Serum Levels of Pregnenolone and 17-hydroxypregnenolone in Patients with Rheumatoid Arthritis and Systemic Lupus Erythematosus: Relation to Other Adrenal Hormones

DANIELA VOGL, WERNER FALK, MONIKA DORNER, JÜRGEN SCHÖLMERICH, and RAINER H. STRAUB

ABSTRACT. Objective. In patients with rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE), low levels of adrenal steroids have been repeatedly demonstrated, but the site of alteration has not been exactly described because measurements of serum pregnenolone and 17-hydroxypregnenolone (17OHPreg) together with other adrenal steroids have never been performed.

Methods. We measured serum levels of adrenal hormones such as pregnenolone, 17OHPreg, dehydroepiandrostone (DHEA), DHEA sulfate (DHEAS), progesterone (P), 17-hydroxyprogesterone (17OHP), androstenedione (ASD), and cortisol in 24 healthy controls, 24 patients with RA, and 24 patients with SLE.

Results. Serum levels of pregnenolone were similar in RA and SLE patients as compared to healthy controls irrespective of prior prednisolone therapy. In all RA and SLE patients (including those with prior prednisolone treatment), serum levels of all measured hormones except pregnenolone were significantly lower as compared to controls. In RA patients without prior prednisolone treatment, serum levels of 17OHPreg, DHEA, cortisol, and ASD were similar to controls, and serum levels of P, 17OHP, and DHEAS were significantly lower as compared to controls. In SLE patients without prior prednisolone treatment, serum levels of 17OHPreg and cortisol were similar, and serum levels of P, 17OHP, ASD, DHEA, and DHEAS were significantly lower as compared to controls.

Conclusion. The primary hormone of the adrenal steroid cascade, pregnenolone, is almost normal in RA and SLE irrespective of corticosteroid treatment. In patients with RA, we believe that there is a near normal P450scc reaction and a normal double step P450c17 reaction. In SLE patients, the P450scc reaction also seems normal but the second step of the P450c17 reaction seems to be inhibited. In both diseases, cortisol levels remain relatively stable at the expense of other adrenal hormones. This study revealed distinct changes of steroid pathways that are related to the disease entities. (J Rheumatol 2003;30:269–75)

Key Indexing Terms:
RHEUMATOID ARTHRITIS
PREGNENOLONE
17-HYDROXYPREGNENOLONE
ADRENAL STEROID HORMONES

Adrenal steroidogenesis consists of 3 major pathways (Figure 1): (1) mineralocorticoid production (endpoint: aldosterone); (2) glucocorticoid production (endpoint: cortisol); and (3) androgen production [endpoint: dehydroepiandrosterone (DHEA), androstenedione (ASD), and DHEA sulfate (DHEAS)]. The physiological roles of mineralocorticoids and glucocorticoids are well known; however, the role of adrenal androgens is currently under investigation. Several groups have found low levels of adrenal androgens in patients with rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE)1-17. Although cortisol serum concentrations were almost normal in the patients, the serum levels were inadequately low in relation to systemic inflammation18-19. Further, it has been demonstrated that there is a shift in hormone secretion from adrenal androgens to cortisol14,17,20,22, which is probably necessary to maintain an adequate cortisol level at the expense of other adrenal hormones (Figure 1). This shift is augmented by prior corticosteroid treatment20,23. However, an exact localization of an altered enzyme step has not been described due to difficulties of measuring the delta3 steroids pregnenolone and 17OHPregnenolone (Figure 1).

We aimed to identify the important adrenal enzyme steps that may be altered in patients with RA and SLE. We mea-
sured serum levels of adrenal hormones such as pregnenolone, 17OH-pregnenolone, DHEA, DHEAS, progesterone, 17OH-progesterone, ASD, and cortisol in patients with and without prior prednisolone treatment.

MATERIALS AND METHODS

Healthy subjects. Twenty-four Caucasian subjects were recruited (mean age: 43.3 ± 3.4 yrs, 12 women, 12 men), and health status was verified by means of a 33 item questionnaire. The questionnaire addressed known diseases in the past and at present, current symptoms of diseases, current medication, prior vaccination, alcohol intake, smoking habits, family history, and surgical history. The questionnaire was adapted to the SENIEUR protocol for immunogerontological studies24. Fertile women were not taking contraceptives and they were in the early to mid follicular phase of the menstrual cycle. Blood was drawn between 10 AM and 12 noon, and serum and plasma was immediately stored at –80˚C in adequate aliquots. All subjects gave written consent for further investigation of blood samples. Due to a different mean age in patients with RA and SLE the healthy subjects were matched accordingly (Table 1).

