Primary Sjögren's Syndrome

Clinical Studies with Reference to Hormonal Status, Psychiatric Symptoms and Well-Being

BY

SIGRÍDUR TH. VALTÝSDÓTTIR
Primary Sjögren’s syndrome (pSS) is a chronic inflammatory connective tissue disease of unknown etiology. The disease primarily involves salivary and lacrimal glands which results in oral and ocular dryness (sicca symptoms). A wide spectrum of extraglandular features from various organs may be seen.

In this thesis, the frequency of psychiatric symptoms in women with primary Sjögren’s syndrome was studied and an attempt was made to assess how these symptoms might influence their well being and quality of life. The main finding was that the women with pSS suffered significantly more often from symptoms of anxiety and depression when compared with age matched, healthy females and female patients with rheumatoid arthritis. The physical and mental well-being of the patients with pSS was significantly reduced compared to patient controls.

The possible link of psychiatric symptoms to the altered function of the hypothalamic-pituitary-thyroid-gonadal axis and adrenal androgen secretion was elucidated. Women with pSS have intact cortisol synthesis but reduced serum concentrations of dehydroepiandrosterone sulphate (DHEA-S) (p<0.05) and an increased cortisol/DHEA-S ratio (p<0.05), compared to healthy controls. These findings may reflect a constitutional or disease-mediated influence on adrenal steroid synthesis. Positive correlation was found between DHEA-S serum levels and quality of sexual life (p<0.01) and mental well-being (p<0.01) in women with pSS.

Key words: primary Sjögren’s syndrome, anxiety, depression, well-being, quality of life, hypothalamic-pituitary-thyroid-gonadal axis, androgens.
Í minningu fōðursystur minnar

Jónu Salvarar Bjarnadóttur
This thesis is based on the following publications, which are referred to by their Roman numerals:

I. Valtýsdóttir S Th, Gudbjörnsson B, Lindqvist U, Hällgren R, Hetta J.  
Anxiety and depression in patients with primary Sjögren’s syndrome  
J Rheumatol 2000;27:165-9

II. Valtýsdóttir S Th, Gudbjörnsson B, Hällgren R, Hetta J.  
Psychological Well-Being in Patients with Primary Sjögren’s syndrome  
Clin Exp Rheumatol 2000;18:597-600

III. Valtýsdóttir S Th, Wide L, Hällgren R.  
Low serum dehydroepiandrosterone sulphate (DHEA-S) in women with primary Sjögren’s syndrome as an isolated sign of impaired HPA-axis function  
Accepted for publication in Journal of Rheumatology

IV. Valtýsdóttir S Th, Wide L, Hällgren R.  
Mental well-being and quality of sexual life in women with primary Sjögren’s syndrome are related to circulating dehydroepiandrosterone sulphate (DHEA-S)  
Submitted for publication

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## ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>ACTH</td>
<td>Adrenocorticotropin hormone</td>
</tr>
<tr>
<td>A-4</td>
<td>Androstenedione</td>
</tr>
<tr>
<td>CNS</td>
<td>Central nervous system</td>
</tr>
<tr>
<td>CRH</td>
<td>Corticotrophin-releasing hormone</td>
</tr>
<tr>
<td>DHEA</td>
<td>Dehydroandrostenedione</td>
</tr>
<tr>
<td>DHEA-S</td>
<td>Dehydroandrostenedione sulphate</td>
</tr>
<tr>
<td>FSH</td>
<td>Follicle stimulating hormone</td>
</tr>
<tr>
<td>GQoL</td>
<td>Gothenburg quality of life instrument</td>
</tr>
<tr>
<td>HAD scale</td>
<td>Hospital anxiety and depression scale</td>
</tr>
<tr>
<td>HPA axis</td>
<td>Hypothalamic-pituitary-adrenal axis</td>
</tr>
<tr>
<td>HPG axis</td>
<td>Hypothalamic-pituitary-gonadal axis</td>
</tr>
<tr>
<td>IL</td>
<td>Interleukin</td>
</tr>
<tr>
<td>LH</td>
<td>Luteinizing hormone</td>
</tr>
<tr>
<td>LHRH</td>
<td>Luteinizing hormone-releasing hormone</td>
</tr>
<tr>
<td>MRH test</td>
<td>Multiple releasing test</td>
</tr>
<tr>
<td>PGWB</td>
<td>Psychological general well-being index</td>
</tr>
<tr>
<td>pSS</td>
<td>Primary Sjögren’s syndrome</td>
</tr>
<tr>
<td>QoL</td>
<td>Quality of life</td>
</tr>
<tr>
<td>RA</td>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td>SHBG</td>
<td>Sex hormone-binding globulin</td>
</tr>
<tr>
<td>SLE</td>
<td>Systemic lupus erythematosus</td>
</tr>
<tr>
<td>T</td>
<td>Testosterone</td>
</tr>
<tr>
<td>TRH</td>
<td>Thyroid releasing hormone</td>
</tr>
<tr>
<td>TSH</td>
<td>Thyroid stimulating hormone</td>
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INTRODUCTION

Primary Sjögren’s syndrome

Primary Sjögren’s syndrome (pSS) is a chronic autoimmune exocrine disease characterised by salivary and lacrimal gland destruction progressing to xerostomia and xerophthalmia (sicca symptoms) (1, 2). In addition to these glandular symptoms, the disease can progress to become a systemic disorder affecting the lungs, kidneys, gastrointestinal tract, joints, muscles and vessels (3, 4) and in some patients it evolves into a B-lymphocyte neoplasia (5). Furthermore, patients with pSS often express neuropshychiatric features such as fatigue, anxiety and depressed mood (6-9).

Primary Sjögren’s syndrome is a common disease, affecting 2.7% of people aged 55-72 in Sweden (10). However, pSS is underdiagnosed and the average time from the onset of symptoms to diagnosis is about three years (11). Like most autoimmune diseases, it is more common in women, with a female:male ratio of about 9:1 (12, 13).

Psychiatric symptoms in rheumatic diseases

There is no evidence that rheumatic diseases are more prevalent among psychiatric patients than in the general population (14-16). Symptoms of anxiety and depression often accompany physical disease. Nevertheless, measurements of psychiatric symptom profiles may reveal important aspects of how individuals are affected by chronic disorders. Among rheumatoid arthritis (RA) patients, the presence of psychological distress such as depression and negative mood is well documented in the literature (17, 18). The frequency of RA patients classified as being depressed differs, however, between studies (17-21). Apart from possible variation due to differences in disease severity between the patient groups studied, a second source of variation could be differences in the type of instrument applied. Patients with RA have a crippling disease with severe joint inflammation and prominent deterioration of functional capacity. It is therefore reasonable to assume that these symptoms in RA may affect their psychiatric symptomatology. In systemic lupus erythematosus (SLE), another immune-mediated disease, it is assumed that the immune system may be involved in the pathophysiology of psychiatric symptoms seen in this disease (22-25). There is strong evidence to support the role of cytokines in depression. Several mechanisms have been suggested to account for cytokine-induced depression. Firstly, cytokines may activate the
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hypothalamic-pituitary-adrenal axis (HPA axis) either directly through their effects on corticotrophin-releasing hormone (CRH) (26) or indirectly through cytokine-induced glucocorticoid-receptor resistance (27), which may lead to HPA hyperactivity by impairing feedback inhibition (28). Secondly, pro-inflammatory cytokines may change monoamine neurotransmitters in multiple regions of the brain (29). For example, the acute-phase response, characterised by elevated serum levels of interleukin-6 (IL-6) and acute phase proteins, may contribute to reduced availability of L-tryptophan (30), which is well known to lead to decreased serotonin availability in the central nervous system (CNS) (31). Lastly, cytokine receptors are expressed in neurons throughout the CNS, which raises the possibility that certain cytokines function as neurotransmitters (32) and thus exert direct CNS effects. Psychiatric illness may be difficult to diagnose in the presence of physical disorders, especially if the disorder is of a chronic nature. In recent years, some investigators have reported frequent and wide spectrum of psychiatric symptoms in patients with pSS (7-9, 33, 34). The first study to investigate the spectrum of neuropsychiatric manifestations associated with pSS was conducted by Malinow et al. (8). Affective disorders, hypochondrias and hysteria were the most common disturbances in their study.

