Renal clearance and daily excretion of cortisol and adrenal androgens in patients with rheumatoid arthritis and systemic lupus erythematosus

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EXTENDED REPORT

Background: In rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE), patients demonstrate low levels of adrenal hormones. Objective: To investigate whether increased renal clearance and daily excretion contribute to this phenomenon.

Methods: Thirty patients with RA, 32 with SLE, and 54 healthy subjects (HS) participated. Serum and urinary levels of cortisol, cortisone, 17-hydroxyprogesterone (17OHP), androstenedione, dehydroepiandrosterone (DHEA), and DHEA sulphate (DHEAS) were measured.

Results: Clearance of DHEAS and DHEA was lower in patients than in HS, and clearance of androstenedione was somewhat higher in patients than in HS, but daily excretion of this latter hormone was low. Clearance of cortisol, cortisone, and 17OHP was similar between the groups. The total molar amount per hour of excreted DHEA, DHEAS, and androstenedione was lower in patients than HS (but similar for cortisol). Serum DHEAS levels correlated with urinary DHEAS levels in HS and patients, whereas HS excreted 5–10 times more of this hormone than excreted by patients. Low serum levels of adrenal androgens and cortisol in patients as compared with HS were confirmed, and proteinuria was not associated with changes of measured renal parameters.

Conclusions: This study in patients with RA and SLE demonstrates that low serum levels of adrenal androgens and cortisol are not due to increased renal clearance and daily loss of these hormones. Decreased adrenal production or increased conversion or conjugation to downstream hormones are the most likely causes of inadequately low serum levels of adrenal hormones in RA and SLE.

In chronic inflammatory diseases, cortisol is reduced relative to the degree of systemic inflammation, as exemplified in African trypanosomiasis,1 Sjögren’s syndrome,2 and systemic lupus erythematosus (SLE).3 This is particularly the case when the disease persists over a long period of time (over weeks). In rheumatoid arthritis (RA), it has been shown that patients have inappropriately low spontaneous and stimulated cortisol secretion in relation to systemic inflammation.4–13 Another significant finding in patients with RA and SLE is that serum levels of dehydroepiandrosterone sulphate (DHEAS) and other adrenal hormones are decreased.14–22 In RA, we have recently discussed how an alteration of the hypothalamus-pituitary-adrenal axis has an impact on perpetuation of the disease.23 Inadequately low serum levels of cortisol and significantly lower levels of adrenal androgens are thought to have a proinflammatory role.24 This is most obvious for cortisol and DHEAS, which has been proved to be a therapeutic alternative in SLE and systemic inflammation.25–27 However, it is still unclear whether increased renal clearance or daily loss of adrenal steroid hormones are significant factors for low serum hormone levels in chronic inflammatory diseases. Although the pioneering work of Masi et al demonstrated that urinary conversion products of adrenal androgens are significantly low in eight women with RA, these authors did not study renal clearance, and DHEAS and androstenedione were not included in their investigations.13 Furthermore, in their study the number of patients was small, only women participated, and the menstrual cycle was not reported.15

In this prospective study we aimed to investigate renal clearance and excretion of the major steroid hormones in patients with RA and SLE and to compare the results with those of healthy control subjects (HS) matched for age and sex. Because we wanted to determine the clearance of these hormones, it was necessary to measure the unconjugated and untransformed hormone of interest in the blood and in the urine. The data of patients of both disease groups are presented with and without prednisolone treatment. Because adrenal hormones were not markedly different in women and men, data were presented irrespective of sex.

SUBJECTS AND METHODS

Patients and healthy control subjects

Thirty white patients with diagnosed RA fulfilling the American College of Rheumatology (ACR) criteria were included.28 Clinical variables of disease activity included the number of swollen and tender joints and erythrocyte sedimentation rate. To study simultaneously patients with another chronic inflammatory disease, we enrolled 32 white patients with SLE according to the criteria of the ACR.29 In these latter patients, clinical activity was assessed by the SLE Disease Activity Index (SLEDAI). Table 1 shows the basic characteristics of both disease groups. Clearly, the patients in both disease groups had mild to moderate disease activity. Because prednisolone treatment influences production of adrenal hormones, data are given with and without prior treatment.
prednisolone treatment (see table 1 and “Results”). Because long term disease and treatment with non-steroidal anti-inflammatory drugs or disease modifying anti-rheumatic drugs may influence renal function, we determined the type of proteinuria and creatinine clearance in order to control for possible kidney damage. Owing to a very different mean age in the two patient groups, patients with RA and SLE should not be directly compared (table 1).

