Adrenal Gland Hypofunction in Active Polymyalgia Rheumatica. Effect of Glucocorticoid Treatment on Adrenal Hormones and Interleukin 6

MAURIZIO CUTOLO, RAINER H. STRAUB, LUCA FOPPIANI, CAMILLA PRETE, LIA PULSATELLI, ALBERTO SULLI, LUIGI BOIARDI, PIERLUIGI MACCHIONI, MASSIMO GIUSTI, CARMEN PIZZORNI, BRUNO SERIOLO, and CARLO SALVARANI

ABSTRACT. ***Objective.*** To evaluate hypothalamic-pituitary-adrenal (HPA) axis function in patients with recent onset polymyalgia rheumatica (PMR) not previously treated with glucocorticoids; and to detect possible correlations between adrenal hormone levels, interleukin 6 (IL-6), and other acute phase reactants at baseline and during 12 months of glucocorticoid treatment.

Methods. Forty-one PMR patients of both sexes with recent onset disease and healthy sex and age matched controls were enrolled into a longitudinal study. Patients were monitored for serum cortisol, dehydroepiandrosterone sulfate (DHEAS), androstenedione (ASD), and clinical and laboratory measures of disease activity such as C-reactive protein and IL-6 concentrations at baseline and after 1, 3, 6, 9 and 12 months of glucocorticoid treatment. To assess dynamic HPA axis function, serum cortisol and plasma adrenocorticotropic hormone (ACTH) levels were evaluated in another 8 patients with recent onset PMR not treated with glucocorticoid in comparison to controls after challenge with ovine corticotropin releasing hormone (oCRH) test. In addition, serum cortisol and 17-hydroxyprogesterone (17-OHP) levels were evaluated after stimulation with low dose (1 μg) intravenous ACTH.

Results. Serum cortisol and ASD levels of all PMR patients at baseline did not differ from controls. During followup, cortisol levels dipped at one and 3 months. Serum DHEAS levels in all patients were significantly lower than in controls at baseline. In female PMR patients a significant correlation was found at baseline between cortisol levels and duration of disease. Serum concentrations of IL-6 at baseline were significantly higher in PMR patients than in controls. During 12 months of glucocorticoid treatment IL-6 levels dropped significantly at one month; thereafter they remained stable and did not increase again despite tapering of the glucocorticoid dose. After oCRH stimulation, a similar cortisol response was found in patients and controls. After ACTH administration, a significant cortisol peak was detected in patients and controls, whereas no significant difference in cortisol area-under-the-curve (AUC) was found between the groups. In contrast, ACTH induced a significantly higher ($p < 0.05$) peak of 17-OHP and AUC in PMR patients than in controls.

Conclusion. This study found reduced production of adrenal hormones (cortisol, DHEAS) at baseline in patients with active and untreated PMR. The defect seems mainly related to altered adrenal responsiveness to the ACTH stimulation (i.e., increased 17-OHP), at least in untreated patients. The 12 month glucocorticoid treatment of patients reduced the production of inflammatory mediators (i.e., IL-6) in a stable manner that persisted after glucocorticoids were tapered. (J Rheumatol 2002;29:748–56)

Key Indexing Terms:
POLYMYALGIA RHEUMATICA GLUCOCORTICOID INFLAMMATION
HYPOTHALAMIC-PITUITARY-ADRENAL AXIS ARTHRITIS INTERLEUKIN 6

From the Division of Rheumatology, Department of Internal Medicine and Medical Specialities; and Division of Endocrinology, Department of Endocrinology and Metabolism, University of Genova, Genova, Italy; Laboratory of Neuroendocrinoimmunology, Department of Internal Medicine, University Hospital Regensburg, Regensburg, Germany; Laboratory of Immunology and Genetics, Istituti Ortopedici Rizzoli, Bologna, Italy; and Rheumatology Service, Arcispedale S. Maria Nuova, Reggio Emilia, Italy.

Supported in part by the Italian Ministry of the University and Research (MC); the Deutsche Forschungsgemeinschaft (Str: 511/5-2); and the Italian Ministry of Public Health (AF: Pathogenesis and therapy of polymyalgia rheumatica).

M. Cutolo, MD, Professor of Rheumatology; C. Prete, MD, Fellow; A. Sulli, MD, Assistant; C. Pizzorni, MD, Fellow; B. Seriolo, MD, Assistant Professor, Division of Rheumatology, Department of Internal Medicine and Medical Specialities, University of Genova; R.H. Straub, MD, Associate Professor of Experimental Medicine, Chief, Laboratory of Neuroendocrinoimmunology, Department of Internal Medicine, University Hospital Regensburg; L. Foppiani, MD, Fellow; M. Giusti, MD, Associate Professor, Division of Endocrinology, Department of Endocrinology and Metabolism, University of Genova, Genova, Italy; L. Pulsatelli, MB, Assistant, Laboratory of Immunology and Genetics, Istituti Ortopedici Rizzoli; L. Boiardi, MD, PhD, Assistant; P. Macchioni, MD, Assistant; C. Salvarani, MD, Chief, Rheumatology Service, Arcispedale S. Maria Nuova.

Address reprint requests to Prof. M. Cutolo, Chief, Division of Rheumatology, Department of Internal Medicine and Medical Specialities, University of Genova, Viale Benedetto XV 6, 16132 Genova, Italy. E-mail: mcutolo@unige.it

Submitted May 9, 2001; revision accepted October 16, 2001.

Polymyalgia rheumatica (PMR) is a common disorder in the elderly characterized by aching and morning stiffness in the neck, shoulders, and pelvic girdle, along with constitutional symptoms (malaise, weight loss, fever) and marked serologic acute phase response[1]. Although PMR occurs in patients older than 50 years of age and PMR incidence increases with age, age associated pathogenic factors are not yet known[2]. The natural decline of several hormones, including dehydroepiandrosterone/sulfate (DHEA/DHEAS) and androstenedione (ASD), with aging may represent one such factor[3]. The decrease of adrenal/gonadal hormones is different in both sexes (in healthy subjects), for example cortisol and 17-hydroxyprogesterone (17-OHP) decrease in women but not in men[4].