Quality of life in rheumatic diseases

By definition, quality of life (QoL) is a subjective parameter, accruing information about the patient’s physical and psychological state (35). One important aspect of the way individuals are affected by the disease are measurements of quality of life and symptom profiles. In recent years, growing interest has been shown in measuring QoL in various patient groups. The impact of RA and SLE on the physical, psychological and social functions of the individual, which are important factors in quality of life, has been well documented (36-40). Less is known about the effects of pSS on QoL. Primary Sjögren’s syndrome is a disease with diffuse symptomatology which may result in a delay in diagnosis. Patients with pSS are characterised by constant discomfort from dryness in almost every mucous membrane, arthralgia and myalgia (3). However, severe fatigue is often the main complaint and reports have also documented frequent sleeping disturbances and difficulties in association with sexual intercourse due to dyspareunia (6, 41, 42). So the disease may influence the life situation of the patients in various ways. Recently, three studies have reported on the way well-being is affected in patients with pSS. Sutcliffe et al. compared 37 pSS patients with SLE patients in a study in which they determined the accumulated end organ damage and
health status (43). They found that patients with pSS seldom had end organ damage, but the degree of functional ability is as great as in SLE. Thomas et al. reported in a population study that pSS could affect approximately 3-4% of adults and in the general population appears to be associated with a clinically significant impairment of a subject’s health and well-being (44). Strömbeck et al. used health-related quality of life instrument to denote that part of quality of life that is influenced by a person’s is health. They found that the health-related quality of life was significantly reduced in pSS women compared to healthy controls and comparable to the levels in women with RA and fibromyalgia (45).

There are two basic types of questionnaires, generic and disease specific (46), for evaluating QoL. Generic instruments are applicable in a wide variety of populations because they cover the complete spectrum of function, disability and distress that is relevant to quality of life. An alternative approach to QoL measurements is to focus on specific aspects of disease, to a certain function (e.g., emotional or sexual function) or to a given condition or problem (e.g., pain) that may be caused by various underlying diseases. Previous studies on the QoL in patients with connective tissue diseases have focused on RA using both generic and disease-specific instruments (36-38, 47).

**Neuroendocrine axis**

*The hypothalamic-pituitary-adrenal (HPA) axis*

The HPA axis and the sympathetic and adrenomedullary (symphatic) systems are the peripheral limbs of the stress system, whose main function is to maintain basal and stress-related homeostasis (48). The HPA axis is regulated by many factors, but, in healthy individuals, the HPA axis is primarily regulated by the hypothalamic peptide corticotropin-releasing hormone (CRH), which stimulates the secretion of adrenocorticotropic hormone (ACTH) in the pituitary (Figure 1). ACTH, in turn, stimulates cortisol and androgen secretion by the adrenal cortex. In a feedback loop, cortisol inhibits both hypothalamic CRH and pituitary ACTH secretion (49, 50). Interaction between the immune system and this axis is particularly important. Hyper- or hypoactivity of the HPA axis has been implicated in various pathophysiological states, including systemic autoimmune diseases (51)(Table 1).
Increased HPA-axis function is a normal response to the stress of inflammation and might be mediated by the central and peripheral action of circulating cytokines (52). In addition to interleukin-1 (IL-1) and tumour necrosis factor-α (TNF-α), IL-6 appears to be a major factor mediating interactions between the activated immune system and both the anterior pituitary cells and steroidogenesis (53, 54). The result in this case would be the suppression of the inflammatory response through the potent anti-inflammatory/immunosuppressive effects of the endogenous glucocorticoids. In patients with chronic RA, adaptations of the HPA axis would be expected to take place. Assuming that chronic inflammation induces enhanced ACTH secretion and, secondary to that, adrenal hypertrophy, one would expect a high secretion rate of glucocorticoids in response to normal ACTH stimulation, as seen in chronically stressed animals or major depression (55-57). However, in a chronic inflammatory disease like RA, a different pattern is seen, characterised by a relative reduction in cortisol responses, despite elevated plasma ACTH levels (58). These findings might be the result of chronic inflammation, but they could also be related to genetic or constitutional factors (59). Furthermore, neuroendocrine abnormalities have been found in fatigue syndromes including fibromyalgia and chronic fatigue syndrome. It is believed that at least some of the lethargy and fatigue symptoms in these conditions may be related to a subtle adrenal insufficiency, which may in some cases be of primary origin and in others of central and hypothalamic origin (60, 61). Few clinical observations exist in patients with pSS when it comes to their HPA axis. A previous study by Johnson et al. of the cortisol/ACTH secretion

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**TABLE 1**

**States associated with hyper- or hypoactivity of the HPA-axis**

<table>
<thead>
<tr>
<th>Increased HPA-axis activity</th>
<th>Decreased HPA-axis activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cushing’s syndrome</td>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td>Pregnancy (last trimester)</td>
<td>Chronic fatigue or fibromyalgia</td>
</tr>
<tr>
<td>Melancholic depression</td>
<td>Adrenal insufficiency</td>
</tr>
<tr>
<td>Chronic alcoholism</td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>Chronic stress</td>
<td>Atypical or seasonal depression</td>
</tr>
<tr>
<td>Long-term excessive exercise</td>
<td>Nicotine withdrawal</td>
</tr>
<tr>
<td>Fischer-rat model</td>
<td>Lewis-rat model</td>
</tr>
<tr>
<td>After glucocorticoid therapy</td>
<td>Postpartum period</td>
</tr>
<tr>
<td>After chronic stress</td>
<td></td>
</tr>
</tbody>
</table>

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*Primary Sjögren’s syndrome*
pattern in eight females with pSS demonstrated slightly yet significantly reduced basal levels of ACTH and cortisol, while their CRH-induced incremental responses appear to be parallel (62). Assuming that there is a physiologically intact HPA-glucocorticoid axis function in pSS, both plasma ACTH and serum cortisol basal levels would be expected to be elevated as a result of an inflammatory process. Patients with pSS often demonstrate a systemic inflammatory reaction of low-grade intensity, in contrast to patients with RA, and it has therefore been suggested that other mechanisms lie behind these perturbations in the HPA axis. Firstly, patients with pSS often express neuropsychiatric features such as fatigue, anxiety and depressed mood (6, 7, 33) and these chronic stress symptoms may be associated with various disturbances in neuroendocrine reactivity. Secondly, they could be related to genetic or intrinsic tendencies.

