No alterations of serum levels of adrenal and gonadal hormones in patients with ankylosing spondylitis

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Key words: Ankylosing spondylitis, cortisol, dehydroepiandrosterone sulphate, progesterone, testosterone, estrogens.

ABSTRACT

Ankylosing spondylitis (AS) is a chronic inflammatory disease with a marked preponderance of affected males compared to females of approximately 6 to 1. During the last two decades, this circumstance stimulated several research groups to investigate serum levels of gonadal and adrenal sex hormones. From available results of cross-sectional studies, there seems to be no particular defect in secretion or production of adrenal, gonadal, and pituitary hormones. This is in striking contrast to diseases such as rheumatoid arthritis and other chronic inflammatory diseases. In the latter diseases, low serum levels of dehydroepiandrosterone (DHEA), DHEA sulphate (DHEAS), and testosterone have been described in an advanced chronic disease stage, whereas estrogen serum levels remain normal. Although AS is an inflammatory disease with signs of systemic inflammation such as elevated erythrocyte sedimentation rate or increased circulating proinflammatory cytokines, serum levels of adrenal and gonadal androgens are normal. It is unclear whether this can be considered as unexpected. It may be that inflammation does not reach the pituitary, adrenal, and gonadal glands or does not alter the aromatase complex in peripheral tissue. Furthermore, the inflammation–induced changes may be subtle so that only specific endocrine examination of these axes may reveal signs of alterations. In conclusion, current data on sex steroid hormones provide no straightforward explanation for the male predominance in AS. At the moment, there is no rationale to treat AS patients with sex steroid hormones.

Introduction

In patients with ankylosing spondylitis (AS) there exists an obvious male to female preponderance of approximately 3 - 6 versus 1 (1-3) and also severity seems to be more pronounced in male patients. Due to this gender dysbalance, and since serum levels of adrenal and gonadal hormones and function of endocrine organs were found to be altered in other rheumatic diseases such as e.g. rheumatoid arthritis (recently reviewed in (4)), several research groups focused on serum levels of gonadal and adrenal hormones in AS during the last two decades (5-20). The subject has been reviewed in 1992 and 2000 (19, 21). In the original studies, hormones such as testosterone, 5α-dihydrotestosterone, androstenedione (ASD), dehydroepiandrosterone sulphate (DHEAS), progesterone, 17α-hydroxyprogesterone (17OH), follicle stimulating hormone (FSH), luteinizing hormone (LH) and 17β-estradiol were measured (Fig. 1).

This review will focus on the available data from cross-sectional studies of serum levels of hormones of the hypothalamic-pituitary-adrenal (HPA) axis and the hypothalamic-pituitary-gonadal (HPG) axis in patients with AS. Before presenting this overview in patients with AS, (1) the physiological role of adrenal androgens and (2) the role of adrenal and gonadal hormones in chronic inflammatory diseases other than AS will be discussed.

Role of adrenal androgens in normal physiology

Steroidogenesis in the human adrenal glands consists of three major pathways (Fig. 1): A) mineralocorticoid production (end point: aldosterone), B) glucocorticoid production (end point: cortisol), and C) androgen production (end point: DHEA and androstenedione). The physiological roles of mineralocorticoids and glucocorticoids are well known, however, the role of adrenal androgens is currently under intense investigation. DHEAS is secreted in large amounts from the adrenal
glands (90% of DHEAS from the adrenal glands, serum concentration in the µmolar range) (22), reflecting the adrenal production of its precursor DHEA (22). DHEAS per se has no effect, but after conversion to the biologically active DHEA in peripheral tissue, the hormone is intracellularly processed, yielding active metabolites such as testosterone and 17β-estradiol and many other sex steroids (Fig. 2) (23, 24). As DHEAS is linearly interconverted to DHEA (25), DHEAS is the hormone pool of DHEA and is a stable serum marker for DHEA availability. In the case of decreased DHEAS serum levels, the active hormone DHEA will also decrease. DHEA is converted to ASD by the 3β hydroxysteroid dehydrogenase (3β-HSD, Fig. 1) (22). ASD is an important precursor of testosterone in the follicular phase of the menstrual cycle and in

Identification:
- DHEAS (DHEA sulphate)
- 3β-HSD
- 5α-R (5α-reductase)
- AROM (aromatase)
- DHEA
- DHEA sulfotransferase
- ST: sulfatase
- StAR: steroidogenic acute regulatory protein

**Fig. 1.** Schematic diagram demonstrating the biosynthesis of important steroid hormones. Hormones and precursors are depicted in light grey boxes, and enzymes are demonstrated in dark grey boxes. The white boxes for the two hormones DHEAS and cortisone indicate that they are ineffective metabolites.