For comparison, 54 white HS were recruited (mean (SEM) age 40.8 (1.5) years), and health status was verified by a 33 item questionnaire, as previously described.18 The questionnaire addressed known diseases in the past and present, current symptoms of diseases, current drugs, alcohol intake, smoking habits, family history, and surgical history. The questionnaire was adapted to the SENIEUR protocol.11 Our protocol established strict admission criteria for immunogerontological studies in man based on clinical information. Fertile women (HS and patients) were not taking contraceptives and they were in the early to mid-luflucric phase of the menstrual cycle as assessed by progesterone serum levels.

Owing to the different age and sex in the disease groups, subgroup analyses were carried out in order to compare correctly the different groups with HS. The subgroups were matched according to age and sex (table 1). Because serum levels of adrenal hormones are largely independent of sex, men and women were not further separated into subgroups.

Patients and HS were instructed to collect urine for 24 hours in special urine containers during the day before the visit. On the day of the visit, between 8.00 and 10.00 am, serum, plasma, and urine for further determination of steroid hormones or creatinine were taken and stored at −30°C in adequate aliquots. All patients and HS gave written consent for further investigation of samples. Owing to the difficulties in recruiting a large number of patients and HS (without contraceptives and in the correct phase of the menstrual cycle), collection of the material took 2 years.

### Laboratory parameters

Several adrenal hormones were considered in order to detect major adrenal pathways of steroidogenesis. Figure 1 demonstrates the steroid cascades in the adrenal gland. We used a radioimmunoassay for the quantitative determination of serum and urine levels of cortisol (Cortisol, Immunochem, Hamburg, Germany; detection limit 10 nmol/l), Serum and urine levels of androstenedione (IBL, Hamburg, Germany; detection limit 0.15 nmol/l), 17-hydroxypregesterone (17OHP; IBL, Hamburg, Germany; detection limit 0.3 nmol/l), DHEAS (IBL, Hamburg, Germany; detection limit 130 nmol/l), and DHEA (Diagnostic Systems Laboratory, Webster, Texas; detection limit 0.13 nmol/l) were measured by immunoenzymatic immunoassays. Plasma adrenocorticotrophic hormone (ACTH) was detected by enzyme immunoassay (Sangui BioTech, Inc, California, USA, via IBL, Hamburg, Germany; detection limit 0.1 pmol/l). For all assays, intra-assay and interassay coefficients of variation were below 10%. Cross reactivities between measured hormone and prednisolone were as follows: for cortisol ≤6%; cortisone 0%; androstenedione <1%; 17OHP <0.1%; DHEA <0.1%; and DHEAS <0.1%. 

Creatinine in serum and urine was measured on an automated Hitachi analyser (Hitachi 917, Wiesbaden, Germany) using the CREA method (Roche Diagnostics, Germany) and semiquantitative detection.32 This technique allows selective glomerular plus tubular proteinuria.

**Table 1** Basic characteristics of patients and healthy controls. Values demonstrate data of patients with and without prior prednisolone treatment. Data of healthy controls were not stratified because the entire group matched in age and sex to the respective patient subgroup.