**FIGURE 1.**
The hypothalamic-pituitary-adrenal axis. Cytokine or neural input stimulate the hypothalamus to secrete CRH and the pituitary to secrete ACTH, resulting in adrenal secretion of cortisol and androgens. CRH = corticotropin; ACTH = adrenocorticotropic hormone.
Hypothalamic-pituitary-gonadal (HPG) axis

Hypothalamic neurons secrete the luteinizing hormone-releasing hormone (LHRH), which drains into the anterior pituitary. The LHRH is secreted in a pulsatile fashion under brain control, and determines gonadotropic cell secretion rates in the anterior pituitary. The gonadotropes secrete both follicle stimulating hormone (FSH) and luteinizing hormone (LH). Under the control of LH, androgens, i.e. androstenedione (A-4) in particular and testosterone, are synthesised by the theca interstitial cells. In turn, under the control of FSH, granulosa cells synthesise oestrogens, by the aromatisation of A-4 and testosterone, respectively (49). Studies of adults with RA, osteoarthritis and ankylosing spondylitis in relation to FSH and LH report conflicting results (63-66). In two studies of patients with SLE, no abnormalities in serum levels of FSH and LH were noted (67, 68). In another study of seven males with SLE, Vilarinho et al. noted significantly higher FSH levels in the patients compared with the controls but no difference in LH levels (69). The authors suggest that the reason for the discordance between LH and FSH both before and after LHRH stimulation may be testicular dysfunction. There are few studies to show that FSH and LH play any direct role in modulating immune response, but these hormones may play a secondary role in autoimmunity.

Hypothalamic-pituitary-thyroid (HPT) axis

Thyroid stimulating hormone (TSH) and prolactin are produced in the anterior pituitary under stimulation from thyroid releasing hormone (TRH)(49). Many stress-related diseases display significant disturbances in thyroid axis function (70, 71) and thyroid dysfunction has been associated with autoimmune conditions such as RA and SLE (72, 73). Several studies of thyroid disease in pSS have been reported and the results reveal that hypothyroidism or thyroiditis was found in 13-54% of the patients, whereas hyperthyroidism was less frequent (74-76). Previous reports on hypothyroidism have suggested an association with a hypothalamic CRH deficiency and Johnson et al. reported that hypoactivity of the HPA axis in pSS was associated with elevated basal TSH concentrations, thus supporting this view (62).

Prolactin is known to stimulate humoral and cellular immune responses (77). Previously, elevated levels of prolactin has been suggested to influence the outcome of the disease in patients with SLE (78) but in a recent studies hyperprolactinemia was found only in few patients (79) and there was a lack of correlation with disease activity (80).
Furthermore, it has been suggested that mild hyperprolacintemia is a risk factor for the development of autoimmunity (77). In fact, hyperprolactinemia has been reported in patients with pSS, especially in patients with active immunological disease with internal organ disease (81).

**Androgens and autoimmunity**

Adrenal steroids are derived from pregnenolone, which in turn is largely synthesised from cholestrol (50). A summary of adrenal steroidogenic pathways are shown in Figure 2.

**FIGURE 2.**
Summary of the human adrenocortical steroidogenic pathways. Adrenal steroids are derived from pregnenolone, which in turn is synthesised from cholesterol. The major biosynthetic pathways of the mineralcorticoids, glucocorticoids (cortisol), DHEA, DHEA-S, androstenedione, testosterone and estradiol are shown.
Dehydroepiandrosterone sulphate (DHEA-S)

The adrenal cortex is the primary source of circulating concentrations of dehydroepiandrosterone (DHEA) and DHEA-S, with DHEA-S as the most abundant product of the adrenals (82). In healthy women, the synthesis of DHEA and DHEA-S occurs exclusively in the adrenal cortex and the adrenal secretion is like that of cortisol stimulated by ACTH (83, 84). Circulating concentrations of DHEA-S are approximately 250 times higher than those of DHEA in women (85) and DHEA has a shorter half-life of 1-3 hours, while the half-life of DHEA-S is 10-20 hours. Secreted DHEA-S can be converted in tissues to the potent androgens testosterone, dihydrotestosterone and androstenedione (A-4) (86). Much has been published about the potential effects of DHEA-S on various systems and changes in endogenous concentrations associated with different diseases (Table 2)(87). Androgens generally tend to suppress both cell-mediated and humoral activity. DHEA and DHEA-S have been found to have immunomodulatory activities by influencing the cytokine production of T lymphocytes (88). In particular, DHEA-S has been found to repress the expression and activity of the human IL-6 gene promoter, thus supporting the concept of anti-inflammatory /immunosuppressive effects exerted by androgenic steroids (89). IL-6 has a strong effect on steroid release and may be one of the factors controlling the long term adrenal response to stress, because this cytokine is able to act synergistically with ACTH on the adrenal cells (90). Previous studies of adrenal androgens and autoimmune diseases have indicated low plasma concentrations of DHEA/DHEA-S due to corticosteroid therapy or disease activity (91-94). There is an hypothesis that sex hormones contribute to the pathophysiology of RA, because of the female predominance of the disease. Data from controlled, prospective studies in women reveal significantly lower mean serum levels of DHEA, four to fifteen years before the onset of RA, compared with non-rheumatic controls, suggesting a link between low levels of androgens and the risk of RA (95, 96). In patients with SLE, several studies have documented low levels of androgenic-anabolic hormones including DHEA and DHEA-S (91, 94). The administration of DHEA to these patients produced a reduction in disease activity (92, 97). No studies of pSS and DHEA can be found in the literature; however, experimental studies in mouse SS models have demonstrated that androgens reduced lymphocytic infiltration in lacrimal and salivary glands, the major target organs in pSS (98-100). DHEA and DHEA-S are classified among the group of steroids known as neurosteroids, so named because they can be synthesised de novo in the CNS (101). Concentrations of DHEA and
DHEA-S are higher in the brain than in other organs. DHEA-S appears to modulate primarily two types of neurotransmitter receptor in the CNS. On the one hand, DHEA-S acts as a GABA-A antagonist and, on the other, it acts as a sigma receptor agonist (102). Through the latter mechanism, DHEA-S enhances NMDA-induced neuronal excitability (103). Receptor studies of the effects of DHEA and/or DHEA-S suggest that these hormones have the potential to exert clinically relevant effects in the CNS. Studies of the CNS effects of DHEA-S include correlations of hormone concentrations with mood and sense of well-being and studies of the effects of DHEA administration on depression and cognition (104).

TABLE 2

Endogenous DHEA and DHEA-S concentrations observed in the presence of disease states.

<table>
<thead>
<tr>
<th>Disease states</th>
<th>DHEA</th>
<th>DHEA-S</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anorexia nervosa</td>
<td>↓</td>
<td>↔</td>
</tr>
<tr>
<td>Burn trauma</td>
<td>NR</td>
<td>↔</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>↔</td>
<td>↓</td>
</tr>
<tr>
<td>Critical illness</td>
<td>NR</td>
<td>↓</td>
</tr>
<tr>
<td>Depression</td>
<td>↓</td>
<td>NR</td>
</tr>
<tr>
<td>End-stage renal disease</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Non-insulin-dependent diabetes mellitus</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>NR</td>
<td>↓</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>↓</td>
<td>NR</td>
</tr>
<tr>
<td>Systemic lupus erythematousus</td>
<td>↓</td>
<td>↓</td>
</tr>
</tbody>
</table>

Abbreviations: ↓ = decrease, ↔ = no difference, NR = not reported

Testosterone (T) and Androstenedione (A-4)

Testosterone is regarded as the most important circulating androgen in both men and women. In most target tissues, testosterone acts via the androgen receptors after conversion to
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the terminal biological active androgen 5α-dihydrotestosterone, but it can also act directly or via the estrogen receptor after conversion to estradiol-17β (105). Testosterone is strongly bound to sex hormone-binding globulin (SHBG) and this limits the biological activity of the steroid (106). Only 20% of circulating testosterone in women is produced by direct ovarian secretion. The remaining 80% is produced by the peripheral conversion of A-4 from the ovaries and from the adrenal cortex and of DHEA and DHEA-S from the adrenal cortex (107). The administration of testosterone has been shown to reduce both humoral and cell-mediated immune responses (12). A-4, DHEA-S and testosterone have been found to be significantly lower in female patients with SLE, particularly those with active disease (94). Furthermore, patients with RA have been shown to have low levels of testosterone (108, 109) and the administration of testosterone has shown a slight disease modifying effect, although it was not statistically significant (110). Recent studies show that testosterone therapy as mentioned above dramatically suppresses lymphocyte infiltration in, and significantly improves the functional activity of, lacrimal glands in Sjögren’s syndrome animal models (98-100) suggesting androgen therapy should be considered as a possible treatment for patients with pSS.

