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Association of Humoral Markers of Inflammation and Dehydroepiandrosterone Sulfate or Cortisol Serum Levels in Patients With Chronic Inflammatory Bowel Disease

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Objectives: **Dehydroepiandrosterone sulfate (DHEAS) and cortisol are multifunctional adrenal hormones with immunomodulating properties. DHEAS levels were found to be very low in chronic inflammatory diseases. This study aimed to shed more light on the interrelation between DHEAS and cortisol (and humoral markers of inflammation) in chronic inflammatory bowel disease.** ***Methods:*** **DHEAS and cortisol serum levels were measured by ELISA in the serum of 66 normal subjects, 115 patients with Crohn's disease (CD) and 64 patients with ulcerative colitis (UC). Humoral markers of inflammation and disease activity scores were assessed by standard techniques.** ***Results:*** **DHEAS was lower in patients with CD ($p < 0.005$) and UC ($p < 0.005$) than in controls, which was, in part, dependent on previous corticosteroid treatment ($p < 0.01$). In CD patients, z-normalized DHEAS was inversely correlated with blood sedimentation rate ($p = 0.017$). Z-normalized DHEAS was negatively correlated with interleukin-6 (IL-6) in the form of a trend ($p = 0.068$), and z-normalized DHEAS was significantly positively correlated with hemoglobin ($p = 0.001$) but not with the Crohn's disease activity index. Cortisol, however, was positively correlated with blood sedimentation rate ($p = 0.034$) and C-reactive protein ($p = 0.006$). In contrast, in UC patients no such correlation of z-normalized DHEAS or cortisol and parameters of humoral inflammatory activity or Rachmilewitz index exist.** ***Conclusions:*** **DHEAS as a marker of inflammation was low in CD and UC. In CD patients, low DHEAS and high cortisol serum levels were associated with higher humoral inflammatory activity. With respect to humoral inflammatory activity in CD patients, DHEAS and cortisol seem to be inversely regulated, which may have an impact on several immune functions, such as IL-6 secretion. (Am J Gastroenterol 1998;93: 2197–2202. © 1998 by Am. Coll. of Gastroenterology)**

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INTRODUCTION

Dehydroepiandrosterone (DHEA) and its sulfated derivative dehydroepiandrosterone sulfate (DHEAS) are the most abundant circulating hormones in humans. DHEAS is secreted from the adrenal glands and interconverted to the active hormone DHEA in the periphery. DHEA is a precursor of androgens and estrogens (1) and has multiple immunomodulating effects (2–5). Various effects are attributed to DHEA and the precise physiological role is currently being investigated. This led to the investigation of the hormone in inflammatory diseases such as in systemic lupus erythematosus, where abnormally low DHEAS levels were described (6, 7). This reduction of DHEAS was, in part, dependent on prior corticosteroid (CS) treatment (6). This is reasonable because DHEAS production is blocked by steroid suppression (8). However, the reasons for the CS-independent DHEAS reduction in chronic inflammatory diseases are not exactly known. DHEA modulates T-helper lymphocyte function (9) and, in general, DHEA has opposing effects, compared with CS (9). A decrease of DHEA with its immunomodulating properties may, thus, influence the disease process in chronic inflammatory diseases.

In Crohn's disease (CD) and in ulcerative colitis (UC), DHEAS and cortisol serum levels have, as yet, not been investigated. Because dysregulation of the intestinal immune system is an important feature of both CD and UC, we determined the serum levels of DHEAS and cortisol in patients with inflammatory bowel disease. One purpose of this investigation was to examine the association between DHEAS or cortisol and humoral markers of systemic inflammation or disease-relevant soluble immune mediators such as interleukin 6 (IL-6), tumor necrosis factor α (TNFα), interleukin 1 receptor antagonist (IL-1RA), soluble interleukin 2 receptor (sIL-2R), and soluble intercellular adhesion molecule (sICAM). Influences of gender, prior CS treatment, and clinically assessed disease activity on serum levels of DHEAS and cortisol were also investigated.