<table>
<thead>
<tr>
<th>Rheumatoid arthritis</th>
<th>With prior prednisolone treatment</th>
<th>Without prior prednisolone treatment</th>
<th>Healthy controls</th>
</tr>
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<tr>
<td>Number</td>
<td>20</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
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<td>58 (3)</td>
<td>51 (5)</td>
<td>52 (1)</td>
</tr>
<tr>
<td>Sex (F/M)</td>
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<td>6/4</td>
<td>10/10</td>
</tr>
<tr>
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</tr>
<tr>
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<td>NA</td>
</tr>
<tr>
<td>Number of painful joints</td>
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<td>NA</td>
</tr>
<tr>
<td>ESR (mm/1st h)</td>
<td>32 (4)</td>
<td>21 (8)</td>
<td>NA</td>
</tr>
<tr>
<td>Drugs</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Prednisolone</td>
<td>20</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>Prednisolone (mg/day)</td>
<td>9 (3)</td>
<td>0 (0)</td>
<td>NA</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>6</td>
<td>6</td>
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</tr>
<tr>
<td>NSAIDs</td>
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<tr>
<td>Leflunomide</td>
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<td>2</td>
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<td>Hydroxychloroquine</td>
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<tr>
<td>Cyclophosphamide</td>
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<tr>
<td>Azathioprine</td>
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<td>6/4</td>
<td>25/17</td>
</tr>
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<td>SLEDAI (points)</td>
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<tr>
<td>Prednisolone (mg/day)</td>
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</tr>
<tr>
<td>Azathioprine</td>
<td>8</td>
<td>4</td>
<td>NA</td>
</tr>
</tbody>
</table>

Anti-TNF strategies are either infliximab or etanercept. Prednisolone treatment was not interrupted during 24 hour collection of urine. Data are given as means (SEM) or as number of patients/controls.

ESR, erythrocyte sedimentation rate; NA, not applicable; NM, not measured; NSAIDs, non-steroidal anti-inflammatory drugs; SLE, systemic lupus erythematosus; SLEDAI, SLE Disease Activity Index.
ultraviolet detector SPD-10A, SCL-10 system controller, and class-LC10 integration software (Shimadzu, Duisburg, Germany). The analytes were separated using two analytical columns (150×4.6 mm), a Synergi Polar-RP followed by a Synergi Max-RP (Phenomenex, Aschaffenburg, Germany), with water-acetonitrile (70:30, v/v) as mobile phase. Prednisolone eluted after 12.3 minutes, cortisol after 12.9 minutes, cortisone after 14.7 minutes, and methyl prednisolone (internal standard) after 19.1 minutes (flow rate 1.0 ml/min, column temperature 40°C). The recoveries of the analytes from serum or urine were 70–80%, imprecision and bias were <10%. Calibration curves for peak heights versus quantity were linear up to about 2700 nmol/l prednisolone/cortisol and about 700 nmol/l prednisolone/cortisone with coefficients of correlation $r _ { s } > 0.996$. The minimal detectable amount injected (signal/noise = 3/1) was about 200 pg of each analyte. The limit of measurement was estimated to be about 12 nmol/l for each compound. In some specimens an endogenous compound (equal to about 15 nmol/l prednisolone in serum and up to fivefold higher in urine) interfered with the determination of prednisolone. Patients with interferences were not included.

**Calculation of renal clearance**

Substance clearance was calculated according to the following formula:

\[
\text{Clearance} = \frac{U \times \text{vol}}{S \times T} \text{ (ml/min)}
\]

where $U$ is the urinary substance concentration (nmol/l), vol is the urinary collection volume (ml), $S$ is the serum substance concentration (nmol/l), and $T$ is the collection time (min). Because creatinine clearance was very similar in HS and patients (including subgroups), a mathematical adjustment of substance clearance using creatinine clearance was not necessary.

**Statistical analysis**

To compare medians in two different groups the Mann-Whitney signed rank test was used (SPSS/PC for Windows, version 10.0.5, SPSS, Inc, Chicago). Investigation of an interrelation between two variables was done using version 10.0.5, SPSS, Inc, Chicago). Investigation of an investigation, as expected, in patients with prednisolone pretreatment, serum levels of cortisol and cortisone were lower than in HS (figs 2A and D). As compared with HS, serum levels of DHEAS and androstenedione were lower in both disease groups, irrespective of prior prednisolone treatment (figs 2B, E and 2C, F), DHEA serum levels were near normal in RA and SLE without prednisolone treatment (figs 2C and F), and they were lower in both disease groups with prednisolone pretreatment (figs 2C and F). As compared with HS, the plasma levels of ACTH were significantly lower in prednisolone pretreated patients of both disease groups (RA+prednisolone $v$ HS 2.6 (0.3) $v$ 7.8 (2.4) pmol/l, $p < 0.001$; SLE+prednisolone $v$ HS 2.0 (0.2) $v$ 4.9 (0.5) pmol/l, $p < 0.001$), and ACTH plasma levels were lower in RA and similar in SLE without prednisolone treatment (RA without prednisolone $v$ HS 2.5 (0.4) $v$ 7.8 (2.4) pmol/l, $p = 0.001$; SLE without prednisolone $v$ HS 3.6 (0.5) $v$ 4.9 (0.5) pmol/l, NS).