Androgen status – effects on sexuality, depression and well-being

The relevance of hormonal changes in general in women which are associated with the menopause, sexuality and well-being is of some clinical importance in view of the widespread use of hormone replacement therapy. Androgens are known to perform several important functions in women, including the maintenance of libido, but there is a little information about the relationship between endogenous androgens and sexual life (111-113). No effect by DHEA on the libido has previously been reported (114), but a recent double-blind, placebo-controlled study reveals that DHEA replacement therapy had profound effects on the libido of elderly women but not on that of elderly men (115). Sarrel et al. reported that sexual desire, satisfaction and frequency in postmenopausal women taking hormonal therapy were improved significantly by combined estrogen-androgen therapy but not by estrogen or estrogen-progestin therapy (116). This suggests that androgens play a pivotal role in sexual function but that estrogens are not a significant factor when it comes to determining the levels of sexual drive and enjoyment. In addition it is important to remember that other factors than the hormonal balance can have an effect on sexual life in women; depression and anxiety
may, for example, cause a progressive decline in interest in sexual behaviour leading to low libido, difficulty in sexual arousal, secondary anorgasmia and/or frank sexual aversion.

The studies relating to sense of well-being and DHEA-S have produced a diffuse picture (114, 117, 118), but a large French epidemiological study of people aged 65 and older demonstrated a correlation between circulating concentrations of DHEA-S and the feeling of well-being (86). Morales et al. reported that restoring DHEA-S to young adult levels in both men and women of advancing age brought about an improvement in physical and psychological well-being in both genders (114), while Wolf et al. failed to observe similar results (119). Reasons for the observed differences could be the length of the treatment, as well as the age of the subjects.

Studies of depression in relation to serum DHEA-S concentrations have also produced conflicting results (87). Barrett-Connor et al. found that reduced levels of DHEA-S were significantly associated with depressed mood in a cohort of community-dwelling post-menopausal women (120), while Cawood et al. found no such connection (121). In spite of this, studies have provided evidence that DHEA treatment may reduce depressive symptomatology in patients with depression or dysthymia, while having no effects on cognition. In a double blind study, Arlt et al. found that DHEA replacement therapy resulted in a significant improvement in well-being and sexuality in women with adrenal insufficiency (122). In the same study, the greatest improvements during DHEA treatment occurred in the levels of depression and anxiety, a finding that supports previous studies suggesting that DHEA exert neurosteroidal action.
AIMS OF THE STUDY

The aims of the studies presented in this thesis were:

• to evaluate anxiety and depression in patients with pSS and assess how psychiatric symptoms might influence their well-being and QoL and to compare this with patients with RA. (Paper I and II)
• to explore the hypothalamic-pituitary-thyroid-gonadal axis and adrenal androgen secretion in women with pSS. (Paper III)
• to investigate, whether or not reduced circulating levels of androgens are linked to the increased frequency of psychiatric manifestations, impaired well-being and quality of sexual life in women in pSS. (Paper IV)
SUBJECTS

In all, 83 patients with primary Sjögren’s syndrome, 70 patients with RA and 63 healthy individuals participated in the studies (Table 3). The diagnosis of pSS was based on the preliminary EEC criteria (123), but the patients also fulfilled the Copenhagen criteria (124). The diagnosis of RA was made according to the ACR criteria (125). The patients with pSS and RA were followed up as outpatients at the Department of Rheumatology, University Hospital of Uppsala, Sweden.

TABLE 3

The subjects in the four papers.

<table>
<thead>
<tr>
<th>Group of subjects</th>
<th>N</th>
<th>Investigations</th>
</tr>
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<tbody>
<tr>
<td>Paper I</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pSS</td>
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<td>HAD scale</td>
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<td>PSS</td>
<td>38</td>
<td>GQoL instrument</td>
</tr>
<tr>
<td>RA</td>
<td>38</td>
<td>GQoL instrument + HAD scale</td>
</tr>
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<td>HC</td>
<td>63</td>
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<tr>
<td>Paper II</td>
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<td>PGWB Index</td>
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<td>RA</td>
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<td>MHR test</td>
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<td></td>
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</tbody>
</table>

Abbreviations: pSS = primary Sjögren’s syndrome, RA = rheumatoid arthritis, HC = healthy controls, HAD scale = hospital anxiety and depression scale, GQoL instrument = the Gothenburg quality of life instrument, PGWB Index = Psychological General Well-Being Index and MHR-test = multiple releasing hormone test.
Primary Sjögren's syndrome

**Paper I**

Sixty-seven patients (mean age 58, range 28-85 years) with pSS were included. The response rate for the HAD scale was 93% and for GQoL 61%. The onset of disease occurred one to eighteen years (mean 6.5 years) prior to the study. Thirty-four patients had extra-glandular manifestations. Eighteen patients were being treated with disease-modifying drugs and eight were taking glucocorticoids at the time of evaluation. Thirty-eight patients with RA with (mean age 60, range 29-84 years) and 63 healthy individuals (mean age 57, range 54-60 years) living in Uppsala and selected from a random population sample, served as healthy controls. There was one male in each group, but all the other participants were females.

**Paper II**

Thirty-four female patients with pSS (mean age 56, range 43-79 years) with a mean disease duration of 6 years (range 1-13 years) were included in the study. Nineteen patients had only glandular symptoms, whereas 11 also had extraglandular manifestations. Nine patients were being treated with hydroxychloroquine and four with glucocorticoids. Thirty-two female patients with RA with mean age 58 (range 34-84) who had the onset of the disease one-40 years (mean 16 years) prior to the study were used as patient controls. In the RA group 19 patients were being treated with disease-modifying drugs and 11 with glucocorticoids. The patients with pSS were the same individuals as in Paper I.

**Paper III**

Ten female patients (mean age 54, range 44-69 years) with pSS with the disease duration of 5 years (range 1-15 years) were included here. Six patients had extraglandular manifestations. No patient was being treated with disease-modifying drugs apart from one who was being treated with hydroxychloroquine. None of the patients was on or had previously been treated with glucocorticoids or hormone replacement therapy. Ten healthy women without any medication served as controls. Their mean age was 53 years (range 44-61 years). None of the patients or the controls was a smoker.

**Paper IV**

This study comprised twenty-one female patients (mean age 56, range 39-71 years) with pSS. The onset of the disease occurred one to 15 years (mean 4 years) prior to the study. Eight patients had extraglandular manifestations, but no one was being treated with disease-
modifying drugs, apart from one patient who was being treated with hydroxychloroquine. Seven patients were on oestrogen treatment and 17 were postmenopausal. All of the patients were cohabiting or married, except for one who was divorced. Ten of the patients participated in the study reported in Paper III.