However, in both sexes, serum cortisol levels are relatively low in relation to plasma adrenocorticotropic hormone (ACTH), which indicates that despite increased ACTH, the production of cortisol decreases during aging[5]. Nevertheless, serum cortisol levels remain relatively high in relation to serum levels of other adrenal and gonadal hormones during aging[4]. In addition, aging is characterized by altered innate immune system function with a loss of phagocytic capacity and an increase of "early" cytokines such as interleukin 6 (IL-6) and tumor necrosis factor (TNF)[6]. Recently, it was reported that DHEA and ASD have a direct inhibitory effect on IL-6 secretion in monocytes and macrophages[7]. All these findings might support a possible link between endocrinosenescence and immunosenescence in the pathogenesis of PMR[4].

The abrupt onset of PMR, with clinical features similar to the steroid withdrawal syndrome (i.e., musculoskeletal pain, malaise, fever) or adrenal insufficiency, and the dramatic and rapid disappearance of these symptoms after glucocorticoid administration, may be a strong clinical argument for an altered function of the hypothalamic-pituitary-adrenal (HPA) axis in these patients[8,9]. Plasma IL-6 concentrations and clinical symptoms during 14 months of glucocorticoid therapy are correlated in patients with PMR[10]. However, no dynamic studies are available on HPA axis function in patients with recent onset PMR not previously treated with glucocorticoids and in relation to their inflammatory condition (i.e., increased IL-6).

In this study, female and male patients with recent onset PMR were monitored for adrenal hormones (cortisol, DHEAS, ASD) and laboratory measures of disease activity, including IL-6 concentrations, during a 12 month period of glucocorticoid treatment. To assess HPA axis function, cortisol and ACTH were evaluated in patients with recent onset PMR not treated with glucocorticoid and in healthy age matched controls after stimulation with ovine corticotropin releasing hormone (oCRH). In addition, cortisol and 17-OHP levels were evaluated after stimulation with low dose intravenous ACTH.

MATERIALS AND METHODS

Patient selection. Forty-one patients of both sexes with active PMR were enrolled in the study after giving informed consent. Patients were clinically evaluated by a rheumatologist at the Reggio Emilia Hospital; diagnosis of PMR was based on the criteria of Chuang, *et al*[11]. Patients with clinical and/or histological evidence of temporal arteritis were excluded. All selected patients had recent onset PMR and had never been treated with glucocorticoids or hormone replacement. Nonsteroidal antiinflammatory drugs were withdrawn 6 days before the study. Sex and age matched healthy controls were analyzed for comparison. Blood samples were collected by venipuncture between 10:00 and 12:00 AM and serum was immediately stored at –80°C until analysis. These 41 patients had prospective followup for at least one year. Patients were clinically assessed by the same physician at presentation, monthly for the first 6 months, then every 3 months during the followup period. All patients received the same schedule of prednisone treatment starting at 17.5 mg/day (occasionally this needed to be increased to 25 mg/day to completely relieve discomfort), administered before breakfast. The initial dosage was then reduced after one month if symptoms had resolved. Small monthly decreases of 1–5 mg were successively scheduled. Serial blood samples were collected between 10:00 and 12:00 AM at baseline, one month after the beginning of therapy, and at 10–12 week intervals during the followup (12 months). A further group of 8 female patients with recent onset untreated PMR were recruited at the Division of Rheumatology of the University of Genova for analysis of HPA axis function, after informed consent was obtained. Eight healthy sex and age matched controls were also analyzed for comparison.

Laboratory evaluations. A standardized medical data collection form was used at every visit. Age, sex, location of aching and morning stiffness, the presence of systemic manifestations, dosage and duration of glucocorticoids, and the development of relapses and recurrences were recorded. The cumulative prednisone dose was computed. The presence of peripheral synovitis (swelling and tenderness of the joints) was carefully assessed at each visit. Joint radiography was performed in all patients with joint swelling at some time during the course of illness. Relapse and recurrence were considered present if articular signs or symptoms occurred [usually with an erythrocyte sedimentation rate (ESR) > 30 mm/h] in a patient receiving glucocorticoids, or after discontinuation of treatment, respectively. All patients were also evaluated at diagnosis and during the followup for the 1987 modified American Rheumatism Association (ARA) criteria for RA[12]. At baseline and during followup, laboratory measures including ESR, C-reactive protein (CRP), mean hemoglobin (Hb), and fibrinogen levels in patients were evaluated by standard methods. IL-6 concentrations were evaluated by immunoassay (DuoSet ELISA Kit, R&D Systems, Minneapolis, MN, USA). Results were expressed as pg/ml. Assay sensitivity was 0.2–0.4 pg/ml. Serum IL-6 levels were 1.4 ± 0.9 pg/ml in the 19 controls.

In the longitudinal study, cortisol was assayed by chemiluminescence assay (Immunolite, DPC, Los Angeles, CA, USA). Assay sensitivity was 5.52 nmol/l. Intraassay and interassay coefficients of variation were 6.1% and 8.2% at 320.5 nmol/l ng/ml and 5.2% and 6.2% at 496.8 nmol/l. Cross reactivity with prednisone was 6.1%. DHEAS was assayed by enzyme immunoassay (EIA) (Biochem Immunosystems Italia, Casalecchio di Reno, Bologna, Italy). Assay sensitivity was 0.135 μmol/l. Intraassay and interassay coefficients of variation were 2.7% and 3.1% at 1.35 μmol/l and 7.4% and 8.8% at 10.8 μmol/l. ASD was assayed by radioimmunoassay (Dixsonin, Minneapolis, MN, USA). Assay sensitivity was 0.1 nmol/l. Intraassay and interassay coefficients of variation were 5.6% and 9.8% at 2.4 nmol/l and 4.3% and 6.0% at 8.1 nmol/l.

In the dynamic study to test the HPA axis, cortisol was evaluated as described above. 17-OHP was assayed by chemiluminescence assay (Immunolite, DPC). Assay sensitivity was 0.02 nmol/l. Intraassay and interassay coefficients of variation were 4.3% and 8.0% at 0.77 nmol/l and 5% and 7% at 2.23 nmol/l. ACTH was detected by IRMA (Nichols Institute Diagnostics, San Juan Capistrano, CA, USA). Assay sensitivity was 0.22

pmol/l. Intraassay and interassay coefficients of variation were 3.0% and 7.8% at 7.7 pmol/l and 3.2% and 6.8% at 8.5 pmol/l.