TABLE 1
Characteristics of the Patients Under Study

	Controls	CD	UC
n (total n = 245)	66	115	64
Gender (female/male)	33/33 (50/50)	61/54 (53/47)	31/33 (48/52)
Age (yr)	31.4 ± 1.0 [18–47]	32.0 ± 1.0 [18–48]	33.1 ± 1.4 [16–47]
Blood sedimentation rate (mm/first hr)	NA	24.3 ± 1.7	20.6 ± 2.4
C-reactive protein (mg/L)	NA	24.2 ± 3.1	15.5 ± 4.0
Leukocytes (per nl)	NA	13.7 ± 4.0	10.4 ± 0.6
Hemoglobin (g/dl)	NA	13.0 ± 0.2	13.0 ± 0.3
Therapy			
Prednisolone	—	58/115 (50.4)	36/64 (35.8)
Budesonide	—	6/115 (5.2)	5/64 (7.8)
Sulfasalazine	—	17/115 (14.8)	13/64 (20.3)
5-ASA	—	57/115 (49.6)	27/64 (42.2)
Azathioprine	—	3/115 (2.6)	1/64 (1.6)

NA = not assessed. Patients with CD and UC did not differ in the parameters mentioned. Data are given as mean ± SEM, with percentages in parentheses and ranges in brackets.

MATERIALS AND METHODS

Control subjects and patients

Sixty-six healthy control subjects (mean age: 31.4 ± 1.0 yr, range: 18–47 yr) were recruited, 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, alcohol intake, smoking habit, family history, and operation history. Thirty-three were men, and 33 were women. Furthermore, 115 patients with CD (32.0 ± 1.0 yr, 18–48 yr) and 64 patients with UC (33.1 ± 1.4 yr, 16–47 yr) were included in the study. All patients were referred to the Department of Internal Medicine at the University Hospital between 1992 and 1997 and entered the study consecutively without prior selection. The patients had no other diseases except CD or UC, had normal body weight, and had no alcoholism. There was an equal number of smokers in the control and patient groups. Table 1 demonstrates the clinical characteristics of control subjects and patients with CD or UC. Disease activity in patients with CD was assessed with the Crohn's disease activity index (CDAI) (10), and, in patients with UC, with the Rachmilewitz index (RI) (11). Patients with a CDAI < 150 and a RI < 5 were classified to have inactive disease, whereas patients with a higher CDAI or RI were said to have active disease. Patients who were not taking CS for more than 6 weeks before drawing the blood sample were regarded as patients without CS treatment.

Laboratory parameters

Blood samples were taken between 8 and 11 AM and rapidly stored at −80°C. We used an immunometric enzyme immunoassay for the quantitative determination of DHEAS (IBL, Hamburg, Germany) and of cortisol (Cortisol Milenia, H. Biermann, Bad Nauheim, Germany). The soluble immune mediators IL1-RA, IL-6, TNFα, sIL-2R, and sICAM were measured by immunometric enzyme immunoassays in patients and controls (Quantikine, R&D Systems, Minneapolis, MN). Blood sedimentation rate, C-reactive protein, leukocytes, hemoglobin, hematocrit, serum protein, and serum albumin were determined according to standard techniques.

Statistical analysis

Multiple group means were compared by one-way analysis of variance using the Scheffé correction for multiple comparisons (12). The homogeneity of variances was tested by the Levine test (12). As DHEAS serum concentrations depend on gender, age, and reproductive status, the serum levels of the hormone were expressed in z-values according to the mean and the standard deviation of the respective control group (z = [patient's value − mean of the control group]/standard deviation of the control group, *e.g.*, a z-transformed value of −2 is a value of 2 SD less than the mean of the respective control group). The relationship between different parameters was demonstrated by Spearman rank correlation analysis because the data were not normally distributed (12). Values were expressed as mean ± standard error of the mean (SEM) with a significance level of $p < 0.05$.