**METHODS**

**The Hospital Anxiety and Depression Scale (HAD) (Paper I)**

The Hospital Anxiety and Depression Scale (HAD scale) is a brief, self-administered rating scale which is designed to measure anxiety and depression in somatically ill individuals (126). It has been validated for screening for psychiatric morbidity in several patient groups (20, 127-129). The questionnaire comprises 14 items for self-assessment on a scale of 0 - 3. Seven questions are related to anxiety and seven to depression. The whole scale range is 0 - 21 for depression and anxiety measurements. Scores of eight or more on each sub-scale represent “possible” psychiatric morbidity and a score of 11 or more presents “definite” clinically anxiety or depression (126). The depression subscale has been constructed in such a way that somatic items are largely excluded.

**The Gothenburg quality of life instrument (GQoL) (Paper I)**

The GQoL instrument is a standardised self-administered questionnaire. The first part, which assesses social, physiological and psychological well-being, uses a scale comprising seven steps (score 1-7) where the extreme points are “excellent”, “could not be better” and “very bad”. The second part includes 30 questions about different symptoms (130). The participants were asked: “Have you been troubled by any of the following symptoms during the past three months? Answer with yes or no”. The GQoL instrument has been validated to assess well-being and symptoms and is useful both as a descriptive tool and as an aid in evaluating treatment (131-133).

**Psychological General Well-Being Index (PGWB) (Papers II and IV)**

The schedule is a self-assessed inventory related to general well-being (134) and has been used in various clinical setting and has been documented with regard to its reliability and validity (135-137). The PGWB index comprises twenty-two items with a six point response scale. The factors of anxiety, depressed mood, positive well-being, self-control, general health
and vitality are related to the total score. The subscales of these measured factors have three to five items. For each item, there are six response options that are rated on a scale of 1 to 6, according to the intensity or frequency of the affective experience. The score range for the PGWB index is 22 to 132; a higher score represents greater well being.

**McCoy Sexual Rating Scale (Paper IV)**

Sexual life was assessed with the McCoy scale which covers sexual experience and responsiveness during the last 30 days (112, 138, 139). This instrument contains ten items on a seven point scale relating to different aspects of sexual life, such as frequency of intercourse, orgasm frequency, sexual pleasure and satisfaction, lubrication, dyspareunia, arousal, sexual fantasies and satisfaction with partner.

**Specific questions about pain and tiredness (Paper IV)**

We used isolated questions to assess tiredness and pain in the patients. In terms of assessed tiredness, we asked how the patients had felt during the past week on a scale of one to six with extreme the points of “none of the time” and “the whole time”. Pain was assessed on a scale one to six with the extreme points “no pain” and “very bad pain”.

**Multiple releasing hormone test (Paper III)**

A multiple releasing hormone test (MRH test) was performed at 8 a.m. after an overnight fast by injecting 100 µg CRH (Bissendorf, Hannover, W-Germany), 100 µg LHRH (Hoechst, Frankfurt, W-Germany) and 200 µg TRH (Hoechst, Frankfurt, W-Germany) intravenously. Venous blood samples for hormone analyses were drawn via an indwelling needle 10 minutes before and immediately prior to the injections of the three releasing hormones and then after +10, +20, +30, +45, +60 and +90 minutes. The blood samples were cooled on ice and centrifuged at 4°C. The serum samples were stored frozen pending analysis. At the same time, 10 ml of venous blood were collected and stored at -20°C pending measurement of plasma ACTH.

**Hormone measurements (Papers III and IV)**

Follicle stimulating hormone (FSH), luteinizing hormone (LH), thyroid stimulating hormone (TSH), prolactin, growth hormone (GH), sex hormone-binding globulin (SHBG) and cortisol were measured with time-resolved fluoroimmunoassays (autoDelfia™ hFSH,
autoDelfia™ hLH Spec, autoDelfia™ hTSH ultra, autoDelfia™ Prolactin, autoDelfia™ hGH, autoDelfia™ SHBG and autoDelfia™ cortisol; Wallac OY, Turku, Finland). ACTH was measured by a chemiluminiscence immunoassay (Nicholas Institute Diagnostics; San Juan Capistrano, CA, USA). 17α-hydroxyprogesterone was measured with a radioimmunoassay kit (OPH-CT; Cis Bio International, Gif-Sur-Yvette Cedex, France). Androstenedione was measured with radioimmunoassay (Androstenedione Radioimmunoassay Kit; Ortho-Clinical Diagnostics, Texas, USA). Total testosterone was measured with a solid phase radioimmunoassay (Coat-A-Count total testosterone; Diagnostic Products Corporation, Los Angeles, USA). Dehydroepiandrosterone sulphate (DHEA-S) was measured with a chemiluminescence immunoassay (Dehydroepiandrostenedione sulphate (DHEA-S); Nichols Institute Diagnostics, San Juan Capistrano, CA, USA).

**Statistical methods**

The data in Papers I and II were evaluated with a Statview SE + Graphics (Abacus Concepts Inc., Berkely, CA), while those in Papers III and IV were evaluated with a Statview for windows (SAS Institute Inc., Cary, NC). Values are given as percentage or as the mean ± SD or SEM (range) as indicated. Non-parametric tests, the Mann-Whitney U-test and the Spearman’s Rank correlation test were used to analyse data between groups and their correlation to clinical data. A correction of factors (Bonferroni) was employed for the comparison of symptoms between the two patient groups and p-values in Paper II.

**RESULTS**

**Paper I**

*Hospital Anxiety and Depression Scale*

The mean score on the HAD scale for anxiety was 7.48 in patients with pSS (Table 4) and 48% of them were in the range for possible clinical anxiety, i.e. score of ≥8. The equivalent score for RA patients was 5.0 (p < 0.05) and 22% of them were in the range for possible anxiety (Figure 3). Nineteen per cent of patients with pSS and 7% of patients with RA had a score of ≥11, reflecting definite anxiety. The mean score on the HAD depression scale was 6.1 for the pSS patients and 32% of them were in the range for possible clinical depression, i.e. a score of ≥8, while only 10% of the RA patients had a score of ≥8 (p<0.05).
The pSS patients therefore had a significantly higher score for depression than the RA group (p < 0.05) (Figure 3). Eight per cent of patients with pSS and 2.5 % of patients with RA had a score of ≥11 reflecting definite depression.

**TABLE 4**

Comparison of the mean scores of the Hospital Anxiety and Depression scale relating to anxiety and depression in the two patient groups (primary Sjögren’s syndrome and rheumatoid arthritis), as well as in group of healthy female controls.

<table>
<thead>
<tr>
<th></th>
<th>pSS</th>
<th>RA</th>
<th>HC*</th>
<th>pSS/RA</th>
<th>pSS/HC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety</td>
<td>7.48(±3.66)</td>
<td>5.0(±2.85)</td>
<td>6.2(±3.3)</td>
<td>0.05</td>
<td>0.05</td>
</tr>
<tr>
<td>Depression</td>
<td>6.1(±3.7)</td>
<td>3.9(±2.77)</td>
<td>4.0(±2.8)</td>
<td>0.05</td>
<td>0.001</td>
</tr>
<tr>
<td>N</td>
<td>62</td>
<td>38</td>
<td>63</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Healthy controls

**FIGURE 3.**

The prevalence of depression and anxiety in patients with primary Sjögren’s syndrome (n=62) and patients with rheumatoid arthritis (n=38) (p<0.05).
**The Gothenburg quality of life instrument**

The prevalence of various symptoms was studied in patients with pSS and RA. The physical and mental well-being of the patients with pSS was significantly reduced compared with controls. Furthermore, patients with pSS complained more frequently of depressed mood, irritability, headache, gastrointestinal symptoms, impaired concentration and memory than the RA patients.

**Conclusion:** Patients with pSS often suffer from psychiatric symptoms and poorer well-being compared with patients with RA. Importantly, their somatic symptoms may be connected to and secondary to their psychiatric disturbance.

