	13.6 ± 1.6	9.7 ± 0.5
DHEA (ng/dL)	420.2 ± 48.1	386.4 ± 40.9	282.1 ± 65.8	268.6 ± 23.2
DHEAS (μg/mL)	1.43 ± 0.23 (n = 10)	0.97 ± 0.18 (n = 10)	0.66 ± 0.07	0.99 ± 0.11
Free testosterone (pg/mL)	3.8 ± 0.4 (n = 11)	5.1 ± 0.9 (n = 11)	3.2 ± 0.2 (n = 6)	3.5 ± 0.3 (n = 6)
Total testosterone (ng/dL)	25.7 ± 2.9 (n = 11)	28.1 ± 4.1 (n = 11)	26.0 ± 5.0 (n = 6)	32.7 ± 8.8 (n = 6)

Two female patients did not have DHEAS measured, and two female patients did not have free and total testosterone levels measured. Values shown are mean hormone levels ± SE. No significant differences were found when compared with controls ($P > 0.05$).

TABLE 2c. Males

	New onset synovitis males <45 (n = 9)	Healthy controls males <45 (n = 9)	New onset synovitis males ≥45 (n = 4)	Healthy controls males ≥45 (n = 4)
ACTH (pg/mL)	15.7 ± 2.4	13.3 ± 1.6	19.7 ± 5.3	27.8 ± 11.6
Cortisol (μg/dL)	10.6 ± 0.9	10.1 ± 1.1	9.9 ± 0.9	8.9 ± 1.9
DHEA (ng/dL)	313.3 ± 47.5	391.2 ± 30.0	247.8 ± 52.1	199.0 ± 23.5
DHEAS (μg/mL)	1.5 ± 0.3	2.4 ± 0.3	1.1 ± 0.3	0.75 ± 0.1
Free testosterone (pg/mL)	113.2 ± 13.6	152.4 ± 17.5	83.3 ± 5.9[a]	116.3 ± 4.5[a]
Total testosterone (ng/dL)	356.3 ± 48.7	464.1 ± 52.5	342.3 ± 53.8	517.0 ± 96.0

Values shown are mean hormone levels ± SE.

[a] New onset synovitis free testosterone levels in males ≥45 yr were significantly decreased when compared with age- and sex-matched controls (*t* test: $P = 0.03$ after Bonferroni correction for multiple comparisons). All others did not show significant differences when compared with controls ($P > 0.05$).

age-associated cross-sectional decline, however, was steeper in both the total patient group and the RA subset than in the control groups (Fig. 2).

Discussion

Many hormones demonstrate immunoregulatory functions. Estradiol may suppress cell-mediated immune function but enhance humoral-mediated immune function (17). Cortisol also suppresses cell-mediated immune function, but has minimal effects on antibody-mediated immunity (18). DHEA (and its sulfate), also produced by the adrenal cortex, also may have multiple functions and is the major androgen in females (19). Moreover, DHEA and testosterone tend to suppress antibody-mediated and cell-mediated immune function (DHEA less so than testosterone) (20, 21). Testosterone and DHEA both repress the expression and activity of the human IL-6 gene promoter (22, 23). DHEA plasma levels negatively correlate with IL-6 levels, and DHEA inhibits IL-6 secretion from mononuclear cells *in vitro* (24).

Multiple non-ACTH factors are involved in regulating adrenocortical functions. These include neurotransmitters (including adrenal medullary products), neural and nonneural neuropeptides, cytokines, growth factors, and vascular-endothelial molecules (25). All may be released in an inflammatory event, such as synovitis.