Patients. We included 24 patients with RA and 24 patients with SLE according to the American College of Rheumatology criteria for the classification of these diseases. The patients were referred to the outpatient Rheumatology Clinic of the Department of Internal Medicine of the University Hospital Regensburg, and they were included into this study without prior selection. Basic characteristics of these patients are depicted in Table 1. In both disease groups, inflammatory activity was assessed clinically and by erythrocyte sedimentation rate (ESR). Blood for further determination of steroid hormones was drawn within 9 AM and 12 noon, and only serum was stored at –20˚C in adequate aliquots.

Due to the differences in age and sex between the disease groups and healthy controls, subgroup analyses were carried out in order to correctly compare the different groups. The subgroups were matched according to age and sex. Table 1 summarizes the number of patients, age, sex, and duration of the disease in the different subgroups.

Laboratory variables. Several adrenal hormones were considered in order to scrutinize major adrenal pathways of steroid metabolism (Figure 1). We used radioimmunometric assays for quantitative determination of serum levels of cortisol (Coulter Immunotech, Marseilles, France; detection limit: 10 nmol/l). Serum levels of progesterone (IBL, Hamburg, Germany; detection limit: 1.0 nmol/l), 17OH-progesterone (IBL; detection limit: 0.3 nmol/l), DHEA sulfate, Enzymes: enzyme 1: P450c21 or 20,22 desmolase; enzyme 2: 3ß-hydroxysteroid dehydrogenase; enzyme 3: P450c21 or 21α-hydroxylase; enzyme 4: P450c11 or 11β-hydroxylase; enzymes 5/6: P450c17 or 17α,20-hydroxylase; enzyme 7: combined reaction of sulfotransferase and sulfatase.

Figure 1. Biosynthesis of the important adrenal hormones. The lines with a bar at the end show the inhibitory effects of indicated mediators transforming growth factor-β (TGF-β), interleukin 1β (IL-1β), TNF, whereas a line with an arrow indicates a stimulatory effect (ACTH, IL-6). ACTH stimulates the P450c17 (enzyme 5 and 6) converts pregnenolone/progesterone to DHEA/androstenedione. The 3ß-hydroxysteroid dehydrogenase (enzyme 2) and P450c21 (enzyme 3) start the first steps via aldosterone and cortisol. The delta4 steroids are pregnenolone, 17OH-pregnenolone, DHEA, and DHEAS. The delta5 steroids are progesterone, 17OH-progesterone, and androstenedione. ACTH: adrenocorticotropic hormone; DHEA: dehydroepiandrosterone; DHEAS: DHEA sulfate. Enzymes: enzyme 1: P450c21 or 20,22 desmolase; enzyme 2: 3ß-hydroxysteroid dehydrogenase; enzyme 3: P450c21 or 21α-hydroxylase; enzyme 4: P450c11 or 11β-hydroxylase; enzymes 5/6: P450c17 or 17α,20-hydroxylase; enzyme 7: combined reaction of sulfotransferase and sulfatase.
Pregnenolone together with [3 H] pregnenolone tracer was extracted from 1 ml of serum into a non-polar solvent, ethyl acetate:hexane (3:2 v/v), for 20 min. A large proportion of pregnenolone sulfate remained in the aqueous phase. The organic phase was then carefully evaporated to dryness under a stream of nitrogen at 37˚C. The steroid was then solubilized in 0.5 ml isooctane and given on a Microcelite Column System I (ICN Biomedicals). By means of constant nitrogen pressure a stable flow through the column of about 6 to 9 drops/min was achieved (constant flow is important). The column was then washed with 3.5 ml isooctane followed by 3.5 ml 5% ethyl acetate in isooctane. The collected solution was again carefully evaporated to dryness under a stream of nitrogen (37˚C). Then, the steroid was solubilized in steroid diluent (ICN Biomedicals) for 30 min (room temperature). This procedure was followed by a displacement radioimmunoassay with the mentioned antibodies against pregnenolone using the charcoal separation method (ICN Biomedicals). Measurement of 17OH-pregnenolone was similar; however, we used the Microcelite Column System II (ICN Biomedicals) and the column washing procedure consisted of 3 steps: (A) 3.5 ml isooctane, (B) 3.5 ml 10% ethyl acetate in isooctane, and (C) 5.0 ml 40% ethyl acetate in isooctane.