RESULTS

DHEAS serum levels in controls and patients

Mean serum DHEAS concentration of male controls was 2.92 ± 0.17 (range: 0.57–4.71) μg/ml and of female controls, 2.30 ± 0.25 (0.44–8.22) μg/ml. Mean serum DHEAS concentration of male patients with CD was 1.39 ± 0.14 μg/ml (0.08–4.40 μg/ml, p for the difference *vs* male controls < 0.01) and that of female patients with CD was 0.69 ± 0.09 μg/ml (0.03–2.61 μg/ml, p for the difference *vs* female controls < 0.01). Mean serum DHEAS concentration of male patients with UC was 1.16 ± 0.27 μg/ml (0.03–2.61 μg/ml, p for the difference *vs* male controls $<$

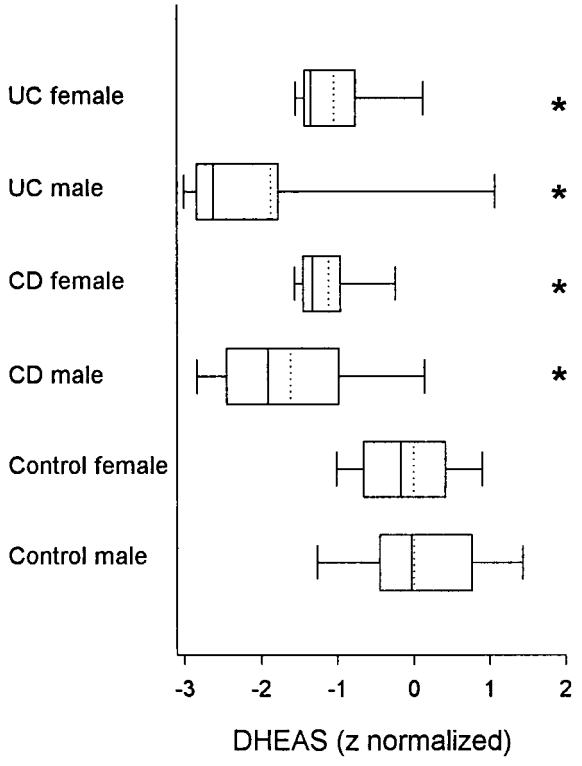

FIG. 1. DHEAS levels in z-transformed values in control male and female subjects and in female and male patients with CD and UC. Box plots represent 10th, 25th, median, 75th and 90th percentiles in solid lines, mean with a broken line. *$p < 0.01$ for the difference *vs* control subjects.

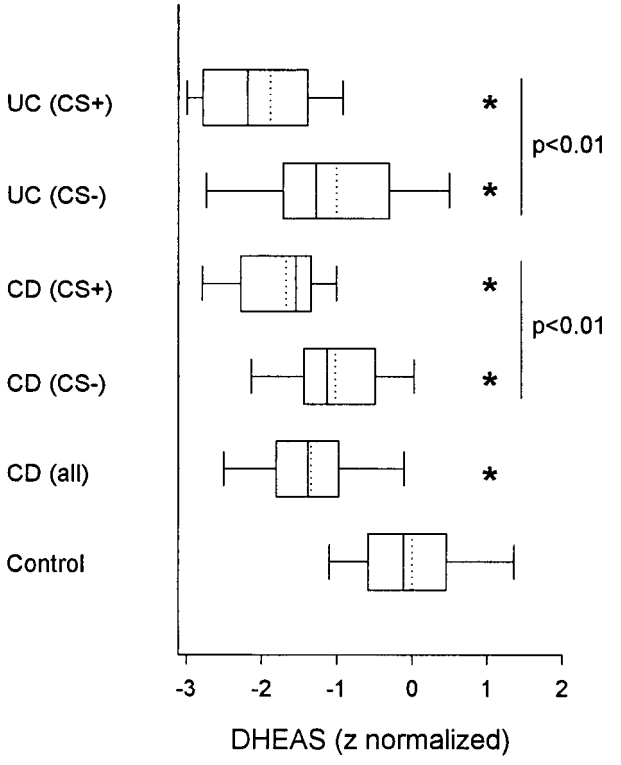

FIG. 2. DHEAS levels in z-transformed values in control subjects, all patients with CD, CD patients without prior corticosteroid treatment (CS−), CD patients with prior CS treatment (CS+), all patients with UC, UC patients without prior CS treatment (CS−), and UC patients with prior CS treatment (CS+). *$p < 0.01$ for the difference *vs* control subjects.

