The Role of Androgens in Rheumatic Diseases

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Knowledge of the physiological effects of sex hormones has advanced considerably since the second century BCE. In China, sex hormones were actually extracted from human urine by the process of sublimation, and estrogens and androgens were purified and used in the treatment of a variety of ailments, including hypogonadism and dysmenorrhea. During the last 50 years, the involvement of estrogens/androgens in the pathophysiology and therapy of rheumatic diseases has been proposed on the basis of new findings regarding their interference in molecular mechanisms of the immune/inflammatory reaction [1,2].

Generally, androgens exert suppressive effects on both humoral and cellular immune responses and seem to function as natural anti-inflammatory hormones [1]. This review discusses current knowledge on androgens and rheumatic diseases.

Biological aspects and genetic background of androgens

Sex hormone concentrations, evaluated particularly in patients with rheumatoid arthritis before glucocorticoid therapy, were frequently found to be altered, especially in men and premenopausal women [3]. In particular, low gonadal testosterone/dihydrotestosterone and adrenal androgens dehydroepiandrosterone and its sulphate levels, as well as reduced androgen/estrogen ratio, were detected in the body fluids (blood, synovial fluid, smears, saliva) of male and female RA patients, supporting the possible pathogenic role for the decreased levels of the immunosuppressive androgens [4].

The pathway of sex steroid synthesis involves the sequential degradation of cholesterol to progestin, then androgens (i.e., testosterone) and finally estrogens (i.e., 17β-estradiol) [Figure 1]. This pathway is found in both genders, and circulating plasma concentrations of sex hormones are representative of the relative conversion of androgens and estrogens. It is the ratio of androgens to estrogens that creates a male and not a female milieu. Sex hormones can exert local actions (paracrine) in the tissues in which they are formed or enter the circulation. Several physiological, pathological and therapeutic conditions may change the sex hormone milieu and/or peripheral conversion. These include the menstrual cycle, pregnancy, postpartum period, menopause, chronic stress, inflammatory cytokines, use of corticosteroids, oral contraceptives and steroid hormonal replacements – each of which induces altered androgen/estrogen ratios and related effects [5].

Recently, considerable interest has focused on endocrine disruption – a new area of endocrinology concerned with chemicals that mimic hormones, in particular sex steroids [6]. Chemicals that mimic estrogens (the so-called estrogenic xenobiotics) have been the main focus of the research. By blocking androgen action, exposure to these anti-androgens may evoke changes similar to those associated with estrogen exposure [7]. Furthermore, genetic polymorphism affecting the levels or function of androgens and estrogens may lead to an imbalance in the complex hormonal-immune system interaction and might contribute to the etiology of RA.

The estrogen synthase (CYP19) locus is the cytochrome p450 that catalyzes the conversion of C19 androgens to C18 estrogens. In RA, a linkage to this locus has been described in sibling-pair families having older age at the onset of disease (> 50 years) [8]. CYP19 polymorphisms that lead to higher levels of CYP19 or a higher enzyme activity lead to reduced levels of androgens, and presumably would make such older subjects hypoandrogenic and more susceptible to RA. The increase in RA incidence that occurs in older ages as androgen production declines in both genders, in addition to the low gonadal and adrenal androgens (that correlate to disease activity) in RA patients, as well as the decline in the female excess with age and the rarity of the disease in young males, add interest to the observed CYP19 polymorphism [9].

Recently, Huang et al. [10] indicated a relationship between CYP17 genotypes and the age at onset of rheumatoid arthritis in female patients. The CYP17 gene, coding for the cytochrome P450c17α, mediates both steroid 17α-hydroxylase and 17,20-lyase activities which represent the key points in human steroidogenesis [Figure 2]. A single base