**Paper II**

The total score for PGWB was 84.9 ±16.2 in patients with pSS. The score for patients with RA was 97.7 ±17.5 and was significantly higher (p=0.001). The patients with pSS reported depression (p=0.0009), as well as poorer well-being (p=0.002) and vitality (p=0.003), significantly more frequently than the RA patients. However, the experience of anxiety, general health and self-control was similar in the two patient groups (Table 5). Those patients with pSS who were on oestrogen therapy (n=19) had a total PGWB score (79.6 ±14) which was lower (p=0.05) than that of the patients who were not taking oestrogen (90 ±16). This kind of influence by oestrogen on the results was not found in patients with RA; the mean PGWB score was 96.4 ±21 for RA patients on oestrogen therapy (n=12) and 100 ±16 for patients without oestrogen. No correlations were seen between the score for the PGWB index and age, disease duration, disease activity (defined by the acute-phase reaction and anaemia) or extraglandular manifestations in patients with pSS.

**Conclusion:** The results suggest that patients with pSS have poorer quality of life, a higher degree of distress and a poorer sense of well-being than patients with RA.
TABLE 5

Mean scores for the Psychological General Well-being scale Index in patients with primary Sjögren’s syndrome (pSS=34) and patients with rheumatoid arthritis (RA=32). The data are presented as mean ± SD.

<table>
<thead>
<tr>
<th></th>
<th>pSS</th>
<th>RA</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total score</td>
<td>84.9(±16.2)</td>
<td>97.7(±17.5)</td>
<td>p=0.001†</td>
</tr>
<tr>
<td>Anxiety</td>
<td>21.6(±4.8)</td>
<td>24.4(±4.6)</td>
<td>p=0.018</td>
</tr>
<tr>
<td>Depressed mood</td>
<td>13.2(±3.0)</td>
<td>15.6(±2.5)</td>
<td>p=0.0009†</td>
</tr>
<tr>
<td>Positive well-being</td>
<td>13.7(±3.1)</td>
<td>16.1(±3.4)</td>
<td>p=0.002†</td>
</tr>
<tr>
<td>Self-control</td>
<td>13.6(±2.6)</td>
<td>15.1(±2.6)</td>
<td>p=0.013</td>
</tr>
<tr>
<td>General health</td>
<td>10.6(±2.8)</td>
<td>11.1(±3.1)</td>
<td>ns</td>
</tr>
<tr>
<td>Vitality</td>
<td>12.2(±4.4)</td>
<td>15.4(±4.4)</td>
<td>p=0.003†</td>
</tr>
</tbody>
</table>

† Significant according to Bonferroni correction

Paper III

Basal hormone concentrations

Baseline serum levels of ACTH and cortisol, the gonadotropins FSH and LH, prolactin, TSH and GH were similar in female pSS patients and healthy female controls. Patients with pSS had a significantly lower mean DHEA-S value (2.4 ± 0.4 vs 3.9 ± 0.3 umol/L respectively; p<0.05) and their cortisol/DHEA-S ratio was significantly higher than that of the healthy controls (171 ± 39 vs 76 ± 5 respectively; p<0.05). A correlation was found between basal values of ACTH and DHEA-S in the patients with pSS (r=0.650; p=0.05) but not in the control group. The androgens testosterone and androstenedione as well as hydroxyprogesterone and sex hormone binding globulin (SHBG) were similar in patients and controls. Subgrouping into pre- or postmenopausal patients and controls had no effect on the results (Table 6).
**TABLE 6**

Baseline concentrations of FSH, LH, prolactin, TSH, GH, testosterone, androstenedione, 17-alfa-hydroxyprogesterone, SHBG, ACTH, cortisol and DHEA-S in 10 patients (p) with pSS compared with 10 controls (c).

<table>
<thead>
<tr>
<th>Hormones</th>
<th>Patients</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FSH (IU/L)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fertile (p=4; c=4)</td>
<td>37.5 ± 19.5</td>
<td>8 ± 2</td>
</tr>
<tr>
<td>Postmenopausal (p=6; c=6)</td>
<td>59 ± 17.5</td>
<td>56 ± 10</td>
</tr>
<tr>
<td><strong>LH (IU/L)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fertile (p=4; c=4)</td>
<td>15.6 ± 7.2</td>
<td>8.4 ± 4.8</td>
</tr>
<tr>
<td>Postmenopausal (p=6; c=6)</td>
<td>28.8 ± 5.4</td>
<td>28.2 ± 5.4</td>
</tr>
<tr>
<td><strong>Prolactin (ug/L)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>5.0 ± 0.8</td>
<td>6.2 ± 1.3</td>
</tr>
<tr>
<td><strong>TSH (mU/L)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3.1 ± 0.9</td>
<td>2.2 ± 0.3</td>
</tr>
<tr>
<td><strong>GH (mU/L)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.1 ± 0.9</td>
<td>2.2 ± 1.2</td>
</tr>
<tr>
<td><strong>Testosterone (nmol/L)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.8 ± 0.1</td>
<td>0.8 ± 0.1</td>
</tr>
<tr>
<td><strong>Androstenedione (nmol/L)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fertile (p=4; c=4)</td>
<td>5.3 ± 0.6</td>
<td>4.8 ± 0.5</td>
</tr>
<tr>
<td>Postmenopausal (p=6; c=6)</td>
<td>4.0 ± 0.5</td>
<td>5.6 ± 0.9</td>
</tr>
<tr>
<td><strong>17-alfa-hydroxyprogesterone (nmol/L)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fertile (p=4; c=4)</td>
<td>3.8 ± 1.4</td>
<td>2.6 ± 1.3</td>
</tr>
<tr>
<td>Postmenopausal (p=6; c=6)</td>
<td>1.1 ± 0.1</td>
<td>1.4 ± 0.2</td>
</tr>
<tr>
<td><strong>SHBG (nmol/L)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>56 ± 10</td>
<td>40 ± 6</td>
</tr>
<tr>
<td><strong>ACTH (ng/L)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>18.7 ± 2</td>
<td>23.7 ± 3.3</td>
</tr>
<tr>
<td><strong>Cortisol (nmol/L)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>309 ± 23</td>
<td>296 ± 28</td>
</tr>
<tr>
<td><strong>DHEA-S (umol/L)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.4 ± 0.4</td>
<td>3.9 ± 0.3 *</td>
</tr>
</tbody>
</table>

Data are presented as the mean ± SEM. Significant level by Mann-Whitney U test ; * p<0.05.

Abbreviations: FSH = follicular stimulating hormone, LH = luteinizing hormone, TSH = thyroid stimulating hormone, GH = growth hormone, SHBG = sex hormone binding globulin, ACTH = adrenocorticotropin hormone, DHEA-S = dehydroepiandrosterone sulphate
Stimulation tests

The ACTH response in the MRH test was lower in patients compared with controls but the difference in the response was not significant (Figure 4); more specifically the peak value for the ACTH response (ng/L) in patients and controls was $51.7 \pm 29$ vs $75.5 \pm 34$ ($p > 0.05$). When it came to cortisol, the responses in patients and controls were fairly similar (Figure 5). The patients had significantly lower serum values of DHEA-S both at baseline and after the MRH test (Figure 6). As expected no appreciable peaks in DHEA-S were detected in either group because of its long half-life in blood. The response of other measured hormones was similar in patients and controls.

**Conclusion:** The results show that women with pSS have intact cortisol synthesis but reduced serum concentrations of DHEA-S compared with healthy controls.

**FIGURE 4.**
The levels of plasma ACTH before and after an intravenous MRH test in 10 patients with pSS compared with 10 healthy controls. Data are presented as the mean ± SEM.
FIGURE 5.
The levels of serum cortisol before and after an intravenous MRH test in 10 patients with pSS compared with 10 healthy controls. Data are presented as the mean ± SEM.