0.01) and that of female patients with UC was 0.78 ± 0.15 μg/ml (0.06–5.70 μg/ml, p for the difference *vs* female controls < 0.01). By definition, the average z-value for DHEAS of all control subjects was zero (0.00 ± 0.18). The average z-value for all CD patients was −1.62 ± 0.15 and for all UC patients −1.88 ± 0.29 (Fig. 1). Figure 1 demonstrates the results of z-normalized data, which are, per definition of z-values, independent of the influence of age, gender, and the reproductive status. There were no significant differences in DHEAS serum levels between male patients with CD and male patients with UC or female patients with CD and those with UC.

DHEAS, cortisol serum levels, and prior corticosteroid therapy

z-normalized DHEAS was significantly lower in all patients with CD and UC than in the control group (for both, $p < 0.01$; Fig. 2). This was more marked in patients receiving prior CS therapy than in patients without prior CS therapy at least 6 wk before study entry (Fig. 2). However, even CD or UC patients without prior CS treatment had significantly lower z-normalized DHEAS serum levels than did control subjects ($p < 0.01$). Furthermore, in CD patients with prior CS treatment cortisol serum levels were also significantly lower than in CD patients without prior CS treatment (10.9 ± 1.2 *vs* 14.7 ± 1.0 μg/dl; $p = 0.019$), which did not reach the significance level in UC patients (14.1 ± 2.0 *vs* 17.0 ± 2.1 μg/dl; $p = 0.315$).

z-normalized DHEAS did not differ in patients with or without therapeutical administration of budesonide, sulfasalazine, 5-ASA, or azathioprine.

DHEAS or cortisol and humoral markers of inflammation

In CD patients, z-normalized DHEAS was inversely correlated with the blood sedimentation rate ($R_{Rank} = -0.241$, $p = 0.017$) and positively correlated with hemoglobin ($R_{Rank} = 0.371$, $p = 0.001$). In these patients, IL-6 was negatively correlated with z-normalized DHEAS in the form of a trend ($R_{Rank} = -0.190$, $p = 0.068$). This was particularly true in CD patients without previous CS treatment (n = 54; blood sedimentation rate: $R_{Rank} = -0.284$, $p = 0.028$; hemoglobin: $R_{Rank} = 0.451$, $p < 0.001$; IL-6: $R_{Rank} = -0.380$, $p = 0.005$). In CD patients, high DHEAS serum levels were associated with less inflammation or low DHEAS serum levels with high inflammation. This association was not found in the smaller group of patients with UC.

In CD patients, cortisol serum levels were significantly positively correlated with blood sedimentation rate ($R_{Rank} = 0.215$, $p = 0.034$) and C-reactive protein ($R_{Rank} = 0.264$, $p = 0.006$). In the smaller group of UC patients, however, no such correlation was found.