All samples were measured in duplicate, and intercolumn coefficient of variation was about 15% for pregnenolone and 18% for 17OH-pregnenolone. Statistical analysis. To compare means in 2 different groups the Mann-Whitney signed rank test was used (SPSS/PC for Windows, V.10.0.5, SPSS Inc., Chicago, IL, USA). P values < 0.05 were considered to be significant and means are given ± SEM.

RESULTS

Adrenal delta5-steroid hormones in healthy controls and patients with RA and SLE. The first enzymatic step is achieved by P450scc, which converts cholesterol into pregnenolone (Figure 1). Serum concentration of pregnenolone did not significantly differ between healthy controls and patients with SLE or RA irrespective of prior prednisolone treatment (Figure 2). In contrast, serum 17OH-pregnenolone concent-

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Serum levels of delta\(^4\)-steroid hormones and cortisol in healthy controls and patients with RA and SLE. Delta\(^5\)-steroid hormones are converted to delta\(^4\)-steroid hormones by the 3\(\beta\)-hydroxysteroid dehydrogenase, a step which provides the important pre-hormones progesterone and 17OH-progesterone for aldosterone and cortisol production, respectively (Figure 1). Serum levels of both hormones progesterone and 17OH-progesterone were significantly lower in patients as compared to healthy controls irrespective of prior prednisolone therapy (Figure 2D).
As expected, serum cortisol levels were lower in all patients (including those with and without prior prednisolone) as compared to controls, but there was no difference between controls and patients without prior prednisolone (Figure 3C). In the latter patients, it is obvious that serum cortisol was inadequately low in relation to systemic inflammation as quantified by erythrocyte sedimentation rate (Table 1). With respect to ASD, another major adrenal androgen, all patients (including those with and without prednisolone) demonstrated significantly lower serum levels as compared to controls (Figure 3D). In addition, SLE patients without prior prednisolone showed lower serum levels as compared to controls but this was not significant in RA patients (Figure 3D).

**DISCUSSION**

Our study provides evidence that multiple enzymatic steps in steroid metabolism may be altered in patients with SLE and RA. In all patients, including those with and without prior prednisolone, there was an overall decrease of serum levels of all measured steroid hormones except pregnenolone. We did not measure adrenocorticotropic hormone (ACTH) because we wanted to focus on adrenal hormones; however, this dramatic decrease in serum levels of adrenal hormones is most probably due to a loss of the stimulating influence of ACTH. Interestingly, the first hormone of the steroid cascade, pregnenolone, which is the pre-hormone for all steroid hormones, was not significantly inhibited (Figure 1). The first enzymatic step from cholesterol to pregnenolone, achieved by the P450scc (enzyme 1 in Figure 1), is the most important step for production of many other steroid hormones such as aldosterone, cortisol, and adrenal androgens, the conservation of which is of particular importance for the entire body (especially for aldosterone production in the case of prior prednisolone therapy). Thus, even with prior prednisolone therapy, in a situation with significantly lower levels of ACTH, adren-

![Figure 3](image-url)
al production and serum levels of pregnenolone remain relatively stable in order to maintain overall homeostasis in these RA and SLE patients.