HPA axis stimulation tests. Study subjects were admitted to the clinical research unit in the early morning (8:00–9:00 AM). During the entire study, subjects were instructed to stay in bed except for bathroom privileges. All subjects underwent stimulus testing at 2 day intervals, in random order, with placebo, oCRH (1 μg/kg body weight; UCB, Brussels, Belgium), and low dose (1 μg) ACTH (ACTH 1-24, Synacthen 250 μg, Ciba, Huningue, France). To obtain 1 μg ACTH 250 μg of the compound was diluted in physiological saline immediately before the test. At the beginning of each test, a fine needle was inserted into the forearm and kept patent by saline solution.

Blood samples were collected at the following time points to measure serum levels of cortisol, 17-OHP, and IL-6 as well as plasma ACTH: –30, 0, +30, +60, +90, +120 minutes. The stimulus (ACTH or oCRH) was administered intravenously as a bolus at Time 0. To improve the sensitivity of the test and to avoid misinterpretation of the results, all tests started at 12:00 noon (Time 0), when HPA axis secretion declines.

An overnight dexamethasone suppression test was performed 7 days after the end of all tests; 1 mg dexamethasone was administered at 11:00 PM and blood samples for determination of serum cortisol were collected at 8:00 AM the following day.

Statistical analysis. Variation of steroid and IL-6 levels throughout the study was evaluated by analysis of variance (ANOVA) followed by Bonferroni adjustment. Correlations between hormonal/IL-6 values, laboratory measures, and steroid dose were performed by Spearman rank correlation analysis. 17-OHP together with their peak and area-under-the-curve (AUC) after stimulus were evaluated by paired and unpaired Student t test. Statistical significance was assumed at $p < 0.05$.

RESULTS

Characteristics of the study population. Complete clinical and demographic data are shown in Table 1. Throughout the followup period, no patient fulfilled the modified 1987 ARA criteria for RA, and no clinical evidence of joint deformity or radiological evidence of erosions was observed[12].

Longitudinal study. Adrenal hormone concentrations. Serum cortisol levels of all PMR patients at baseline did not differ from the cortisol levels of controls. However, mean baseline levels were significantly lower in female patients compared to female controls ($p < 0.05$), a difference not found in male subjects (Table 2). During the followup, serum cortisol levels at one and 3 months were found to be reduced compared to baseline ($p < 0.001$ and $p < 0.05$, respectively). At 9 and 12 months, however, serum cortisol levels were restored in female patients compared to values at one month ($p < 0.01$ and $p < 0.05$, respectively) (Table 3). As expected, serum cortisol levels during the followup were negatively correlated with the dose of glucocorticoid in both male (nonsignificant) and female ($p < 0.001$) PMR patients (Figures 1A, 2A). Serum DHEAS levels in all PMR patients at baseline were significantly lower than in controls ($p < 0.01$). In female patients, serum DHEAS levels were significantly lower compared to both their female controls and male patients ($p < 0.001$). This was not the same for male patients compared to their controls (Table 2). During the followup, DHEAS levels at one month were found to be remarkably reduced compared to baseline levels in female patients only ($p < 0.05$) (Table 3). Serum DHEAS levels decreased shortly after the beginning of glucocorticoid treatment (one month) and remained stable during the followup in both male and female patients (Figures 1B, 2B).

At baseline, serum ASD levels of all patients did not differ from controls. However, baseline ASD levels were significantly lower in female patients versus their female controls and versus male patients ($p < 0.05$ for both) (Table 2). During the followup, ASD levels in all patients at one and 3 months were significantly reduced compared to baseline ($p < 0.01$ and $p < 0.05$, respectively) (Table 3). In a separate analysis this was significant only in female patients, not in male patients. As expected, serum ASD levels during the followup were negatively correlated with the dose of glucocorticoid in female patients (nonsignificant) (Figures 1C, 2C).

Mean adrenal hormone variations in all patients during the 12 months of glucocorticoid treatment are shown in Figure 3.

Hormonal correlations with clinical and laboratory variables. In female PMR patients a significant correlation was found at baseline between cortisol levels and duration of disease ($p < 0.05$).

ESR and CRP levels decreased significantly ($p < 0.01$ and $p < 0.05$, respectively) after one month of glucocorticoid treatment and remained stable during the followup (Figure 4).

Table 1. Complete clinical and demographic data of the PMR patients included in the longitudinal and dynamic studies (basal values) (no significant differences were found).

	All PMR Patients	Female PMR Patients	Male PMR Patients	Female Controls
Longitudinal study	n = 41	n = 28	n = 13	—
Mean age, yrs ± SD	71.2 ± 6.2	71.4 ± 8.2	72.1 ± 6.1	—
Mean PMR duration, mo ± SD	2.6 ± 0.2	2.4 ± 0.3	2.9 ± 0.6	—
Mean starting dose of prednisone, mg/day	17.4 ± 2.1	18.3 ± 2.1	16.8 ± 2.5	—
Dynamic study		n = 8		n = 8
Mean age, yrs ± SD	—	72.6 ± 1.8	—	72.9 ± 4.0
Mean PMR duration, mo ± SD	—	2.5 ± 0.5	—	

Table 2. Basal serum values of cortisol, DHEAS, and ASD in PMR patients and controls in the longitudinal study.

	All Healthy Controls, n = 50	All PMR Patients, n = 41	Female Controls, n = 30	Female PMR Patients, n = 28	Male Controls, n = 20	Male PMR Patients, n = 13
Cortisol, nmol/l ± SE	406.5 ± 21.5	460.6 ± 23.1	387.8 ± 30.5	485.2 ± 26.8*	442.4 ± 21.0	408.5 ± 43.6
DHEAS, μmol/l ± SE	2.2 ± 0.4	1.25 ± 0.12**	1.82 ± 0.33	0.97 ± 0.07***	2.59 ± 0.9	1.8 ± 0.31
ASD, nmol/l ± SE	4.2 ± 0.4	5.7 ± 0.46	4.3 ± 0.6	4.9 ± 0.37	4.1 ± 0.3	7.17 ± 1.1†

* Versus female healthy controls $p < 0.05$; ** versus healthy controls $p < 0.01$: *** versus female healthy controls and male PMR patients $p < 0.01$; † versus healthy controls $p < 0.05$.

Table 3. Serum cortisol, DHEAS, and ASD levels during followup of the PMR patients during glucocorticoid treatment.