**Fig. 2.** Downstream conversion products of DHEA in macrophages. Monocyte-derived macrophages were cultivated for 1 to 5 days in vitro, and the medium was initially supplemented with 360 nmolar radiolabelled DHEA (*DHEA). After 1 and 5 days, the supernatant was collected and conversion products were investigated by thin layer chromatography and HPLC (24). All mentioned hormones appeared in the supernatant and yielded the indicated concentrations. This study indicated that macrophages (peripheral tissue) are able to convert prohormones to downstream effector hormones.

Abbreviations: DHEA: dehydroepiandrosterone; OH: hydroxy; testo.: testosterone.
postmenopausal women (22). DHEA and ASD account for a significant part of testosterone in aged male subjects when the testicular production is markedly decreased (22). Thus, adrenal androgens play an important role in women and men when gonadal glands undergo gradual age-related involution. The immune modulating capabilities of androgens and estrogens will be shortly discussed in the following chapter.

**Role of adrenal and gonadal hormones in chronic inflammatory diseases other than AS**

For both, acute and chronic inflammatory diseases states, alterations of serum levels of hormones of the HPA axis and the HPG axis are demonstrated in Table I. Chronic inflammatory diseases such as inflammatory bowel diseases, rheumatoid arthritis, systemic lupus erythematosus, progressive systemic sclerosis, polymyalgia rheumatica, and pemphigus are characterised by a decrease of serum levels of adrenal and gonadal androgens (26-33) but normal serum levels of estrogens (34,35). Beside this reversal of the molar estrogen / androgen ratio in various chronic inflammatory diseases importance of this ratio will be discussed below), we and others observed a shift to cortisol in relation to DHEA, ASD and DHEAS in chronic inflammatory diseases (31, 33, 36-39). Even short-term inflammation due to cholestasis over 5 to 12 days induced a profound shift to cortisol in relation to adrenal androgens (40). Interestingly, very similar findings can be observed in patients with long-term disease states such as HIV or syphilis infection (41, 42), chronic heart failure (43), or in patients on intensive care units (reviewed in (44)). During an acute inflammatory response, one would expect a parallel increase of serum levels of aldosterone, cortisol, and adrenal androgens due to an increase of the serum levels of the stimulating adrenocorticotropic hormone (45, 46), which also happens in acute inflammatory rheumatic diseases (47). During chronic inflammation, the reason for the unexpected decrease of serum levels of adrenal and gonadal androgens relative to cortisol and estrogens is not yet known. However, a decrease of serum levels of adrenal androgens may lead to a more proinflammatory disease state because DHEA and testosterone have been shown to inhibit pro-inflammatory cytokines such as secretion of TNF and IL-6 (48-56). Furthermore, it was demonstrated that testosterone inhibits the inflammatory disease process in animal models and in human subjects (57-64). In contrast, estrogens, in physiological concentrations, serve to enhance immune responses and may act as important stimulators of human humoral immunity [reviewed in (65)]. It was reported that 17β-estradiol enhances IgG and IgM production by PBMC both in men and women without altering cell viability or proliferation (66). One study confirms that 17β-estradiol has the capacity to increase the production of polyclonal IgG, including IgG anti-DNA in PBMC of SLE patients by enhancing B cell activity via IL-10 (67). Concerning the effects of estrogens on proinflammatory cytokine production (IL-1, IL-6, TNF), these effects seem to be bimodal with decreased synthesis using pharmacological concentrations (10^6 M) and increased synthesis using physiological concentrations (10^4 M) (68-70). Recently, it has been demonstrated that estrogens are able to enhance secretion of matrix metalloproteinases from human fibroblast-like synoviocytes (71). Estrogens inhibit immune cell apoptosis (72) and induce neovascularisation (73). From this point of view, an increase of serum levels or an increase of local levels of estrogens relative to androgens such as DHEA or testosterone will lead to a