RA = rheumatoid arthritis

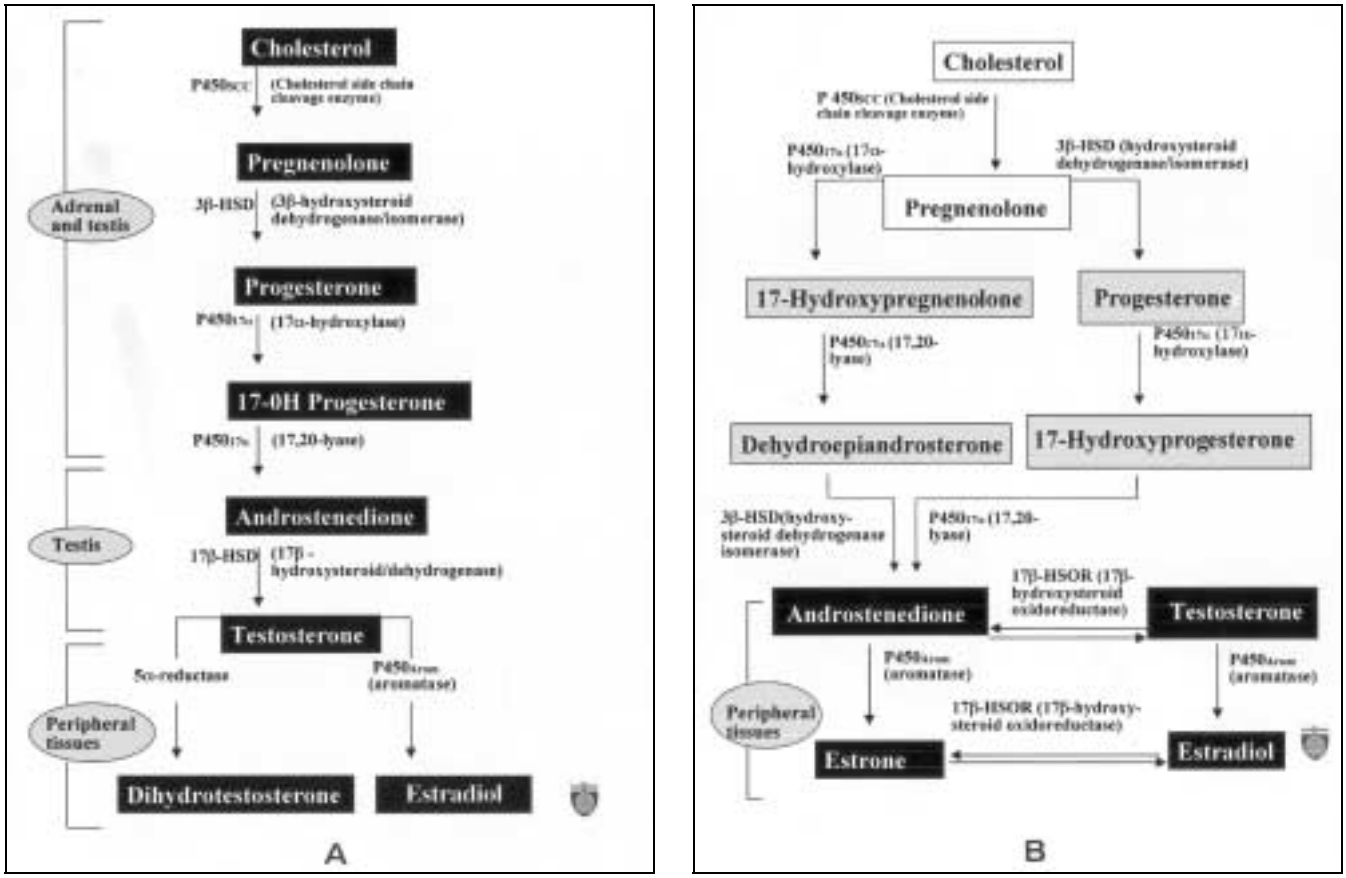

Figure 1. The principal pathway of steroid hormone biosynthesis in the testis **[A]** and the ovary **[B]**, and the conversion of androgens to other active hormones in peripheral tissues.