We have previously shown that IL-6 can act synergistically with ACTH on the adrenal glands to release cortisol (26). Local release of tumor necrosis factor-α and transforming

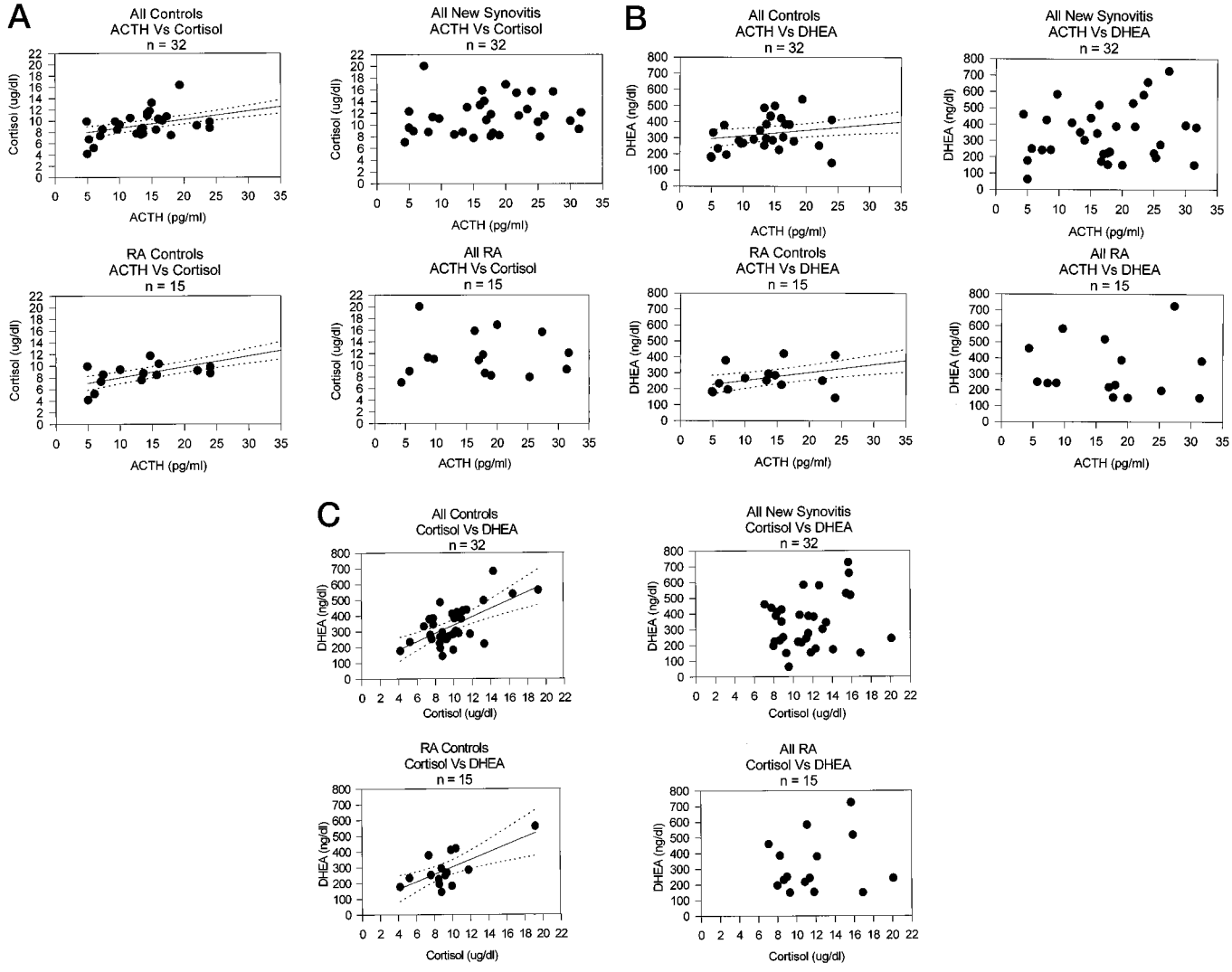

FIG. 1. a, ACTH and cortisol: all controls (*top left*; linear regression, r = 0.72, $P < 0.0001$); all new onset synovitis (*top right*; linear regression, r = 0.13, $P = 0.48$); controls for RA subset (*bottom left*; linear regression, r = 0.86, $P < 0.001$); RA subset (*bottom right*; linear regression, r < 0.0004, $P = 1.0$). *Straight lines* show linear regression. *Dotted lines* show 95% confidence intervals. Three controls had elevated ACTH levels of more than 35 pg/mL (67 pg/mL, 45 pg/mL, and 60 pg/mL). One of these controls was used as a RA control. For display purposes, the x-axis range was limited to 35 pg/mL. b, ACTH and DHEA: all controls (*top left*; linear regression, r = 0.40, $P = 0.02$); all new onset synovitis (*top right*; linear regression, r = 0.18, $P = 0.32$); controls for RA subset (*bottom left*; linear regression, r = 0.69, $P = 0.005$); RA subset (*bottom right*; linear regression, r = 0.03, $P = 0.92$). *Straight lines* show linear regression. *Dotted lines* show 95% confidence intervals. Three controls had elevated ACTH levels of more than 35 pg/mL (67pg/mL, 45pg/mL, and 60pg/mL). For display purposes, the x-axis range was limited to 35 pg/mL. One of these controls was used as a RA control. c, Cortisol and DHEA: all controls (*top left*; linear regression, r = 0.64, $P < 0.0001$); all new onset synovitis (*top right*; linear regression, r = 0.2, $P = 0.27$); controls for RA subset (*bottom left*; linear regression, r = 0.70, $P = 0.004$); RA subset (*bottom right*; linear regression, r = 0.14, $P = 0.62$). *Straight lines* show linear regression. *Dotted lines* show 95% confidence intervals.