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Alteration in acute inflammation</th>
<th>Alteration in chronic inflammation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenocorticotropic hormone</td>
<td>Increased</td>
<td>Normal, low in relation to inflammation</td>
</tr>
<tr>
<td>Cortisol</td>
<td>Increased</td>
<td>Normal, low in relation to inflammation</td>
</tr>
<tr>
<td>Progesterone</td>
<td>Decreased</td>
<td>Decreased</td>
</tr>
<tr>
<td>17-hydroxyprogesterone</td>
<td>Decreased</td>
<td>Decreased</td>
</tr>
<tr>
<td>DHEA, DHEAS</td>
<td>Increased</td>
<td>Decreased</td>
</tr>
<tr>
<td>Androstenedione</td>
<td>Normal</td>
<td>Normal to decreased</td>
</tr>
<tr>
<td>Molar ratio of cortisol / DHEA (DHEAS, ASD)</td>
<td>Normal</td>
<td>Increased</td>
</tr>
<tr>
<td>Molar ratio of cortisol / 17-hydroxyprogesterone</td>
<td>Increased</td>
<td>Increased</td>
</tr>
</tbody>
</table>

**Hypothalamic-pituitary-gonadal axis**

<table>
<thead>
<tr>
<th>Follicle stimulating hormone and luteinizing hormone</th>
<th>Normal to increased</th>
<th>Increased (response to low serum levels of peripheral hormones)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone, 5α-dihydrotestosterone</td>
<td>Decreased</td>
<td>Decreased</td>
</tr>
<tr>
<td>17β-estradiol</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Molar ratio of 17β-estradiol / testosterone</td>
<td>Increased</td>
<td>Increased in acute and chronic disease</td>
</tr>
</tbody>
</table>

**Table I.** Typical changes of serum levels of adrenal, gonadal, and pituitary hormones in patients with inflammatory diseases such as rheumatoid arthritis, inflammatory bowel disease, systemic lupus erythematosus, and polymyalgia rheumatica. Compare also figure 1 for steroidogenesis.

**ASD:** androstenedione; **DHEA:** dehydroepiandrosterone; **DHEAS:** dehydroepiandrosterone sulphate.
more proinflammatory situation.

In recent years, importance of DHEA substitution has been investigated in studies in chronic diseases such as ulcerative colitis (74), systemic lupus erythematosus (75, 76), and adrenal insufficiency (77, 78). The positive effect of DHEA has been demonstrated as a reduction of disease activity (74, 75), increase of bone mineral density (79, 80), and an improvement of well-being and mental health (77). Thus, the third major route of adrenal steroidogenesis – androgen production – may be important in normal physiology and in some inflammatory diseases due to immunomodulatory properties of DHEA or downstream hormones.

Beside the decrease of the adrenal androgens, in rheumatoid arthritis or reactive arthritis cortisol secretion is also inadequately low in relation to systemic inflammation (47,81). This means that the increase of serum cortisol is relatively low in relation to the increase of serum levels of IL-6 and TNF in the acute disease state and, particularly, in the chronic situation. Furthermore, inadequate secretion of cortisol in relation to IL-6 was associated with a more severe form of arthritis (47).

In conclusion, in many chronic inflammatory diseases, serum levels of adrenal and gonadal androgens are decreased, whereas serum levels of estrogens and cortisol remain relatively stable (Table I). An increase of estrogens relative to androgens and relatively low serum levels of cortisol may contribute to the inflammatory disease process. The relative high serum levels of estrogens may be due to an increased conversion of androgens to estrogens in gonadal glands and peripheral tissue, which was found in synovial fluid and synoviocytes of patients with rheumatoid arthritis (unpublished observation).

**Serum levels of hormones of the hypothalamic-pituitary-adrenal (HPA) axis in patients with AS**

Generally, most studies focused only on very distinct sex hormones, and often pituitary hormones were not measured. This does not provide a full picture of endocrine changes of the HPA and HPG axis in AS. Table II summarises five independent studies, which focused on serum levels of cortisol, DHEAS, ASD, and 17OHP. In one study, serum levels of cortisol were found to be normal (14). The degree of inflammation in relation to serum levels of cortisol has not been mentioned in detail. Thus, relative low levels of serum cortisol in relation to inflammation, as demonstrated in rheumatoid arthritis, can not be confirmed.