	Month 0	1	3	6	9	12
Cortisol, nmol/l ± SE						
All PMR patients, n = 41	460.6 ± 23.1	248.5 ± 24	292.8 ± 22.1	341.7 ± 22.9	429.4 ± 74.5	408.5 ± 17.9
Female, n = 28	485.2 ± 26.8	188.5 ± 22.6*	288.1 ± 27.6**	338.6 ± 28.4	358.8 ± 27.6***	411.8 ± 25.1†
Male, n = 13	408.5 ± 43.6	345.3 ± 48.3	302.8 ± 37.5	348 ± 39.5	331.5 ± 24.8	389.7 ± 26.2
DHEAS, μmol/l ± SE						
All PMR patients, n = 41	1.25 ± 0.12	0.78 ± 0.07	0.84 ± 0.09	0.88 ± 0.08	0.89 ± 0.09	0.99 ± 0.12
Female, n = 28	0.97 ± 0.08	0.53 ± 0.04††	0.65 ± 0.07	0.69 ± 0.07	0.68 ± 0.07	0.67 ± 0.07
Male, n = 13	1.80 ± 0.31	1.30 ± 0.14	1.24 ± 0.21	1.28 ± 0.16	1.36 ± 0.19	1.62 ± 0.3
ASD, nmol/l ± SE						
All PMR patients, n = 41	5.70 ± 0.46	3.54 ± 0.4	3.89 ± 0.36	4.30 ± 0.36	4.29 ± 0.3	5.00 ± 0.4
Female, n = 28	4.90 ± 0.38	2.72 ± 0.41#	2.98 ± 0.28§	3.94 ± 0.39	4.09 ± 0.35	4.43 ± 0.4
Male, n = 13	7.17 ± 1.1	5.25 ± 0.73	6.07 ± 0.67	5.14 ± 0.73	4.73 ± 0.79	6.30 ± 0.9

* versus baseline $p < 0.001$; ** versus baseline $p < 0.05$; *** versus month 1 $p < 0.01$; † versus month 1 $p < 0.05$; †† versus baseline $p < 0.05$; # versus baseline $p < 0.01$; §versus baseline $p < 0.05$.

In female patients, cortisol and DHEAS levels were significantly correlated with ESR ($p < 0.001$ and $p < 0.05$, respectively), whereas CRP was strongly correlated with cortisol, DHEAS, and ASD levels ($p < 0.001$, $p < 0.005$, $p < 0.001$). In male patients cortisol levels were significantly correlated (negative) with CRP ($p < 0.01$) (data not shown). Finally, in both female and male PMR patients cortisol and ASD were significantly correlated (negative) with fibrinogen levels ($p < 0.0001$, $p < 0.05$) (data not shown).

IL-6 concentrations and correlations. Serum concentrations of IL-6 at baseline were significantly higher in PMR patients than in healthy controls (25.9 ± 4.6 versus 1.4 ± 0.9 pg/ml; $p < 0.01$) (Table 4). Serum IL-6 levels decreased significantly after the beginning of glucocorticoid treatment (one month) in all PMR patients ($p < 0.05$), with evident differences between female and male patients (even if limited by the lower sample size) ($p < 0.05$ and $p < 0.01$, respectively) (Table 4). IL-6 levels remained stable during the followup in all patients (Figure 4).

Regarding the correlations between IL-6 levels and adrenal hormones, a significant positive correlation was observed with cortisol in all PMR patients ($p < 0.006$), whereas DHEAS was found to be significantly correlated (negative) with IL-6 only in female patients ($p < 0.05$) (data not shown). Using the values at the different time points during the 12 month followup, IL-6 levels were significantly correlated with ESR and serum levels of CRP and fibrinogen in both male and female patients ($p < 0.0001$) (data not shown).

Dynamic study. HPA axis stimulation tests. After oCRH stimulation, a significant increase of ACTH levels from basal values ($p < 0.05$) was found in both PMR patients and controls (Figure 5A). However, the ACTH AUC after oCRH was found to be similar in both groups (see inset, Figure 5A). After oCRH stimulation, a similarly significant cortisol peak ($p < 0.01$) was found in patients and controls (Figure 5B), whereas cortisol AUC were similar between the groups (see inset, Figure 5B).

As expected, after ACTH administration, significant cortisol peaks ($p < 0.01$) were detected in PMR patients and in controls (Figure 6A), whereas no significant difference in cortisol AUC was found between the groups (see inset, Figure 6A).

After low dose ACTH stimulation, both groups showed a significant increase of 17-OHP ($p < 0.05$) versus basal levels (Figure 6B). However, the 17-OHP peak and 17-OHP AUC

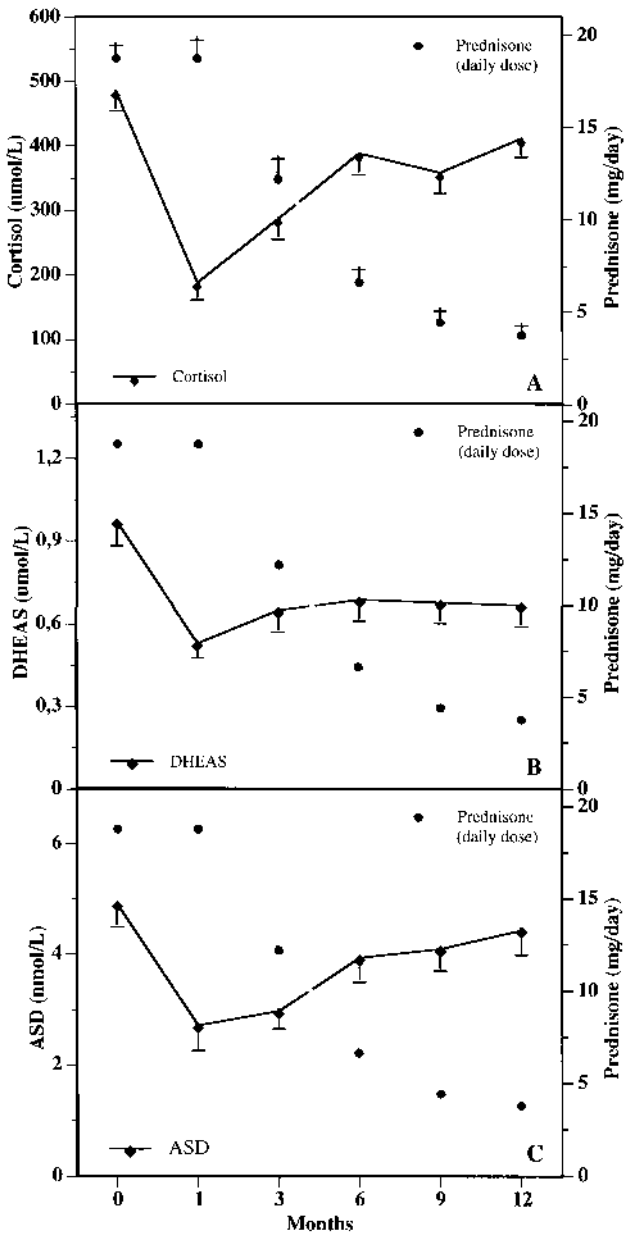

Figure 1. Serum cortisol, DHEAS, and ASD variations in female patients with PMR in relation to mean daily prednisone dose during the 12 months of treatment.