growth factor-β can suppress cortisol and adrenal androgen production (27). Despite its positive effects on the secretion of cortisol from the *zona fasciculata*, IL-6 also suppresses adrenal androgen production (28).

Numerous studies have examined the role of serum hormones in the pathogenesis of RA. One review (29) demonstrated significant baseline DHEAS differences from controls in premenopausal women as well as differences in testosterone among men. No differences were found with respect to estrogens (29, 30). RA patients, however, do display a blunted cortisol response to surgical stress (31). Circadian studies of the HPA axis reveal normal secretion of ACTH and cortisol despite elevated levels of IL-6 (32). Gudbjornsson *et al.* (33) demonstrated that RA patients have normal/high basal plasma ACTH with normal serum cortisol levels (*i.e.* inappropriate in the presence of severe inflammation). These findings imply that relative "adrenal insufficiency" exists in chronic RA. Cutolo *et al.* (34) found decreased DHEA and DHEAS levels in 10 premenopausal females with RA (average disease duration, 4.7 yr). Statistically significant adrenal hyporesponsiveness was noted after provocation with ACTH. Masi (35) examined premorbid hormone levels in 35 female RA patients before the development of RA and found mean DHEAS levels decreased before the development of RA (mean, 12 yr), most significantly within the premenopausal group (11 patients). In contrast, Heikkila *et al.* (36)