Three other studies found normal serum levels of ASD, the major precursor of testosterone and estrogens (Fig. 1). This does not indicate a marked alteration of adrenal and gonadal androgen secretion. Two independent studies demonstrated increased serum levels of 17OHP, the precursor of cortisol (Fig. 1) (10,14). This is interesting because 17OHP was found to be decreased in other acute and chronic inflammatory diseases (47, 82). It was speculated that this increase may be due to a deficiency of the enzyme steps of P450c21 and P450c11 (14, 16), which convert 17OHP to cortisol (Fig. 1). However, no specific testing of this pathway has been carried out.

The major adrenal androgen DHEAS was found to be normal in two studies and decreased in one study (11,16, 20). However, in the latter study decrease of serum levels of DHEAS was attributed to prior corticosteroid treatment which is known to reduce the overall adrenal hormone production. From this point of view, this important adrenal androgen precursor seems to be normal in AS. Interestingly, phenylbutazone treatment was shown to influence the assay systems so that a false positive increase of DHEAS and testosterone was observed (16).

**Serum levels of hormones of the hypothalamic-pituitary-gonadal (HPG) axis in patients with AS**

Table III summarises the data of nine independent studies on patients with

### Table II. Changes in serum levels of hormones of the hypothalamic-pituitary-adrenal axis in patients with ankylosing spondylitis.

<table>
<thead>
<tr>
<th>Reference no. and diagnosis</th>
<th>Cortisol</th>
<th>DHEAS</th>
<th>Other findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tapia-Serrano 1991</td>
<td></td>
<td></td>
<td>Elevated 17OHP</td>
</tr>
<tr>
<td>22 male AS</td>
<td></td>
<td></td>
<td>Normal ASD</td>
</tr>
<tr>
<td>Hedman 1992</td>
<td></td>
<td>Normal in AS</td>
<td>Normal pregnenolone sulphate</td>
</tr>
<tr>
<td>25 male AS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arniaud 1998</td>
<td>Normal in AS</td>
<td></td>
<td>Elevated 17OHP, probably due to 21-hydroxylase deficiency. Normal ASD</td>
</tr>
<tr>
<td>57 male AS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Giltay 1998</td>
<td></td>
<td>DHEAS elevated but this is due to prior phenylbutazone treatment</td>
<td>Normal ASD</td>
</tr>
<tr>
<td>50 male AS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dessein 2001</td>
<td></td>
<td>DHEAS is low which most probably depends on prior corticosteroid treatment</td>
<td></td>
</tr>
<tr>
<td>29 male AS</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AS: ankylosing spondylitis; DHEAS: dehydroepiandrosterone sulphate; 17OHP: 17-hydroxyprogesterone.
Sex hormone levels in AS patients / R.H. Straub et al.

Table III. Changes of serum levels of the hypothalamic-pituitary-gonadal axis in patients with ankylosing spondylitis.