change in the 5' promoter region of the CYP17 creates an additional Sp-1-type promoter site that might cause increased expression. These authors found a new recognition site presented as two alleles (A1 and A2). Interestingly, they observed that female RA patients with the A2 allele tended to develop the disease at a younger age than those without, and having the A2 allele was a protective factor against older age onset of female RA. The results of the study suggest that the A2 allele is related to early onset and the A1 allele to late onset. In fact, the A2 allele, being an expression of increased CYP17 activities, is thought to be linked to elevated production of both estrogens and androgens through increased transcription [10]. Given that androgens function generally as immunosuppressors, whereas estrogens function as immunostimulants,, and that having the A2 allele could modify the onset of RA, Huang et al. [10] suggest that the effects of the androgen increase induced by the A2 presence might not be biologically influential in the fertile age (i.e., younger RA female patients), which is characterized by high estrogens (immunostimulant). However, the same induction of increased production of androgens (immunosuppressive) might become an influential resisting factor in older women, who are characterized by physiologically reduced estrogens [11]. The conclusions of Huang's study induced us to reevaluate the results of an investigation we published 15 years ago of statistically higher concentrations of androgens – particularly testosterone, androstenedione and DHEAS – in the serum of postmenopausal women affected by RA when compared to age-matched healthy controls [12,13]. A role for CYP17-altered activity is presently under investigation.

In view of the possible role played by androgens in the pathogenesis of the rheumatic diseases, the association between repeat lengths of CAG microsatellites and the androgen receptor gene in RA patients was recently studied [14]. Shorter CAG repeats of the androgen receptor gene, presenting high levels of transactivation activity, were found to be related to younger age onset of male RA, further suggesting the possible role of androgens as a modulating factor in autoimmunity.

Finally, an association between HLA phenotype and serum testosterone levels was identified [15], in particular the demonstration of low testosterone levels in men with HLAB15, DR2, DR5 haplotytes. A recent study has confirmed that major histocompatibility complex phenotypes influence serum testosterone concentration [16].

DHEAS = dehydroepiandrosterone sulphate

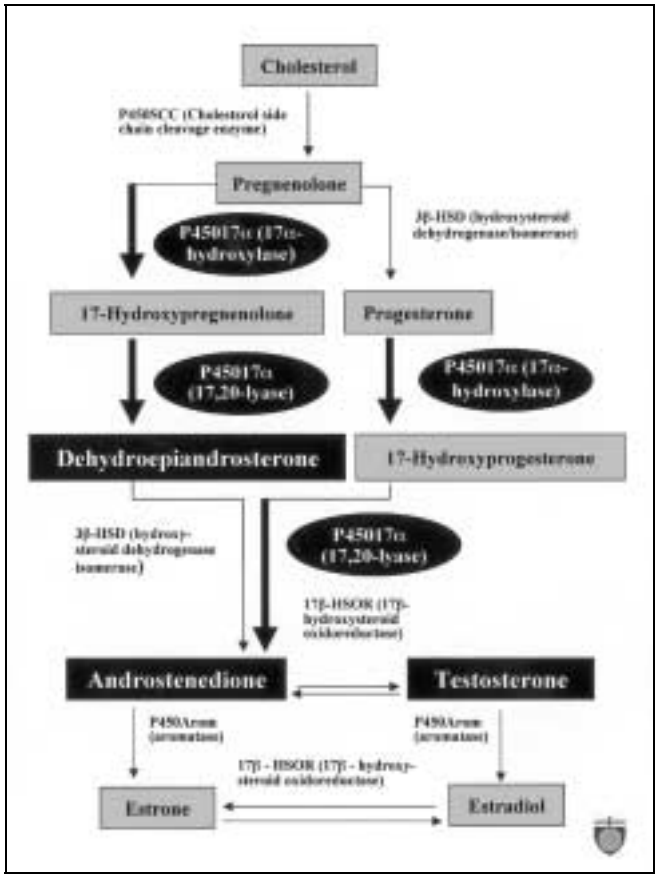

Figure 2. Key enzymes involved in steroidogenesis. The CYP17 gene, coding for the cytochrome P450c17α, mediates both steroid 17α-hydroxylase and 17,20-lyase activities. Increased transcription of these enzymes (presence of the allele A2) might determine increased synthesis of androgens (androestenedione, DHEA and testosterone).