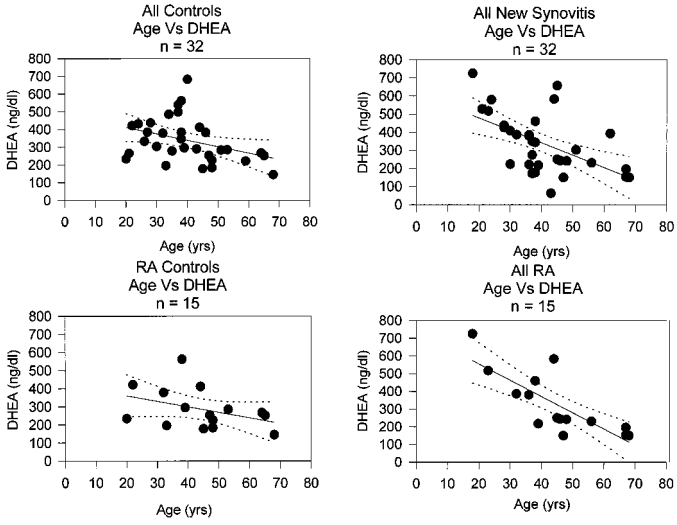

FIG. 2. Age and DHEA: all controls (*top left*; linear regression, r = −0.37, P = 0.04); all new onset synovitis (*top right*; linear regression, r = −0.55, $P = 0.001$); controls for RA subset (*bottom left*; linear regression, r = −0.39, P = 0.15); RA subset (*bottom right*; linear regression, r = −0.79, $P = 0.0005$). *Straight lines* show linear regression. *Dotted lines* show 95% confidence intervals.

measured testosterone and DHEAS levels before the development of RA in 116 patients and compared these with 329 controls (36). No significant differences were noted between RA and controls. Subset analysis of 18 women less than 50-yr-old at onset of RA also showed no significant differences from controls. Templ et al. (37) examined pituitary dysfunction in 10 RA patients who were newly diagnosed and untreated. No significant differences were noted in basal levels ACTH, cortisol, TSH, PRL, LH, and FSH compared with controls. When the pituitary was stimulated by CRH, TRH, GHRH, and GnRH, no differences were found compared with controls. This led to a conclusion that anterior pituitary function is normal in early RA.

We examined 32 patients with persistent synovitis within the 1st yr from disease onset. Only one other study, which included only five patients, has examined the status of the HPA axis in untreated RA patients with new or "early onset" RA (26). It is important to view these data in the context of an inflammatory event (synovitis) in which ACTH and cortisol should be elevated compared with healthy controls. We did not find any significant differences in the overall levels of ACTH, cortisol, DHEA, DHEAS, and total testosterone when comparing patients, and patient subsets, with controls. This was despite statistically significant elevations in the inflammatory indices (ESR and CRP) in patients when compared with controls. We did, however, find that free testosterone was decreased ($P = 0.03$) in males ≥45 yr of age. Because the majority of free testosterone in males is gonadal, this is likely the result of inflammatory cytokines inhibiting gonadal testosterone production. Both inflammatory cytokines and stress are known to result in inhibition of the hypothalamic-pituitary-gonadal axis.

We also observed that the positive relationships of ACTH to cortisol, ACTH to DHEA, and cortisol to DHEA, as seen in the control groups, were weakened or abolished in both the total patients group and the RA subset. These abnormalities included some patients who produced high levels of cortisol and DHEA relative to ACTH and some patients who produced low levels, particularly DHEA. Dissociation between plasma cortisol and DHEA levels were previously demonstrated in normal controls in response to both psychological and physiological acute stress (38). Patients with baseline-decreased adrenal function may, therefore, be hypothesized to show even greater dissociation during stress. To prove this, early RA patients could be compared with normal controls during an acute inflammatory event of similar duration.

In our studies we found an inverse relationship exists between androgens (both DHEA and testosterone) and acute phase reactants such as CRP and ESR. This suggests that androgen levels are negatively associated with the degree of inflammation and may have a protective effect in an inflammatory event. Our study did not directly address causality, although it established the association for patients in the 1st yr of disease activity. Moreover, we observed that even cross-sectionally, new onset synovitis patients had an accelerated age-associated decline in their adrenal androgens. The normal age-associated decline in DHEA, observed in healthy controls, is associated with increased IL-6 production (39). IL-6 is an inflammatory cytokine that is directly involved in the production of acute phase proteins, such as CRP, and in the suppression of androgens (40). Our findings, therefore, support the concept that a relative pituitary-adrenal inability to respond to inflammatory cytokines in RA patients may contribute to chronic inflammation. Alternatively, sustained or intermittent adrenal activation secondary to inflammation may lead to progressive atrophy of the *zona reticularis*. Our data demonstrate that this inability to respond to inflammatory cytokines occurs within the 1st yr of disease activity or possibly earlier, as reviewed by Masi *et al.* (41).

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