<table>
<thead>
<tr>
<th>Reference no., gender, diagnosis</th>
<th>Testosterone</th>
<th>Estrogens</th>
<th>LH, FSH</th>
<th>Other findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gordon 1986</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>31 male RA</td>
<td>Low in RA</td>
<td>Elevated</td>
<td>Normal</td>
<td>Negative correlation of T with ESR, positive correlation of T with haemoglobin</td>
</tr>
<tr>
<td>33 male AS</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>Spestor 1989</td>
<td>Low in RA</td>
<td></td>
<td></td>
<td>No evidence of hyperandrogenicity in AS</td>
</tr>
<tr>
<td>87 male RA</td>
<td>Normal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>48 male AS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jimenez-Balderas 1990</td>
<td></td>
<td>Lower in menstruating women with active disease (also progesterone)</td>
<td></td>
<td>Negative correlation of E2 with ESR</td>
</tr>
<tr>
<td>17 female AS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tapia-Serrano 1991</td>
<td>Normal</td>
<td>Slightly increased E2, inversion of E2/T ratio</td>
<td></td>
<td>Injection of HCG increases E2 and ameliorates the disease</td>
</tr>
<tr>
<td>22 male AS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hedman 1992</td>
<td>Low in RA</td>
<td>Normal</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>25 RA</td>
<td>Normal</td>
<td>Normal E2/T ratio</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25 male AS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arniaud 1998</td>
<td>Normal</td>
<td>Normal E2/T ratio</td>
<td></td>
<td></td>
</tr>
<tr>
<td>57 male AS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Giltay 1998</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>SHBG was normal, phenylbutazone treatment interferes with T measurement (increase of T)</td>
</tr>
<tr>
<td>50 male AS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronson 1998</td>
<td>Normal</td>
<td>Normal</td>
<td></td>
<td>SHBG was lower, no association of T serum levels with fractures</td>
</tr>
<tr>
<td>19 male AS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mitra 1999</td>
<td>Normal</td>
<td>Normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>56 male AS, mild disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AS: ankylosing spondylitis; E2: 17β estradiol; ESR: erythrocyte sedimentation rate; HCG: human chorion gonadotropin; RA: rheumatoid arthritis; SHBG: sex hormone binding globulin; T: testosterone.

AS. A total number of eight studies demonstrated that serum levels of testosterone were normal in male patients with AS (5,7,8,10,11,14-16,18). Three studies directly compared the results of AS patients to data of patients with rheumatoid arthritis and found normal hormone levels in AS but decreased levels in rheumatoid arthritis (5,7,11). Furthermore, there was a subtle increase of 17β-estradiol in relation to testosterone in one study (10), which was not confirmed by others (14,16). In addition, the serum levels of gonadotrophins such as LH and FSH were found to be normal in patients with AS (5,16,18). The sex hormone binding globulin, the major transport protein of sex hormones in blood, was found to be normal in one study and slightly lower in another (16,18). In conclusion, there is no indication for hyper- or hypoandrogenicity in these male patients with AS.

It is not surprising that studies on serum levels of sex hormones in women with AS are rare. One study investigated 10 female menstruating women with AS and found normal serum levels of 17β-estradiol and progesterone as compared to 6 menstruating controls, which was confirmed by Giltay et al. (16). Two other studies found similar serum levels of 17β-estradiol in postmenopausal AS patients as compared to controls (8, 16). In conclusion, there are no changes of sex hormones in female patients with AS.

Conclusion

In contrast to the earliest uncontrolled studies in patients with AS, serum hormone levels of testosterone, DHEAS, 17β-estradiol, and gonadotrophins are normal. The importance of the small elevation of serum 17OHP, has to be confirmed by further studies. These findings in AS are in striking contrast to diseases such as rheumatoid arthritis and other chronic inflammatory diseases. In the latter diseases, low levels of dehydroepiandrosterone (DHEA), DHEA sulphate (DHEAS), and testosterone have been described in an advanced chronic disease stage, whereas estrogen serum levels remain normal. Recent research in rheumatoid arthritis pointed to an increased activity of the aromatase complex in inflamed tissue due to elevated local proinflammatory cytokines stimulating this enzyme (unpublished observation). This mechanism would explain normal serum levels of estrogens and low serum levels of testosterone and the precursors DHEA and DHEAS in rheumatoid arthritis. Although AS is an inflammatory disease with signs of systemic inflammation such as elevated erythrocyte sedimentation rate or increased circulating proinflammatory cytokines, serum levels of adrenal and gonadal androgens...
remain normal. It is unclear whether this can be considered as unexpected. It may be that the inflammatory process does not reach the pituitary, adrenal, and gonadal glands or does not alter the aromatase complex in peripheral tissue. Furthermore, the inflammation-induced changes may be subtle so that only specific endocrine examination of these axes may reveal signs of alterations. These data provide no straightforward explanation for the male predominance in AS. Furthermore, the present studies do not suggest a major role for adrenal and gonadal hormones in perpetuation of the disease. Since these data are from cross-sectional studies of patients with long-standing AS, the role of these hormones during the initiation phase of the disease is unclear. At the moment, there is no rationale to treat AS patients with sex steroid hormones.

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