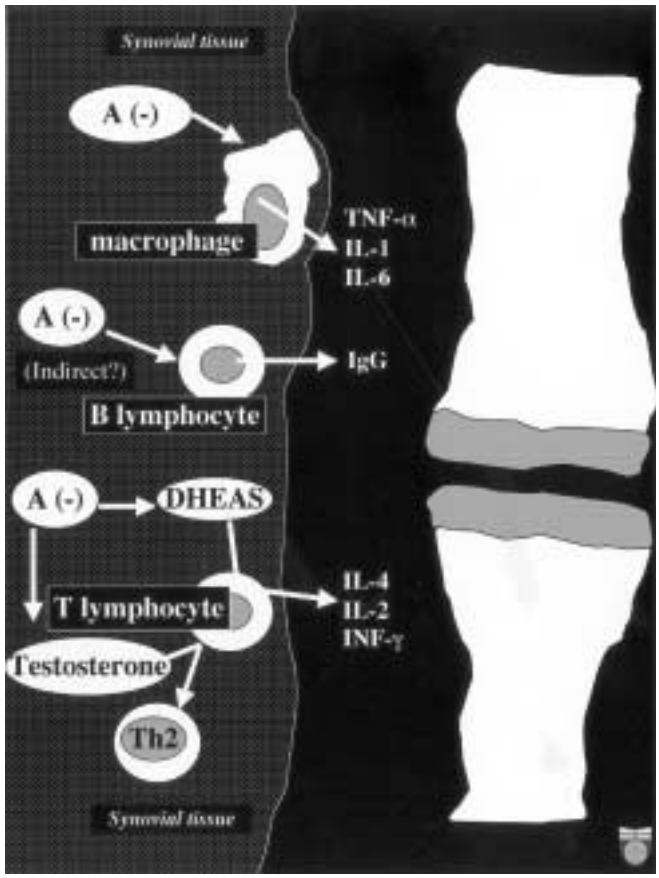

Figure 3. Major stimulatory (+) or inhibitory (-) effects (direct and indirect) of androgens on cytokine/immunoglobulin production by synovial/immune cells in synovial tissue of RA patients.
A = androgens, E = estrogens, IgG = immunoglobulin G, IL = interleukin, TNF = tumor necrosis factor.

Mechanisms of action of androgens on immune cells

Effects of androgens on B lymphocytes

The effects of testosterone have been tested on the production of immunoglobulin M by an Epstein-Barr virus-transformed human B cell line (SKW6-CL4) [17]. Testosterone at both physiological and supraphysiological levels, as expected because of the absence of functional receptors, does not influence either IgM production or the proliferation of the human SKW6-CL4 cells. In contrast, putative contradictory data were reported in another study on the effects of testosterone on human peripheral blood mononuclear cells – namely, a dose-dependent inhibition of IgG and IgM production by cells from normal males and females [18]. The magnitude of the suppressive effect on isolated B cells was much lower than on whole PBMCs. In addition, testosterone treatment reduced monocyte interleukin-6 production compared with controls but did not appear to directly affect isolated B or T cells. A follow-up study on PBMCs from patients with systemic lupus erythematosus confirms that testosterone suppresses both IgG anti-dsDNA antibody and total IgG production [19]. Antibody production in B lymphocytes in that study was suppressed by testosterone, although the magnitude of its effect on B cells was lower than on PBMCs [Figure 3]. Similar to normal monocytes, testosterone reduced IL-6 production. Moreover, exogenous IL-6 partially restored the testosterone-induced decrease in antibody production by PBMCs. Thus, these data indicate that testosterone may modulate susceptibility to human autoimmune diseases, at least indirectly through actions on monocytes. The end result is decreased B cell activity.

17β-estradiol treatment of male and female mice, as noted earlier, induces earlier and substained expression of IgG anti-dsDNA antibodies compared to controls, whereas orchidectomy or administration of dihydrotestosterone to orchidectomized

Ig = immunoglobulin
PBMCs = peripheral blood mononuclear cells
IL = interleukin

DHT = dihydrotestosterone

male mice has minimal effects on the production of these antibodies [20].

Effects of androgens on T lymphocytes

The role of androgens in T cells is also complex and inadequately studied in both humans and animals. Direct exposure of murine T cells to DHT reduces the amount of IL-4, IL-5 and interferon-gamma produced after activation with anti-CD3 without affecting the production of IL-2 [21]. The authors observed differences in the production of IL-2, IL-4 and IFN-gamma between males and females at a given age. Both IL-4 and IFN-gamma production is elevated in females.