FIGURE 6.
The serum levels of DHEA-S before and after an intravenous MRH test in 10 patients with pSS compared with 10 healthy controls. Data are presented as the mean ± SEM.
Paper IV

The total mean score ± SD for the PGWB scale was 88.9 ±13 in the pSS patients. The total PGWB score was correlated to serum DHEA-S (r=0.60; p<0.01) (Figure 7) but not to the serum levels of testosterone and androstenedione or the testosterone/SHBG ratio. The PGWB subscale data in relation to hormone levels are shown in Table 7. The variables of depression, mental well-being, general health and self-control were all related to the DHEA-S values. General health and self-control were also correlated to serum levels of testosterone and androstenedione.

FIGURE 7.
Correlation between DHEA-S serum levels and total PGWB score in 21 patients with primary Sjögren’s syndrome (r=0.60; p<0.01).
TABLE 7

Correlation coefficients between the mean scores of the Psychological General Well-being scale Index and androgen hormone levels in 21 patients with primary Sjögren’s syndrome.

<table>
<thead>
<tr>
<th></th>
<th>Total score</th>
<th>Anxiety</th>
<th>Depression</th>
<th>Well-being</th>
<th>General health</th>
<th>Vitality</th>
<th>Self-control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.11</td>
<td>-0.33</td>
<td>-0.14</td>
<td>-0.50</td>
<td>0.02</td>
<td>0.57*</td>
<td>0.02</td>
</tr>
<tr>
<td>DHEA-S</td>
<td>0.60**</td>
<td>0.17</td>
<td>0.62**</td>
<td>0.64**</td>
<td>0.67**</td>
<td>0.23</td>
<td>0.67**</td>
</tr>
<tr>
<td>T</td>
<td>0.37</td>
<td>0.05</td>
<td>0.03</td>
<td>0.10</td>
<td>0.51*</td>
<td>0.05</td>
<td>0.51*</td>
</tr>
<tr>
<td>A-4</td>
<td>0.39</td>
<td>0.16</td>
<td>0.28</td>
<td>0.34</td>
<td>0.49*</td>
<td>-0.06</td>
<td>0.50*</td>
</tr>
<tr>
<td>T/SHBG</td>
<td>0.05</td>
<td>0.11</td>
<td>-0.08</td>
<td>-0.08</td>
<td>0.12</td>
<td>-0.22</td>
<td>0.12</td>
</tr>
</tbody>
</table>

Spearman’s rank correlation coefficients. Significant correlations *=p<0.05, **=p<0.01.
†T= testosterone, A-4= androstenedione, SHBG= sex hormone binding globulin.

Four of our patients had no active sex life and were therefore excluded from the calculations relating to a possible relationship between McCoy rating scale and hormone serum levels. Significant positive correlations were seen between serum DHEA-S and total McCoy score (r=0.62;p<0.01) (Figure 8), the item assessing arousal and the subscores for desire and satisfaction (Table 8). No such correlation was seen between the total McCoy score or its subscores and testosterone and androstenedione levels or the T/SHBG ratio, except between testosterone and dyspareunia. Ten (59%) and nine (53%) patients complained about vaginitis sicca and dyspareunia, respectively. No differences in hormone levels were found in postmenopausal or premenopausal patients, or between those who were or were not on hormone replacement therapy. No association was found between vaginitis sicca and the hormone variables. There was no correlation between age and DHEA-S levels or total McCoy score. The serum levels of the measured hormones and the sexual or psychological well-being variables were not related to tiredness, pain or laboratory inflammatory activity.

Conclusion: The circulating levels of the DHEA-S are positively related to the quality of sexual life and mental well-being in women with pSS.
TABLE 8

Correlation coefficients between psychosexual and androgen hormone variables in 17 women with primary Sjögren’s syndrome.

<table>
<thead>
<tr>
<th></th>
<th>Total McCoy</th>
<th>Arousal</th>
<th>Desire</th>
<th>Satisfaction</th>
<th>Dyspareunia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>-0.13</td>
<td>-0.21</td>
<td>-0.23</td>
<td>-0.07</td>
<td>-0.36</td>
</tr>
<tr>
<td>DHEA-S</td>
<td>0.62**</td>
<td>0.59*</td>
<td>0.52*</td>
<td>0.66**</td>
<td>0.65**</td>
</tr>
<tr>
<td>T†</td>
<td>-0.31</td>
<td>-0.16</td>
<td>-0.07</td>
<td>-0.26</td>
<td>0.47*</td>
</tr>
<tr>
<td>A-4†</td>
<td>-0.20</td>
<td>0.10</td>
<td>0.08</td>
<td>0.44</td>
<td>0.33</td>
</tr>
<tr>
<td>T/SHBG</td>
<td>-0.39</td>
<td>-0.18</td>
<td>-0.29</td>
<td>-0.42</td>
<td>0.13</td>
</tr>
</tbody>
</table>

Spearman’s rank correlation coefficients. Significant correlations *p<0.05, **=p<0.01. †T= testosterone, A-4= androstenedione.

FIGURE 8.

Correlation between DHEA-S serum levels and total McCoy score in 17 patients with primary Sjögren’s syndrome (r=0.62; p<0.01).
DISCUSSION

Primary Sjögren’s syndrome is a chronic, slowly progressive disorder, characterised by constant discomfort from dryness in almost every mucous membrane, arthralgia and myalgia (2-4). However, severe fatigue is often the main complaint among patients with pSS and the reason for the lethargy is still unknown. Furthermore, patients with pSS have a high frequency of sleep disturbance (6) and difficulty performing sexual intercourse due to dyspareunia (42). Patients with pSS express a wide range of constitutional symptoms with diffuse symptomatology which may result in a delay in diagnosis. The disease may therefore affect the life situation of the patients in various ways and our clinical impression has been that effects on psychiatric health are common in patients with pSS. In the first part of this current work, this suspicion is confirmed by the finding that almost half the patients with pSS suffered from various degrees of anxiety and depression was present in one-third of the patients. In contrast, patients with RA, who often have severe joint inflammation and prominent deterioration in functional capacity, had these symptoms to the same extent as healthy controls.

In the same study, we investigated the prevalence of various symptoms with regard to aspects of well-being. With regard to physical and mental well-being, the patients with pSS were significantly more affected than the patients with RA, as patients with pSS complained more frequently of depressed mood, irritability, headache, gastrointestinal symptoms and impaired concentration and memory. In Paper II, was demonstrated that quality of life (QoL) is substantially affected in patients with pSS not only in comparison with patients with RA but also compared with a number of other somatic conditions (135-137). This may seem surprising as RA is a disease more frequently characterised by inflammatory activity and can have a crippling outcome, while pSS is a disease with more discrete somatic symptoms. Previously reported studies of the way well-being is affected in patients with pSS have produced similar results and also correspond with our finding in Paper II that significantly impaired QoL was not related to the extraglandular manifestations in pSS.

The reason why patients with pSS experience a reduction in QoL and well-being is unknown, but it may be related to hormonal status, as patients with pSS who were taking oestrogen had a low PGWB index score (Paper II). No such negative influence by oestrogen was seen in the RA group. This observation made us suspect that a change in the hormonal

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balance may contribute to the poorer quality of life in females with pSS. This possible negative impact of oestrogen on the quality of life in pSS may be related to an oestrogen-dependent upregulation of immune activity in the disease process, in accordance with what is seen in SLE, another B-cell-driven immune disease (140). An important question arises from the fact that pSS and rheumatoid arthritis, two classic autoimmune diseases associated with opposing immune responses, appear to respond in opposite fashion to female hormones, although both diseases are more prevalent in women (12). Obviously, the female hormonal environment is complicated and the female connection is not simple; however, it is not likely to be explained by the preponderance of a single hormone.