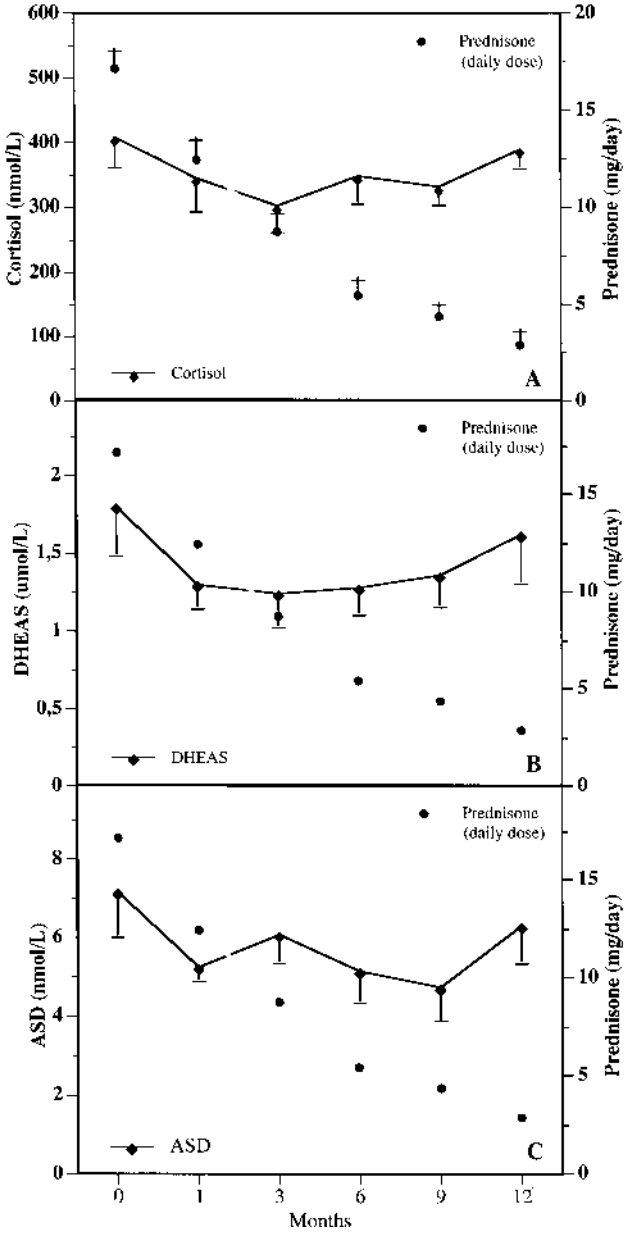

Figure 2. Serum cortisol, DHEAS, and ASD variations in male patients with PMR in relation to mean daily prednisone dose during the 12 months of treatment.

were significantly higher (both $p < 0.05$) in patients compared to controls (see Figure 6B and inset, respectively). Further, baseline levels of 17-OHP were significantly higher in patients than in controls ($p < 0.05$).

All PMR patients showed a normal plasma cortisol inhibition (< 138 nmol/l) following the dexamethasone test.

DISCUSSION

By considering the inflammatory status, a lower than expected basal production of adrenal steroids was observed in active and glucocorticoid-untreated patients with PMR, particularly in female patients. The 12 month glucocorticoid treatment of PMR patients, by reducing in a stable manner the inflammatory mediator levels (i.e., IL-6) that persist even after tapering of glucocorticoids, at the same time restored baseline levels of serum adrenal hormones.

A significant increase of 17-OHP levels in both basal condition and after ACTH stimulation was found in patients with recent onset untreated PMR compared to healthy age matched controls. Since 17-OHP represents a precursor of cortisol biosynthesis at the adrenal level, a possible partial impairment of the enzyme (21α-hydroxylase) may be

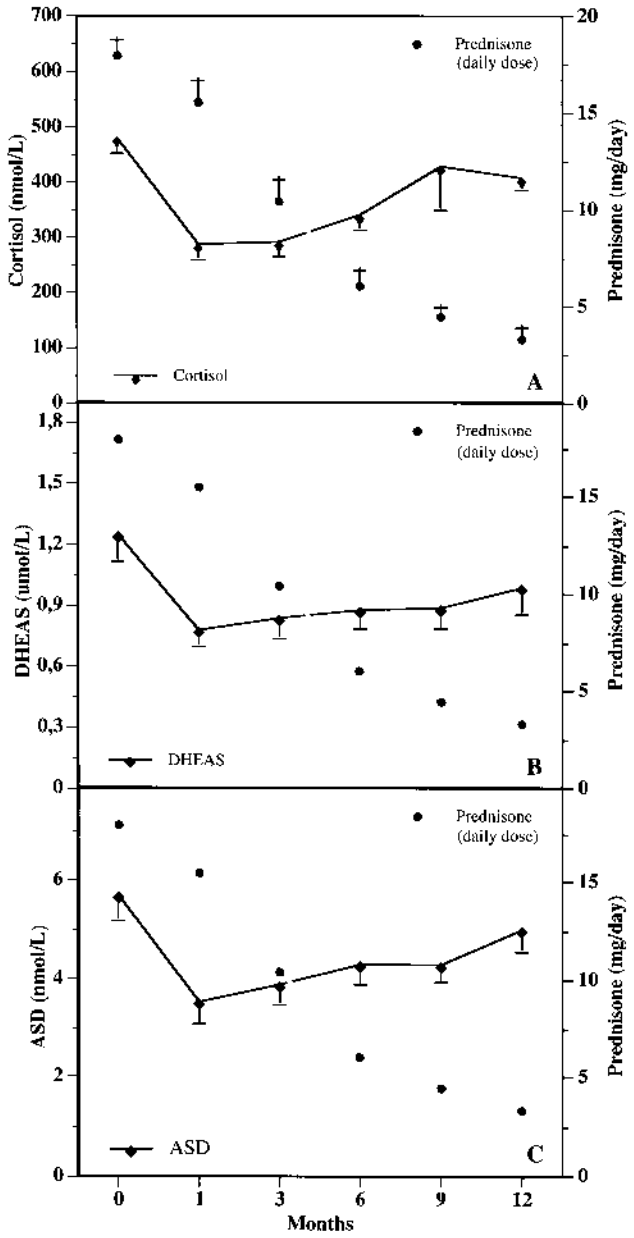

Figure 3. Serum cortisol, DHEAS, and ASD variations in all PMR patients in relation to mean daily prednisone dose during the 12 months of treatment.