More recently, another experimental study observed that testosterone exerts a protective effect on experimental autoimmune encephalomyelitis. The data suggested that this protective effect resulted from the induction of a Th2 bias in autoantigen-specific T lymphocytes [22]. Enhanced IL-10 production by the autoantigen-specific T lymphocytes may explain these observations. This study was the first to demonstrate the ability of testosterone to shift an autoantigen-specific T lymphocyte response toward the Th2 phenotype, *in vivo*, coupled with an observed effect on a clinical autoimmune disease [Figure 3].

Effects of androgens on monocytes/macrophages

Human macrophages appear to contain the key enzymes of steroidogenesis, as shown at least by their capability to create, in the short term, the active metabolites of testosterone [23]. In particular, macrophages are endowed with 5α-reductase enzymes that catalyze the formation of DHT from testosterone, the more biologically active metabolite, after a relatively short exposure (24 hours). In cultured human macrophages, the rate and amount of conversion of testosterone into active metabolic products (i.e., DHT) is very close to that observed in classical target cells for androgen activity, such as human prostate cancer cells. Recent studies have shown that both physiologic (10^{-8} M) and pharmacologic (10^{-6} M) concentrations of testosterone inhibit IL-1β secretion by PBMCs obtained from RA patients [24]. In addition, physiologic concentrations of testosterone inhibit IL-1 synthesis in primary cultured human synovial macrophages [25] [Figure 3]. In related studies, DHT was found to repress the expression and activity of the human IL-6 gene promoter in human fibroblasts, thus supporting the concept of anti-inflammatory/immunosuppressive effects of androgens.

Clinical associations and androgen adjuvant therapy in RA

The striking observation by Nobel Prize laureate P. Hence in 1949 of the beneficial effect of daily administration of 17-hydroxy-11-dehydrocorticosterone (cortisone) and pituitary adrenocorticotropic hormone in RA represented the brightest hope for alleviating the manifestations of the disease. Moreover, the lack of sufficient knowledge on the long-term metabolic effects of cortisone and the unavailibility of cortisone in the early 1950s for general therapeutic use prompted the search for some related steroids. Several studies used testosterone propionate to treat RA, concluding that significant improvement or remissions could be expected following therapy in early-onset cases. However, the appearance of undesirable side effects, mainly masculinization and menstrual disturbances, curtailed the further use of androgen treatment in female RA patients.

The use of the anabolic androgenic steroid 19-nortestosterone (nandrolone) to treat postmenopausal RA patients was found after 6 months to ameliorate only chronic anemia. In SLE patients, nandrolone therapy returned suppressor T cell levels to normal, suggesting that this agent has a modulating activity on the immune system [26]. The main side effect of nandrolone was hoarseness. Danazol, another synthetic androgen, derived from ethinyltestosterone, was also found to be effective in the treatment of SLE, exerting a clear immunosuppressive activity.

In a recent open study, oral testosterone undecanoate was administered daily for 6 months to male RA patients in an attempt to evaluate the immunologic response, the overall clinical changes, and the sex hormone effects of such replacement therapy [27]. At the end of the 6 months, results showed a significant increase in serum testosterone levels, an increase in the number of CD8+ T cells, and a decrease in the CD4+(helper):CD8+ T cell ratio. The IgM rheumatoid factor concentration decreased significantly. A concurrent, significant reduction was noted in the number of affected joints and in the daily intake of non-steroidal anti-inflammatory drugs. There were no notable side effects [27].

In another recent double-blind placebo-controlled study of testosterone administration as an adjuvant treatment in 57 postmenopausal RA women, this androgen was found to improve the pain score and erythrocyte sedimentation rate, and reduce disability, and 21% of patients showed a clinically relevant improvement [28]. In general, treatment was well tolerated. The authors concluded that apart from its known positive anabolic effect, this therapeutic agent might also exert a slight disease-modifying effect, albeit not statistically significant. A further study showed limited effects of androgen replacement in RA male patients, possibly because serum testosterone levels failed to rise significantly in relation to the limited dosage administered [29].

Other double-blind placebo-controlled studies [30] demonstrated an overall clinical improvement in female SLE patients following administration of the adrenal androgen DHEA. In SLE patients, low levels of DHEAS/DHEA are associated with decreased secretion of IL-2 and elevated levels of IL-6. DHEA administration has been shown to increase secretion of IL-2 by stimulating T cells in both human and murine systems and by normalizing the excessive production of IL-4, IL-5 and IL-6. DHEA may also offer promise to the treatment of selected female RA patients, particularly in view of the low frequency of

SLE = systemic lupus erythematosus
DHEA = dihydroepiandrosterone

side effects [31]. However, since anti-inflammatory effects have not yet been demonstrated in RA, reliable studies are still needed.