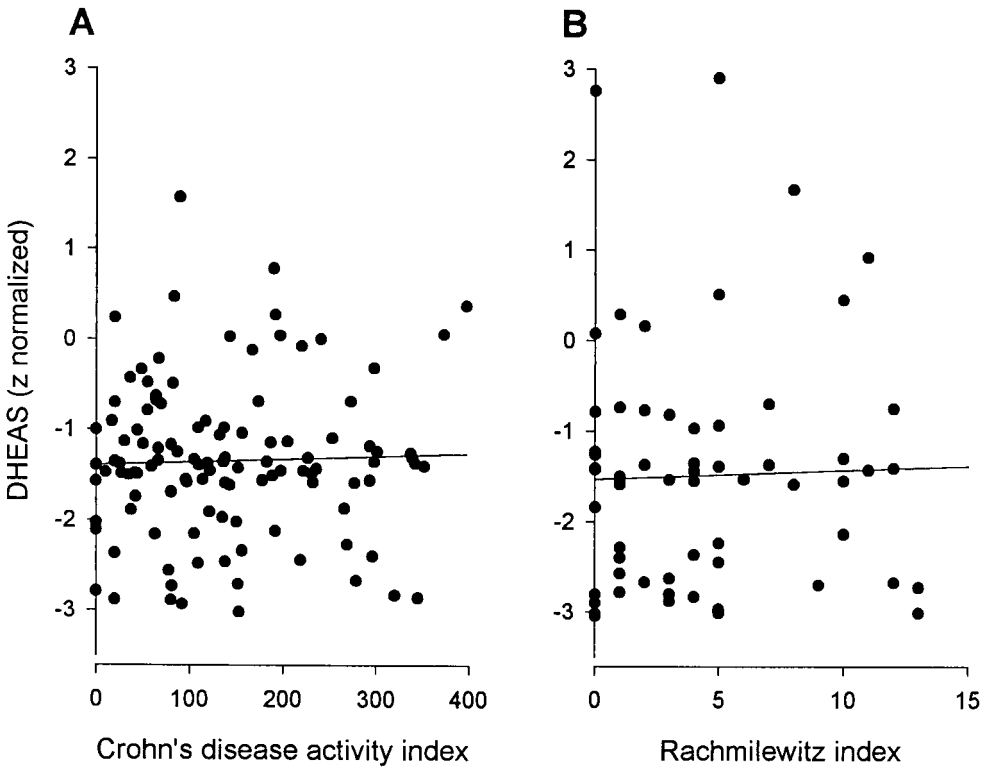

FIG. 3. Correlation of Crohn's disease activity index (*A*) and Rachmilewitz index (*B*) with z-normalized DHEAS. The regression lines are given ($R_{Rank} \cong$ zero in *A* and *B*).

DHEAS or cortisol and clinically assessed disease activity

The average z-normalized DHEAS of inactive CD was -1.68 ± 0.11 and of active CD, -1.70 ± 0.14 (both: p for the difference *vs* control < 0.01). Patients with inactive UC had an average z-normalized DHEAS of -1.82 ± 0.16 and those with active UC, of -1.54 ± 0.26 (both: p for the difference *vs* control < 0.01). With respect to patients with CD or UC, inactive and active disease groups did not differ in z-normalized DHEAS or cortisol serum levels. Figure 3 demonstrates the relationship between CDAI or RI and z-normalized DHEAS. It is obvious that CDAI or RI did not correlate with z-normalized DHEAS (Fig. 3).

Molar ratio of serum levels of cortisol/DHEAS

The molar ratios of serum levels of cortisol/DHEAS in relation to previous CS therapy are given in Figure 4. In patients with CD and UC, serum levels of cortisol are higher in relation to DHEAS. This indicates a shift in biosynthesis into the direction of cortisol in relation to DHEA (Fig. 4). Previous CS therapy increased this effect (Fig. 4). In patients with CD, there was a correlation between the molar ratio of serum levels of cortisol/DHEAS and serum levels of IL-6 ($R_{Rank} = 0.278$, $p = 0.003$), C-reactive protein ($R_{Rank} = 0.246$, $p = 0.011$), hemoglobin ($R_{Rank} = -0.408$, $p < 0.001$), or blood sedimentation rate ($R_{Rank} = 0.423$, $p < 0.001$). However, the molar ratio of serum levels of cortisol/DHEAS did not correlate with the CDAI. In UC patients, no correlation between the molar ratio of serum levels of cortisol/DHEAS and humoral markers of inflammation or RI was detected.