Evidence suggests that rheumatic diseases are associated with the hypoactivity of the hypothalamic-pituitary-gonadal axis. Furthermore, several studies have documented low serum levels of androgenic-anabolic hormones including DHEA and DHEA-S (94, 141). Few clinical observations exist in patients with pSS when it comes to their HPA axis or sex hormone status. In the present study, the HPA axis function demonstrated normal basal and CRH-stimulated cortisol levels in female patients with pSS, in spite of a tendency towards low ACTH levels at baseline and after stimulation. In a previous study by Johnson et al. of the cortisol/ACTH secretion pattern in females with pSS, demonstrated, significantly reduced basal levels of ACTH and cortisol while the CRH-induced incremental responses appeared to be parallel (62). Assuming that there is a physiological intact HPA-glucocorticoid axis function in pSS, both plasma ACTH and serum cortisol basal levels would be expected to be elevated as a result of an inflammatory process. Products of the immune system, such as pro-inflammatory cytokines, stimulate parts of the CNS including the hypothalamus, thereby activating the HPA-glucocorticoid axis through both an endocrine and a neural spinal route (52, 142). The result in this case would be the suppression of the inflammatory response through the potent anti-inflammatory/immunosuppressive effects of the endogenous glucocorticoids. However, in a chronic inflammatory disease like RA, a different pattern is seen, characterised by a relatively reduction in cortisol responses in spite of elevated plasma ACTH levels (58). These findings might be the result of chronic inflammation, but they could also be related to genetic or constitutional factors (59). Like our investigated patients, patients with pSS often demonstrate a systemic inflammatory reaction of low-grade intensity in contrast to patients with RA.

In the present study, we have demonstrated that female patients with pSS have a significantly lower secretion of both baseline and stimulated levels of DHEA-S than healthy female controls. Similar levels for the androgens, testosterone and A-4, were seen in both
groups (Paper III). These findings could reflect hypoactivity in the adrenal cortex with the intact secretion of both ACTH and cortisol both before and after CRH stimulation, since the HPA-androgen axis appears to be a more sensitive indicator of adrenocortical hypofunction. Alternatively, these findings could suggest that either the pituitary or the hypothalamus is hyporesponsive and, in order to maintain normal cortisol secretion it may be a shift from DHEA/DHEA-S production to glucocorticoid synthesis. Fatigue is one of the most prominent symptoms in patients with pSS (41) but the reason for the lethargy is unknown. Studies of chronic fatigue syndrome (60, 61, 143) suggest that CRH deficiency rather than glucocorticoid deficiency contributes to the lethargy and fatigue seen in these patients.

DHEA, DHEA-S and A-4 are the major circulating adrenal androgens in females. Testosterone is produced to a limited extent but has a stronger androgen activity. ACTH is documented as a hormone which stimulates the adrenal cortical synthesis of androgens without feedback control (83, 84, 107). In Paper III, we demonstrated that female patients with pSS have decreased circulating levels of DHEA-S but normal testosterone and androstenedione serum levels at baseline and after stimulation. Previous studies of adrenal androgens and autoimmune diseases have suggested low plasma DHEA/DHEA-S due to ongoing or previous glucocorticoid therapy or even inflammatory activity (91-94). However, an influence of this kind can be excluded in our study since the patients with pSS had never been treated with glucocorticoids and had low laboratory inflammatory activity. Furthermore, investigators have suggested that lower levels of serum androgens may contribute to the incidence and severity of RA (96), which is the most frequent autoimmune connective tissue disease and, like SLE and pSS, predominantly afflicts women. Whether low DHEA-S levels predispose to these diseases or the levels are influenced by disease variables remain unsettled. DHEA and DHEA-S have been found to have an immunomodulatory effect by influencing the cytokine production of T lymphocytes (88, 100) and may be of relevance for the induction and maintenance of autoimmune diseases. The administration of androgens including DHEA has been used to ameliorate disease signs in animal models of pSS (98-100) and to reduce various symptoms in humans with SLE and RA (92, 97, 144).

Several studies have shown an association with hypothyroidism or thyroiditis in patients with pSS (74-76). In the present study, we found similar basal and TRH stimulated levels of TSH in patients and controls. Prolactin is known to exert profound pro-inflammatory effects by stimulating humoral and cellular responses (145, 146) and hyperprolactemia has been associated with a number of autoimmune diseases including SLE (70, 78). However, the association of hyperprolactemia with SLE has been questioned in recent studies (79, 80).
found similar prolactin serum levels in pSS and controls, both at baseline and after TRH stimulation. Haga et al. reported moderately increased levels of basal serum prolactin in patients with pSS and especially in those who had an active inflammatory disease with internal organ manifestations (81).

DHEA and DHEA-S are classified among the group of steroids known as neurosteroids and are believed to have effects on brain excitability and animal behaviour (101, 104). Studies of depression and sense of well-being in relation to serum DHEA-S concentrations have produced conflicting results (87). However, studies have shown that reduced levels of DHEA-S were significantly associated with depressed mood and feeling of well-being (86, 120). Restoring DHEA-S in both men and women have produced an improvement in physical and psychological well-being (114) and, in an open-labelled study, DHEA administration had beneficial effects on symptoms of depression (147). In the current study, we observed an association between low DHEA-S levels and a lower total score in the PGWB index in females with pSS. Furthermore, there were strong correlations between serum DHEA-S and the subscales for depression, sense of well-being, general health and self-control.

For a variety of reasons, it can be assumed that rheumatic diseases influence sexual function. There are several studies that investigate the influence of rheumatic diseases on sexual motivation and the results show that many patients have problem with sexuality (148-151). Women with pSS have diminished vaginal lubrication, which may cause painful intercourse (42). About 60% of our patients had difficulty with intercourse because of vaginal dryness and dyspareunia, but we found no association between total McCoy score and decreased vaginal lubrication. Our knowledge of the influence of endogenous androgens on sexual life in women is limited (111, 113). In a longitudinal study of the effects of menopause on sexuality, it has been shown that testosterone is associated with the frequency of sexual behaviour (112). In the present study, we found correlation between decreased psychosexual function and low levels of serum DHEA-S but not with testosterone or androstenedione. This may support the notion that DHEA-S is important for the androgen status and sexual function in women with pSS.

This current work has demonstrated that females with pSS frequently suffer from psychiatric symptoms and poorer well-being, which can affect their quality of life. Patients with pSS have lower circulating levels of DHEA-S but intact cortisol synthesis. The low circulating serum levels of DHEA-S are positively related to their quality of sexual life and mental well-being. We suggest that replacement therapy with DHEA should be considered as a possible future strategy to improve well-being and sexual life in women with pSS.
GENERAL CONCLUSIONS

• Anxiety and depression are common in patients with pSS. The symptoms are more frequent than in control groups. The physical and mental well-being of these patients were significantly reduced, which may affect their quality of life.

• When evaluating the hypothalamic-pituitary-adrenal (HPA) axis we found that females with pSS had significantly lower mean DHEA-S values both at baseline and after stimulation. We also demonstrated normal basal and CRH-stimulated ACTH and cortisol levels. These findings may therefore reflect an intrinsic or disease-mediated influence on adrenal androgen synthesis.

• The circulating levels of DHEA-S are positively related to mental well-being and quality of sexual life in women with pSS.
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Primary Sjögren’s syndrome