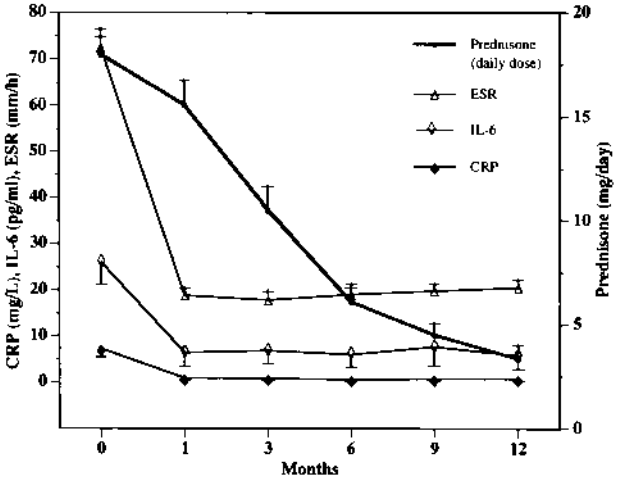

Figure 4. Serum IL-6 and CRP levels and ESR in all PMR patients in relation to mean daily prednisone dose during the 12 months of treatment.

present that leads to accumulation of the precursor 17-OHP.

The reasons for a functional 21α-hydroxylase impairment in PMR may include genetic defects, or an age related increase of serum TNF in healthy women, or elevated serum IL-6 and TNF levels during chronic systemic inflammatory stimuli (i.e., PMR)[9]. Indeed, TNF was shown to inhibit the 21α-hydroxylase in adrenal cell cultures, and high concentrations of IL-6 and TNF have been shown to interfere with enzymes involved in peripheral steroid hormone metabolism[13-16].

In addition, several factors might be responsible for a continuous stimulation of the HPA axis in PMR patients, including age related decrease of antiinflammatory hormones such as gonadal and adrenal hormones (i.e., testosterone, DHEA, ASD), chronic stress system activation (i.e., psychosocial stressors and variables such as coping and personality), and chronic systemic inflammatory stimuli (i.e., chronic infections) characterized by elevated serum IL-6 and TNF levels[8]. As shown, IL-6 and ACTH act synergistically to stimulate direct release of corticosterone from the adrenal glands[17].

Thus the continuous stimulation of the HPA axis at different levels might make the system unresponsive to the acute rise of these cytokines during inflammatory exacerbation of a disease, as in rheumatoid arthritis (RA)[18]. The changes observed in serum levels of adrenal hormones in the patients with recent onset untreated PMR might suggest an overall significant shift to cortisol synthesis (although not sufficient as antiinflammatory) in relation to DHEAS, as observed in patients with PMR or RA treated with glucocorticoid[9,18].

The reduction of serum DHEAS is a general feature of chronic inflammatory diseases, and the enzymes involved in the synthesis of DHEAS and ASD (17α and 17,20-hydroxylase) are suppressed during aging and in response to inflammatory mediators such as IL-1 or even by transforming growth factor-ß[19-25]. Thus, during aging and under systemic inflammation, as observed during recent onset of PMR, low DHEAS and normal cortisol serum levels may be expected. In addition, since DHEA (the nonsulfated adrenal hormone) inhibits IL-6 secretion the chronic reduction of this hormone in PMR patients might represent a further factor for increased serum IL-6 levels[26].

A recent study analyzed the interrelation between inflammatory cytokines (IL-6, TNF) and adrenal hormones (cortisol, DHEAS, ASD) in more than 100 PMR patients with both new onset and chronic disease[9]. Serum levels of

Table 4. IL-6 serum level variations during the 12 months of glucocorticoid treatment in all PMR patients and selected female and male patient groups.

	Month					
	0	1	3	6	9	12
IL-6, pg/ml ± SE						
All PMR patients, n = 41	25.96 ± 4.62	6.37 ± 2.6*	6.82 ± 2.627	6 ± 2.39	7.63 ± 3.8	5.74 ± 2.63
Female, n = 28	25.17 ± 5.28	7.53 ± 3.73**	8.33 ± 3.78	7.57 ± 3.43	9.88 ± 5.99	7.58 ± 3.91
Male, n = 13	27.64 ± 9.45	3.87 ± 1.68***	3.68 ± 1.848	2.62 ± 1.17	3.82 ± 1.36	2.04 ± 0.68

* Versus baseline $p < 0.05$; ** versus baseline $p < 0.01$; *** versus baseline $p < 0.05$.