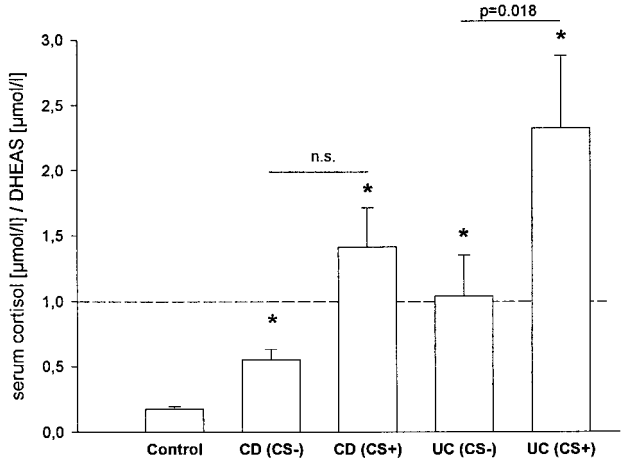

FIG. 4. Molar ratio of serum levels of cortisol/DHEAS in control subjects, CD patients without prior corticosteroid treatment (CS−), CD patients with prior CS treatment (CS+), UC patients without prior CS treatment (CS−), and UC patients with prior CS treatment (CS+). *$p < 0.01$ for the difference *vs* control subjects.

Serum levels of soluble immune mediators in controls and in patients with IBD

IL-6 and TNFα were not detectable in control subjects. IL-1RA, IL-6, and sIL-2R did not differ between control subjects and patients with CD or UC, with or without CS

TABLE 2

Comparison of IL-1RA, IL-6, TNFα, sIL-2R, and sICAM Between Controls, All Patients With CD, Patients With CD Without Corticosteroids (CS), Patients With CD Taking CS Therapy, All Patients With UC, Patients With UC Without CS, and Patients With UC Taking CS Therapy

Parameter	Controls (n = 66)	All Patients With CD (n = 115)	CD Without CS (n = 57)	CD With CS (n = 58)	All Patients With UC (n = 64)	UC Without CS (n = 28)	UC With CS (n = 36)
IL-1RA (pg/ml)	227 ± 62	279 ± 47	280 ± 65	278 ± 51	284 ± 47	279 ± 50	295 ± 117
IL-6 (pg/ml)	ND	5.9 ± 0.8	4.6 ± 1.0	7.3 ± 1.3	4.5 ± 1.1	2.8 ± 0.7	5.9 ± 1.8
TNFα (pg/ml)	ND	19.9 ± 0.9	18.3 ± 1.2	21.6 ± 1.3	17.5 ± 1.3	13.3 ± 1.3*	20.8 ± 1.9*
sIL-2R (U/ml)	272 ± 15	617 ± 56†	662 ± 101†	569 ± 40†	682 ± 41†	669 ± 61†	693 ± 55†
sICAM (ng/ml)	378 ± 22	424 ± 20†	444 ± 27†	402 ± 30†	329 ± 20‡	326 ± 32	332 ± 27

* $p < 0.05$ for the difference between UC without CS *vs* UC with CS; † $p < 0.01$ for the difference *vs* controls; ‡ $p < 0.01$ for the difference *vs* all patients with CD. ND = not detectable. The data are mean ± SEM.

therapy (Table 2). UC patients with CS therapy had significantly higher TNFα then UC patients without CS (Table 2). Patients with CD, irrespective of CS treatment, had significantly elevated sICAM serum levels than control subjects and patients with UC (Table 2). With the exception of IL-6, no significant association was found between DHEAS or cortisol serum levels and the above-mentioned serum cytokines.

DISCUSSION

This study demonstrates significantly decreased serum levels of DHEAS in patients with CD or UC, compared with control subjects. The reduction of DHEAS was dependent on prior CS treatment. However, even patients without CS therapy had significantly decreased DHEAS serum levels than control subjects. With respect to patients with CD, high z-normalized DHEAS (cortisol) was associated with less (high) humoral inflammatory activity and *vice versa*, assessed by the blood sedimentation rate, IL-6, and hemoglobin.

Recent studies showed DHEAS to be abnormally low in patients with chronic inflammatory diseases such as systemic lupus erythematosus (6, 7), rheumatoid arthritis (13), and systemic sclerosis (14). In the present study we demonstrated that DHEAS is also abnormally low in patients with inflammatory bowel disease. As was demonstrated for patients with systemic lupus erythematosus (6), z-normalized DHEAS serum levels in CD and UC were significantly lower in patients with prior CS therapy than in patients without prior CS therapy. This is understandable because DHEAS and cortisol production are inhibited by prior steroid administration (8). Nevertheless, DHEAS serum levels were also reduced in patients without prior CS treatment, compared with control subjects.