In RA patients, testosterone therapy seems to increase DHEAS levels significantly, which further suggests the involvement and therapeutic effects of androgens in the pathophysiology of the disease [32]. The use of androgen replacement therapy for unapproved indications in men continues to expand.

Interestingly, among the immunosuppressive agents administered for therapy of RA, cyclosporin A induces, as a side effect, a dose-dependent hypertrichosis in both males and females. This effect is related to the clinical improvement and suggests an androgenizing activity. The influence of this agent on peripheral androgen metabolism was evaluated in RA patients treated with low dose cyclosporin (3.5 mg/kg/day) during a 12 month period. Plasma levels of testosterone and 5α-androstane-3α,17β-diol glucuronide (Adiol-G), an important peripheral testosterone metabolite, were assayed, and the clinical and laboratory parameters of RA were monitored. At the final observation, a significant increase in the mean plasma Adiol-G level was noted in both male and female patients. The increase was evident after 1 month of treatment in male patients and after 3 months in female patients. Almost all the patients experienced the side effect of a low degree hypertrichosis after a mean period of 1–2 months [33,34]. These results were confirmed by another study on cyclosporin treatment in male RA patients, together with the observation of increased concentrations of the serum-free prostatic antigen [35]. Furthermore, the metabolism of physiologic concentrations of testosterone was evaluated in primary cultures of RA synovial macrophages in the presence of cyclosporin concentrations close to pharmacologic immunosuppressive doses [34]. Results from *in vitro* experiments of testosterone metabolism by cultured synovial macrophages showed a significantly greater formation of DHT at 24 and 48 hours following administration of cyclosporin, when compared to untreated controls [34].

In conclusion, the increase in serum androgen metabolism induced by treatment with cyclosporin should be regarded as a possible marker of androgen-mediated immunosuppressive activities, at least in RA and at the level of target cells and tissues (i.e., synovial macrophages).

In a recent study evaluating the antiproliferative effects of methotrexate on cultured RA synovial macrophages, the presence of both methotrexate and physiologic concentrations of testosterone was found to induce a significant cell apoptosis [36]. If the above experimental results are confirmed, they might support the value of androgens as adjuvant therapy in RA in combination with other disease-modifying drugs (namely, cyclosporin and methotrexate).

A very recent study supports the modulating role of androgens in inflammatory rheumatic diseases [37]. Patients with new onset arthritis (< 1 year) prior to treatment with corticosteroids were analyzed for plasma ACTH, cortisol, DHEA, free and total testosterone as well as erythrocyte sedimentation rate and C-reactive protein. Lower basal morning levels of free testosterone were observed when compared to the controls. An inverse relationship was found between androgens (both DHEA and testosterone) and acute-phase reactants such as C-reactive protein and erythrocyte sedimentation rate [37]. These results further suggest that androgen levels are negatively associated with the degree of inflammation and may have a protective effect in inflammation [37].

ACTH = adrenocortitropic hormone

Conclusions

All the data discussed here seem to indicate that gonadal androgens (testosterone and DHT) exert their modulatory effects via both a direct influence on cytokine production by activated monocytes/macrophages (inhibition of IL-1, IL-6 and tumor necrosis factor-alpha production) and an indirect influence on cytokine production by activated T cells (inhibition of IL-4, IL-5 and IFN-gamma production). On the other hand, adrenal androgens (DHEAS and DHEA) may exert a direct effect on cytokine production by T cells (increase of IL-2 and IFN-gamma synthesis).

The presence of both decreased gonadal and adrenal androgens – as observed for genetic causes (such as Klinefelter's syndrome, 5α-reductase deficiency, mutations), chronic stress or during aging – along with immunomediated inflammatory conditions, further point to the importance of physiologic levels of androgens. While these observations are better investigated in RA patients, they might be shared by all immunomediated rheumatic diseases (such as lupus and scleroderma). In conclusion, cell-specific metabolism of androgens may well represent a natural means of control over tissue-specific immune responses [38–40].

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