**RESULTS**

**Serum hormone concentrations**

In confirmation of previous studies, serum cortisol levels in the group of patients without corticosteroid treatment were lower (in SLE) or did not differ (in RA) from those in HS (figs 2A and D). This was similar for serum cortisone in both disease groups with prior prednisolone treatment (figs 2A and D). Because of an increased renal clearance of cortisol in both disease groups with prednisolone pretreatment, serum levels of cortisol and cortisone were lower than in HS (figs 2A and D). As compared with HS, serum levels of DHEAS and androstenedione were lower in both disease groups, irrespective of prior prednisolone treatment (figs 2B, E and 2C, F), DHEA serum levels were near normal in RA and SLE without prednisolone treatment (figs 2C and F), and they were lower in both disease groups with prednisolone pretreatment (figs 2C and F). As compared with HS, the plasma levels of ACTH were significantly lower in prednisolone pretreated patients of both disease groups (RA+prednisolone $v$ HS 2.6 (0.3) $v$ 7.8 (2.4) pmol/l, $p < 0.001$; SLE+prednisolone $v$ HS 2.0 (0.2) $v$ 4.9 (0.5) pmol/l, $p < 0.001$), and ACTH plasma levels were lower in RA and similar in SLE without prednisolone treatment (RA without prednisolone $v$ HS 2.5 (0.4) $v$ 7.8 (2.4) pmol/l, $p = 0.001$; SLE without prednisolone $v$ HS 3.6 (0.5) $v$ 4.9 (0.5) pmol/l, NS).

**Urinary hormone concentrations and daily hormone excretion**

If systemic steroid hormone loss is due to an increased renal excretion, one would expect increased urinary concentrations of these steroid hormones and increased molar amounts in the urine as compared with HS. Figures 3A and D show that urinary concentration of cortisol was higher in patients with RA and tended to be higher in patients with SLE with prednisolone pretreatment than in HS. This was not the case for urinary cortisone, which was significantly lower in both patient groups with prednisolone pretreatment (figs 3A and D). Average concentrations of all other steroid hormones tended to be lower or were significantly lower in both patient groups than in HS (fig 3). This was particularly true for urinary levels of DHEAS, DHEA, and androstenedione (fig 3). In a correlation analysis, it is obvious that serum and urinary

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**Figure 1: Cascades of adrenal steroidogenesis.** A line with an arrow at the end indicates that the respective mediator stimulates the enzyme step (ACTH, IL6, IL1, TGFβ). A line with a bar at the end demonstrates that the respective mediator inhibits the enzyme step (IL1, TNF, TGFβ). Enzymes and abbreviations: 1, P450scc = side chain cleavage enzyme; 2, 3β-hydroxysteroid dehydrogenase; 3, P450c17 = 17b-hydroxylase; 4, P450c11 = 11b-hydroxylase; 5 and 6, P450c17 = 17b-hydroxylase and 17/20-lyase (double enzyme step); 7, DHEA sulphohydroxylase and DHEAS sulphatase; 8, 11b-hydroxysteroid dehydrogenase types 1 and 2; 9, aromatase complex; ACTH, adrenocorticotropic hormone; DHEA, dehydroisoandrosterone; DHEAS, DHEA sulphate; IL1, interleukin 1; IL6, interleukin 6; TGFβ, transforming growth factor β; TNF, tumour necrosis factor.
levels of DHEAS are significantly interrelated (fig 4). The slopes of the regression lines in fig 4 are very similar, which indicates that the excreted amount of DHEAS largely depends on the serum level of this hormone.