The exact reasons for low DHEAS serum levels, specifically in chronic inflammatory diseases (6, 7, 13, 14), are not yet known. Chronic stressful events and continuous inflammation result in high endogenous serum levels of ACTH (15) and cortisol. ACTH and cortisol were found to be elevated, for example, after intravenous administration of IL-1 (16) or IL-6 (17, 18). In the larger group of CD patients, a positive association of cortisol serum levels and high humoral inflammatory activity was confirmed in our study (blood sedimentation rate and C-reactive protein). This association was not shown for clinically assessed disease activity indices, which probably indicates that these indices did not change rapidly, compared with humoral markers of inflammation. Furthermore, in our group of CD patients, high serum levels of DHEAS were significantly associated with decreased inflammation (lower IL-6, lower blood sedimentation rate, higher hemoglobin). This may indicate that CD patients with less inflammation may have lower cortisol levels and higher DHEAS levels, and *vice versa*. This was also shown with respect to the molar ratio of serum levels of cortisol/DHEAS. Because IL-1 (19) and TGFβ1 (20) inhibit the adrenal 17,20 lyase, the shift to cortisol in relation to DHEAS can be explained. From this point of view, low serum levels of DHEAS in relation to cortisol seem to reflect the systemic humoral inflammation in patients with inflammatory bowel diseases. However, the question remains whether DHEAS is only an ample marker of chronic inflammation and stimulated hypothalmus-pituitary-adrenal axis or a pathogenetic factor in these chronic diseases.

With the understanding that DHEA is an important immunomodulator (2–5), it was used to treat autoimmune diseases and was found to be effective (21). However, it is not known by which mechanisms DHEA has positive effects in autoimmune diseases. It may modulate several immune responses, such as cytokine production (2–5, 22). Therefore, the second aim of our study was to correlate DHEAS serum levels with soluble immune mediators in CD and UC. DHEAS did not correlate with any of the measured soluble immune mediators with the exception of the negative correlation between IL-6 and DHEAS in CD patients without prior CS treatment. In an earlier study, we demonstrated IL-6 to be an important pleiotropic cytokine in patients with inflammatory bowel disease, particularly in patients with CD (23). DHEA normalizes excessive IL-6 production in mice, which indicates that DHEA inhibits immune cell responses (24). In a recent study in humans, we demonstrated that DHEA induced inhibition of IL-6 secre-

tion from monocytes and peripheral blood mononuclear cells in healthy subjects and found an inverse correlation between serum levels of DHEA or DHEAS and IL-6 (22). In the large group of CD patients without prior CS treatment, we were able to demonstrate a significantly negative correlation between DHEAS and IL-6, which presumably reflects the downregulation of leukocyte function by this hormone. In patients with prior CS treatment, this correlation may be masked because prior CS treatment significantly influences leukocyte function. Therefore, DHEA decreases and cortisol increases in inflammatory diseases may play an important role in the regulation of immune functions such as IL-6 production. This is also evident with respect to the molar ratio of serum levels of cortisol/DHEAS. The ratio correlated significantly positively with IL-6, C-reactive protein, and blood sedimentation rate, and negatively with hemoglobin. This indicates that high levels of cortisol in relation to DHEAS stimulate IL-6 secretion or *vice versa*. A recent study demonstrates an endotoxin-induced IL-6 increase after prior CS therapy (25), whereas CS administration to cultured cells normally inhibits IL-6 production (26). Under conditions *in vivo*, the CS-induced regulation of IL-6 may be stimulatory or inhibitory, depending on the CS levels available. Because DHEA inhibits IL-6 secretion (22), reduction of DHEA in relation to cortisol, which may be stimulatory, may be of pathogenetic importance in patients with inflammatory bowel disease.

In conclusion, the sex prehormone DHEAS is substantially decreased in patients with inflammatory bowel disease. This may reflect the continuous systemic inflammation, especially in patients with CD. Moreover, because DHEA is an important immunomodulating hormone the lack of this hormone may be of pathogenetic significance in inflammatory bowel disease, which has yet to be demonstrated in longitudinal therapy studies.

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