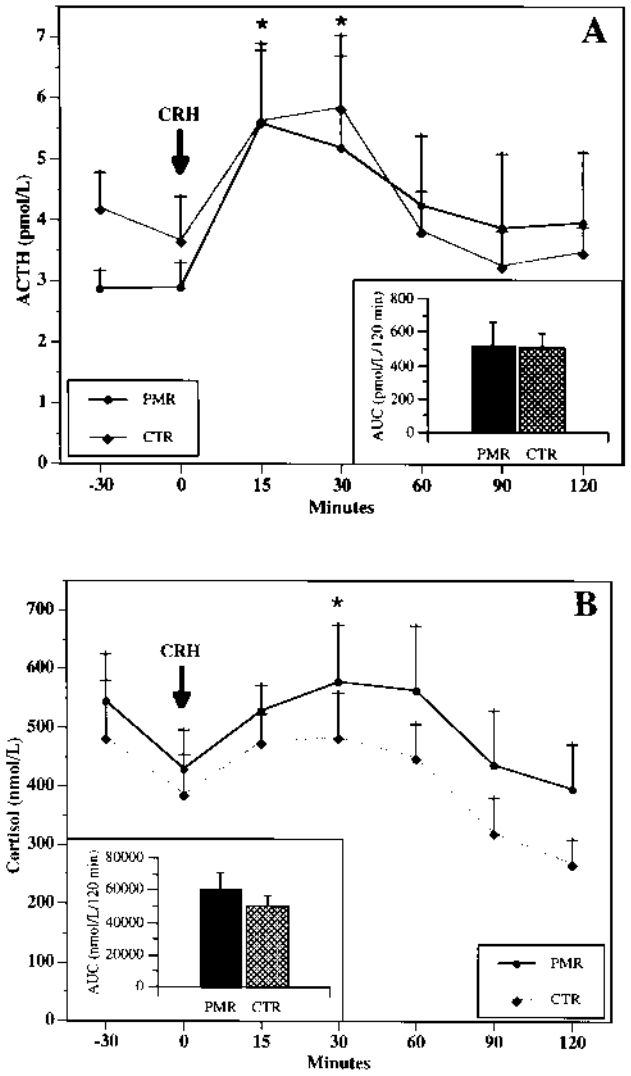

Figure 5. A. Mean (± SE) ACTH response to IV oCRH (arrow, 1 mg/kg body weight) over 120 min in 8 female patients with recent onset PMR and 8 healthy controls (CTR). Inset: ACTH net AUC in controls and PMR patients. *$p < 0.05$ vs basal values. B. Mean (± SE) cortisol response to IV oCRH (arrow, 1 μg/kg body weight) over 120 min in 8 female patients with recent onset PMR and 8 healthy controls. Inset: cortisol net AUC in controls and PMR patients. *$p < 0.01$ vs basal values.

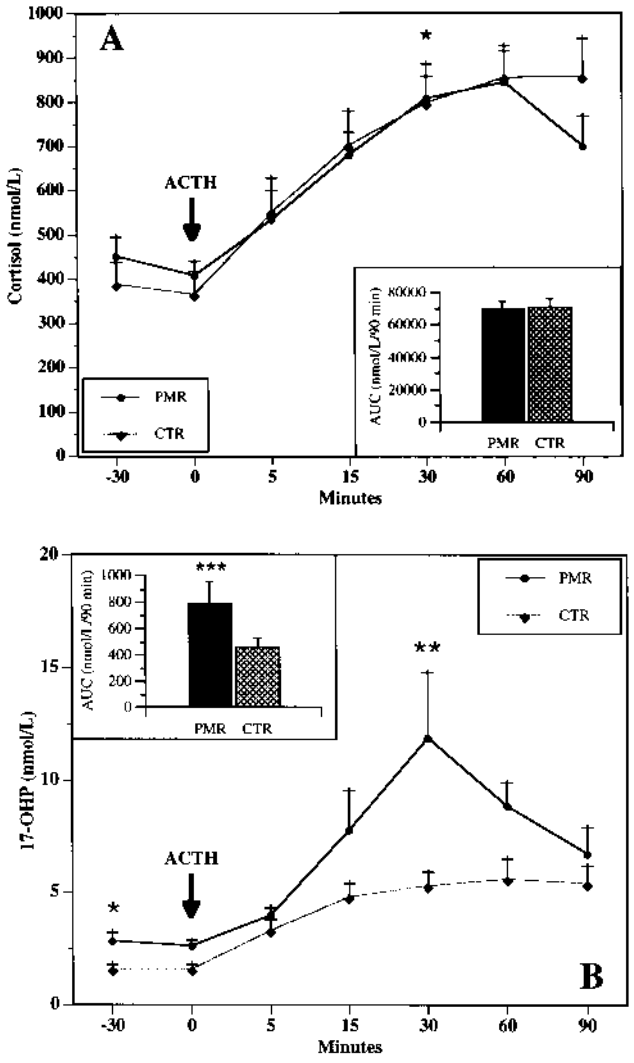

Figure 6. A. Mean (± SE) cortisol response to IV low dose ACTH (arrow, 1 μg) over 90 min in 8 female patients with recent onset PMR and 8 healthy controls. Inset: cortisol net AUC in controls and PMR patients. *$p < 0.01$ vs basal values. B. Mean (± SE) 17-OHP response to IV low dose ACTH (arrow, 1 μg) over 90 min in 8 female patients with recent onset PMR and 8 healthy controls. Inset: cortisol net AUC in controls and PMR patients. *$p < 0.01$, baseline 17-OHP levels in PMR patients versus healthy controls; **$p < 0.05$ versus basal values; ***$p < 0.01$ between groups (17-OHP AUC).

cortisol in relation to IL-6 were found to be significantly lower in patients with chronic disease and long lasting glucocorticoid administration compared to patients with recent onset PMR and no glucocorticoid therapy. Indeed, healthy adrenal glands are capable of secreting increased amounts of endogenous cortisol necessary to control pathologic conditions in circumstances with strong activation of the HPA axis including acute stress (i.e., surgery, infections, severe interpersonal stress)[27,28]. However, adequate activation of the HPA axis does not appear to be the case in PMR.

Aging seems to be the predisposing condition for the observed HPA axis hyporesponsiveness and for the innate immune system dysfunction. In particular, during aging serum cortisol levels are relatively low in relation to ACTH, which indicates that despite increased ACTH, the production of cortisol decreases, and as well a loss of phagocytic capacity and increase of "early" cytokines such as IL-6 and TNF is observed[5,6]. These findings might well support a possible link between endocrinosenescence and immunosenescence in the pathogenesis of PMR[4].

Therefore, the abrupt onset of PMR with clinical features similar to the steroid withdrawal syndrome or adrenal insufficiency (i.e., musculoskeletal pain, malaise, fever, sleepiness, anorexia, etc.) might be induced by intense stimulation and an inefficient response of the HPA axis in response to different acute stressors (i.e., surgery, infections, severe interpersonal stress) in elderly people that are already predisposed (by aging) to an inadequate adrenal and antiinflammatory response[29].

We observed reduced production of adrenal hormones (i.e., cortisol, DHEAS) at baseline in patients with active and untreated PMR. The defect seems mainly related to altered adrenal responsiveness to ACTH stimulation (i.e., increased 17-OHP, possible related to CYP21A2 21-hydroxylase deficiency), at least in patients with untreated PMR[30]. The 12 month glucocorticoid treatment of PMR patients reduces the production of inflammatory mediator levels (i.e., IL-6) in a stable manner that persists even after the tapering phase of the glucocorticoids.