In a situation without prior prednisolone therapy, serum levels of several hormones did not differ between healthy controls and patients (Table 2). However, serum levels of progesterone and 17OH-progesterone were markedly lower (Table 2). Since serum levels of pregnenolone and 17OH-pregnenolone were similar in patients without prior prednisolone and controls and serum levels of progesterone and 17OH-progesterone were markedly lower in patients as compared to healthy subjects, 2 explanations are possible: (A) the concentrations of the 2 delta4-steroids progesterone and 17OH-progesterone are low because downstream conversion to aldosterone or cortisol via P450c21 and P450c11 (enzyme 3 and 4 in Figure 1) is upregulated to maintain an adequate aldosterone or cortisol level at the expense of other hormones, and (B) concentrations of these 2 steroids are low due to inhibition of the 3ß-hydroxysteroid dehydrogenase (enzyme 2 in Figure 1). Although it has been demonstrated that some proinflammatory cytokines such as tumor necrosis factor (TNF) and interleukin 1 can inhibit the 3ß-hydroxysteroid dehydrogenase in steroid-producing cells27, the first explanation is more reasonable because serum cortisol levels remain relatively normal in patients without prior prednisolone. Thus, we would argue that conversion from pregnenolone to progesterone and 17OH-pregnenolone to 17OH-progesterone via the 3ß-hydroxysteroid dehydrogenase is upregulated, and further, conversion of progesterone to downstream aldosterone and 17OH-progesterone to downstream cortisol is also upregulated (Figure 1). Upregulation of these 2 pathways is achieved at the expense of adrenal androgens such as DHEA and ASD, which reached the significance level in patients with SLE but not in patients with RA (cross-hatched bars in Figures 2C and 3D). The reason for the different behavior of DHEA and ASD in patients with RA and SLE is unclear. One may speculate that upregulation of the aldosterone/cortisol pathways may be somewhat higher in SLE as compared to RA patients. Interestingly, in a recent study in early untreated patients with polymyalgia rheumatica (duration 2.5 mo), it was demonstrated that 17OH-progesterone is elevated even before and during an ACTH test28. The reasons for the different results remain speculative but it may be that patients with the mentioned diseases have different changes in adrenal enzyme pathways. One can argue that patients with polymyalgia rheumatica may have a block in downstream conversion of 17OH-progesterone to cortisol, which is not the case in patients with RA and SLE.

With respect to serum levels of DHEAS, there is a severe reduction irrespective of prior prednisolone therapy, which confirms previous studies on DHEAS levels in patients with long-standing RA and SLE. In SLE one can argue that the serum level of the pre-hormone DHEA was low, which should necessarily lead to low serum levels of the sulfated downstream hormone DHEAS. However, this argument does not fit the results of RA patients because DHEA levels are similar as compared to healthy subjects or even elevated in early RA patients (Table 2). Thus, in patients with long-standing RA and SLE, other reasons for low serum levels of DHEAS must be present. In long-standing chronic diseases, such reasons may be inhibition of conversion from DHEA to DHEAS, or, more likely, renal loss of DHEAS since renal excretion of different substances may be increased during inflammation (proteinuria, etc). Thus, we believe that further investigation in various chronic inflammatory diseases is necessary in order to focus on renal excretion of DHEAS.

In conclusion, prior prednisolone therapy downregulates all measured adrenal hormones except pregnenolone, which is probably necessary to maintain an adequate aldosterone secretion in patients with corticosteroid treatment. In RA patients without prior prednisolone, there seems to be a shift to cortisol (aldosterone) and to DHEA and ASD. In SLE patients without prior prednisolone, there seems to be a shift to cortisol (aldosterone) but not to DHEA or ASD. Our study revealed distinct changes of steroid pathways that are related to the disease entity (Table 2). We believe that there will be no strong inhibition of the P450scc reaction and the double-step P450c17 reaction in patients with RA (Table 2). In SLE patients, there may be a near normal P450scc reaction but the second step of the P450c17 reaction seems to be inhibited (Table 2). In both patient groups there is a severe decrease of serum DHEAS, and future studies have to address the possible renal loss of this hormone.

Table 2. Summary of findings in patients with RA and SLE without prior prednisolone treatment (in parentheses: patients with prior prednisolone). In all cases, serum hormone levels were compared with those of healthy age and sex matched control subjects (see Table 1).

<table>
<thead>
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<th>Adrenal delta^1-steroid hormones</th>
<th>RA</th>
<th>SLE</th>
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<td>Normal (normal)</td>
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<tr>
<td>17OH-pregnenolone</td>
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<td>Normal (low)</td>
</tr>
<tr>
<td>DHEA</td>
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<td>Low (low)</td>
</tr>
<tr>
<td>Adrenal delta^4-steroid hormones</td>
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<td>Low (low)</td>
</tr>
<tr>
<td>17OH-progesterone</td>
<td>Low (low)</td>
<td>Low (low)</td>
</tr>
<tr>
<td>(17OH-pregnenolone*)</td>
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<td>Low (low)</td>
</tr>
<tr>
<td>Androstenedione (DHEA*)</td>
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<td>DHEAS</td>
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<tr>
<td>Cortisol (17OH-progesterone*)</td>
<td>Normal (low)</td>
<td>Normal (low)</td>
</tr>
</tbody>
</table>

*Important precursor of the respective hormone upstream of 3ß-hydroxysteroid dehydrogenase. See Figure 1.

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