To estimate the relative contribution of each hormone to excretion of all hormones, the total excreted molar amount per day of each hormone was calculated (table 2). In both disease groups and HS, the total nanomolar amount per day of excreted DHEAS was about 10–2500 times higher than that of other steroid hormones (table 2). This reflects markedly higher serum levels of DHEAS than other steroid hormones (fig 2). Thus, DHEAS is the most important excreted adrenal hormone. In both disease groups, irrespective of prednisolone pretreatment, the total nanomolar amounts per day of excreted DHEA and DHEAS were markedly lower than those for HS (table 2). As compared with HS, the nanomolar amount of excreted cortisol per day was increased in RA with prednisolone pretreatment and tended to be increased in SLE with prednisolone pretreatment (table 2). Because the radioimmunoassay for cortisol measurement detects 6% of excreted prednisolone (cross-reactivity = 6%, see “Subjects and methods”), we attempted to estimate the contribution of excreted prednisolone to the measurement of cortisol. In patients with RA and SLE, including prednisolone pretreated patients, urine levels of cortisol highly significantly correlated with urine levels of prednisolone (RA: $R_{rank} = 0.885, p<0.001$; SLE: $R_{rank} = 0.885, p<0.001$). Patients with RA and SLE, including those with prednisolone treatment, excreted 2256 and 2040 nmol prednisolone per day, respectively (6% are 135 and 122 nmol/day, respectively). Thus, it is likely that prednisolone contributes to the increased urinary cortisol concentration and total molar amount in both disease groups with prednisolone treatment (not for cortisone).

**Urinary substance clearance**

Renal clearance of a substance is the plasma volume per time which is totally cleared from the respective substance (in ml/min). Figure 5 shows that for creatinine, the creatinine cleared plasma volume per minute is about 100 ml. This value is markedly lower for steroid hormones (fig 5). In both disease groups, clearance of DHEAS and DHEA tended to be

**Figure 2**  Serum hormone concentration of adrenal steroid hormones. (A-C) Data of patients with RA; (D-F) results of patients with SLE. Data are given as means (SEM).

$p<0.05$; $t_p<0.005$; $t_p<0.001$ for the comparison of the respective group with HS. CSN, cortisone; DHEAS, DHEA sulphate; 17OHP, 17-hydroxyprogesterone; ASD, androstenedione; DHEA, dehydroepiandrosterone.
lower or were significantly lower than in HS (fig 5). Interestingly, clearance of androstenedione tended to be increased or was significantly increased in both disease groups in comparison with HS (fig 5). No differences were observed for clearance of 17OHP (fig 5). The increased clearance of cortisol in both disease groups with prednisolone pretreated patients is most likely due to the erroneous detection of urine cortisol as mentioned above. In addition, no differences for cortisone clearance were found between HS and patients groups.

**Proteinuria and urinary hormones**

Table 3 demonstrates the frequencies of different types of proteinuria in HS, patients with RA, and patients with SLE. If we separate patients with RA and SLE according to proteinuria into two different groups, with (all types) and without proteinuria, then creatinine clearance between the groups was not significantly different. Furthermore, they did not differ with respect to measured serum, plasma, or urinary levels of hormones or parameters of hormone excretion. Thus, the presented forms of proteinuria led to only mild deterioration of renal function.

**DISCUSSION**

Low serum levels of adrenal androgens and inadequately low serum cortisol in chronic inflammatory disease are thought to be caused by (a) increased renal excretion of steroid hormones; (b) increased conversion or conjugation to downstream hormones such as cortisone (upstream are 17OHP and cortisol, see fig 1) or oestrogens (upstream are DHEA and androstenedione); and (c) inadequate adrenal production or secretion of these hormones. This study demonstrates that increased renal clearance and daily excretion of these hormones are not a likely reason for this phenomenon in the tested chronic inflammatory diseases. It is confirmed that DHEAS is the major excreted steroid hormone in both disease groups and HS. Its excretion is 10 to 1000 times higher than that of other measured steroid hormones. The urinary concentration directly depends on the available serum concentration, which is significantly higher in HS than in...
patients with RA and SLE. Thus, the decrease of serum DHEAS in these two chronic inflammatory diseases is not due to exaggerated renal clearance and daily loss. Similarly, an increased renal clearance and excretion is not the reason for the loss of other measured steroid hormones. The slightly increased clearance for androstenedione in both disease groups in patients with and without prednisolone treatment is most probably not an indication of an increased loss of this hormone because the absolute molar amount of androstenedione is certainly not increased in patients as compared with age matched and sex matched HS (table 2). These results corroborate a recent study which looked at the profile of disappearance of total cortisol from plasma.\textsuperscript{34} Rovensky \textit{et al} suggested that alterations in cortisol clearance are not likely to have a role in cortisol availability in patients with RA.