REFERENCES

1. Salvarani C, Macchioni PL, Boiardi L. Polymyalgia rheumatica. Lancet 1997;350:43-7.
2. Salvarani C, Gabriel SE, O'Fallon WM, Hunder GG. Epidemiology of polymyalgia rheumatica in Olmsted County, Minnesota, 1970-1991. Arthritis Rheum 1995;38:369-73.
3. Orentreich N, Brind JL, Rizer RL, Vogelman JH. Age changes and sex differences in serum dehydroepiandrosterone sulfate concentrations throughout the adulthood. J Clin Endocrinol Metab 1984;59:551-5.
4. Straub RH, Miller LE, Schölmerich J, Zietz B. Cytokines and hormones as possible links between endocrinosenescence and immunosenescence. J Neuroimmunol 2000;109:10-5.
5. Zietz B, Hrach S, Schölmerich J, Straub RH. Differential age-related changes of hypothalamus-pituitary-adrenal axis hormones in healthy women and men — Role of interleukin 6. Exp Clin Endocrinol Diabetes 2001;109:93-101.
6. Pawalec G, Solana R. Immunosenescence. Immunol Today 1997;18:514-6.
7. Straub RH, Konecna L, Hrach S, et al. Serum dehydroepiandrosterone (DHEA) and DHEA sulfate are negatively correlated with serum interleukin-6 (IL-6), and DHEA inhibits IL-6 secretion from mononuclear cells in man in vitro: possible link between endocrinosenescence and immunosenescence. J Clin Endocrinol Metab 1998;83:2012-7.
8. Cutolo M, Straub R. Polymyalgia rheumatica: evidence for a hypothalamic-pituitary-adrenal axis-driven disease. Clin Exp Rheumatol 2000;18:655-8.
9. Straub RH, Glück T, Cutolo M, et al. The adrenal steroid status in relation to inflammatory cytokines (interleukin-6 and tumor necrosis factor) in polymyalgia rheumatica. Rheumatology 2000;39:624-31.
10. Roche NE, Fulbright JW, Wagner AD, Hunder GG, Goronzy JJ, Weyand CM. Correlation of interleukin-6 and disease activity in polymyalgia rheumatica and giant cell arteritis. Arthritis Rheum 1993;9:1286-94.
11. Chaung TH, Hunder GG, Ilstrup DM, Kirkland LT. Polymyalgia rheumatica: a 10 year epidemiological and clinical study. Ann Intern Med 1982;97:672-80.
12. Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;91:315-24.
13. Jaattela M, Ilvesmaki V, Voutilainen R, Stenman UH, Saksela E. Tumor necrosis factor as a potent inhibitor of adrenocorticotropin-induced cortisol production and steroidogenic P450 enzyme gene expression in cultured human fetal adrenal cells. Endocrinology 1991;128:623-9.
14. Nestler JE. Interleukin-1 stimulates aromatase activity of human placental cytotrophoblasts. Endocrinology 1993;132:566-70.
15. MacDiarmid F, Wang D, Duncan LG, Purohit A, Ghilchick MW, Reed MJ. Stimulation of aromatase activity in breast fibroblasts by tumor necrosis factor. Mol Cell Endocrinol 1994;106:17-21.
16. Purohit A, Ghilchic MW, Duncan L, et al. Aromatase activity and interleukin-6 production by normal and malignant breast tissues. J Clin Endocrinol Metab 1995;80:3052-8.
17. Salas MA, Evans SW, Levell MJ, Whicher JT. Interleukin-6 and ACTH act synergistically to stimulate the direct release of corticosterone from adrenal gland cells. Clin Exp Immunol 1990;79:470-3.
18. Cutolo M, Foppiani L, Prete C, et al. Hypothalamic-pituitary-adrenocortical axis function in premenopausal women with rheumatoid arthritis not treated with glucocorticoids. J Rheumatol 1999;26:282-8.
19. Lahita RG, Bradlow HL, Ginzler E, Pang S, New M. Low plasma androgens in women with systemic lupus erythematosus. Arthritis Rheum 1987;30:241-8.
20. Straub RH, Zeuner M, Antoniou E, Schölmerich J, Lang B. Dehydroepiandrosterone sulfate is positively correlated with soluble interleukin 2 receptor and soluble intercellular adhesion molecule in systemic lupus erythematosus. J Rheumatol 1996;23:856-61.
21. Straub RH, Zeuner M, Lock G, Schölmerich J, Lang B. High prolactin and low dehydroepiandrosterone sulfate serum levels in patients with systemic sclerosis. Br J Rheumatol 1997;36:426-32.
22. Robinzon B, Cutolo M. Viewpoint: Should dehydroepiandrosterone (DHEA) replacement therapy be provided with glucocorticoids? Rheumatology 1999;38:488-95.
23. Bijlsma JWJ, Cutolo M, Masi AT, Chikanza I. Neuroendocrine immune basis of the rheumatic diseases. Immunol Today 1999;20:298-301.
24. Hales DB. Interleukin-1 inhibits Leydig cell steroidogenesis primarily by decreasing 17 alpha-hydroxylase/C 17-20 lyase cytochrome P450 expression. Endocrinology 1992;131:2165-72.

25. Perrin A, Pascal O, Defaye G, Feige JJ, Chambaz EM. Transforming growth factor beta 1 is a negative regulator of steroid 17 alpha-hydroxylase expression in bovine adrenocortical cells. Endocrinology 1991;128:357-62.
26. Daynes RA, Araneo BA, Ershler WB, Maloney C, Li GZ, Ryu SY. Altered regulation of IL-6 production in normal ageing. Possible linkage to the age-associated decline in dehydroepiandrosterone and its sulfate derivative. J Immunol 1993;150:5219-30.
27. Cutolo M, Prete C, Walker J. Is stress a factor in the pathogenesis in autoimmune rheumatic diseases? Clin Exp Rheumatol 1999;17:515-8.
28. Straub RH, Cutolo M. Impact of the hypothalamic-pituitary-adrenal/gonadal axis and the peripheral nervous system in rheumatoid arthritis: viewpoint based on a systemic pathogenic role. Arthritis Rheum 2001;44:493-507.
29. Hunder GG. Clinical features of GCA/PMR. Clin Exp Rheumatol 2000;18:S4-8.
30. White PC, New MI, Dupont B. Congenital adrenal hyperplasia: part 1. New Engl J Med 1987;316:1519-24.