In HS and in patients with RA and SLE, serum levels of downstream cortisone are lower than those of cortisol (and urinary cortisone excretion is also lower than urinary cortisol excretion). Furthermore, serum levels of oestrogens are also 5–10 times lower than upstream androstenedione.\textsuperscript{35} These facts do not stimulate the belief that increased peripheral conversion of either cortisol to cortisone or DHEA/androstenedione to oestrogens may be an important reason for low serum levels of these hormones. Nevertheless, we do not

![Graph showing the interrelation between serum DHEAS and urinary DHEAS in HS, patients with RA, and patients with SLE, including those with prednisolone treatment. The x axis and the y axis were adjusted to the different numerical levels because the HS had clearly higher serum and urine concentrations than both patient groups. The panels include the linear regression line, the Spearman rank correlation coefficient, and the respective p value.]

**Figure 4**  Interrelation between serum DHEAS and urinary DHEAS in HS, patients with RA, and patients with SLE, including those with prednisolone treatment. The x axis and the y axis were adjusted to the different numerical levels because the HS had clearly higher serum and urine concentrations than both patient groups. The panels include the linear regression line, the Spearman rank correlation coefficient, and the respective p value.

### Table 2 Renal hormone excretion in nmol/day. Values are data of patients with and without prednisolone treatment. Patients with RA and SLE should not be compared owing to their different mean age.

<table>
<thead>
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<th>Hormone (nmol/day)</th>
<th>Patient subgroup</th>
<th>With prednisolone</th>
<th>Without prednisolone</th>
<th>Healthy controls*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Rheumatoid arthritis</td>
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<tr>
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<td>39.1 (10.8)%</td>
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<tr>
<td>17-Hydroxyprogesterone</td>
<td>9.9 (1.8)*</td>
<td>11.8 (3.1)%</td>
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<td>80.0 (16.4)|</td>
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</tr>
<tr>
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<td>23833 (6301)|</td>
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<td>72.9 (7.6)|</td>
<td>74.9 (5.4)</td>
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<td>17-Hydroxyprogesterone</td>
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<td>26.0 (5.2)|</td>
<td>44.8 (6.4)</td>
<td></td>
</tr>
<tr>
<td>Cortisone</td>
<td>64.6 (17.5)*</td>
<td>213.2 (19.9)|</td>
<td>181.1 (10.2)</td>
<td></td>
</tr>
<tr>
<td>Cortisol</td>
<td>325.7 (148.0)|</td>
<td>125.8 (21.5)|</td>
<td>115.0 (9.2)</td>
<td></td>
</tr>
</tbody>
</table>

Data are given as means (SEM).

*Data of healthy controls were not stratified because, for age and sex, the entire control group matched the respective patient subgroups. **In the subgroup of patients with prior prednisolone treatment, two outliers with 1232 and 2295 nmol/day were excluded from the analysis, which did not change the statistical comparison due to the non-parametric test.

1p<0.05, 2p<0.01, 3p<0.005, 4p<0.001 for the comparison versus healthy controls.
indicate that inadequate production of cortisol, DHEA, DHEAS, and androstenedione may be due to inflammation induced reduction of adrenal steroidogenesis. In addition, inadequately low plasma levels of ACTH in relation to serum TNF or IL6 levels have been described in chronic inflammatory diseases such as RA and reactive arthritis. Thus, the most important stimulus from the pituitary gland may fail to stimulate an adequate adrenal response during systemic inflammation.

In conclusion, in patients with RA and SLE, independently of corticosteroid treatment, the measured excretion of adrenal steroid hormone is not increased compared with that of HS. In contrast, the total excreted amount of DHEAS, and androstenedione is clearly decreased or is similar to that of HS. Thus, renal clearance and daily loss of these adrenal androgens and the inadequately low serum levels of cortisol in relation to systemic inflammation.

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Renal clearance and daily excretion of cortisol and adrenal androgens in patients with rheumatoid arthritis and systemic lupus erythematosus

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