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Estrogens and Arthritis

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Sex hormones and autoimmune diseases

Epidemiologic evidence indicates that during the fertile period women are affected by rheumatic diseases, particularly autoimmune diseases, more often than men [1]. Rheumatic disorders with autoimmune involvement, such as rheumatoid arthritis (RA) or systemic lupus erythematosus (SLE), result from the combination of several factors. These include the relationships between epitopes of the trigger agent (ie, virus) and histocompatibility epitopes (ie, HLA); the status of the stress response system, including the hypothalamic-pituitary-adrenocortical axis and the sympathetic nervous system; and the effects of the gonadal hormones (hypothalamic–pituitary–gonadal axis) [2].

The pre- or postmenopausal sex hormone status of the patient is another factor that influences the rate of rheumatic diseases. It is important, whenever possible, to evaluate epidemiologic according to age (eg, 10-year age band) and gender before making inferences [3]. Sex hormones seem to play an important role as modulators of disease onset and perpetuation [4].

Sex hormones also are implicated in the immune response, with estrogens as enhancers of humoral immunity and androgens and progesterone (and glucocorticoids) as natural suppressors of the immune response [4,5]. Decreased concentrations of gonadal and adrenal androgens (testosterone, dihydrotestosterone, and dehydroepiandrosterone [DHEA] and its sulfate [DHEAS]), as well as a

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reduced androgen:estrogen ratio in the serum and body fluids (eg, blood, synovial fluid, smears, saliva) of male and female patients who have RA or SLE, support, in a simple way, the possible pathogenic role for decreased levels of immunosuppression [6]. Levels of estrogens are not changed significantly in patients who have RA [4].

Several physiologic, pathologic, and therapeutic conditions may change the serum estrogen levels and the peripheral conversion rate of the steroid. These conditions include the menstrual cycle, pregnancy, postpartum period, menopause, aged state, chronic stress, an increase of inflammatory cytokines, and the use of corticosteroids, oral contraceptives, and steroid hormonal replacements. All of these conditions can induce altered androgen:estrogen ratios [5–7].

Sex hormones also can exert local actions (paracrine) in the tissues in which they are formed or enter the circulation. Testosterone and 17-β estradiol (E_2) seem to exert dose and time-dependent effects on cell growth and apoptosis [2,4]. These effects, as well as important influences on the gene promoters of T helper cells 1 and 2 (Th1 and Th2) cytokines and the recently discovered increased synovial fluid estrogen concentrations, suggest new and interesting roles for estrogens in RA [8–11].

Peripheral sex hormone metabolism in autoimmune diseases

Several facts suggest an accelerated metabolic conversion of upstream androgen precursors to E_2 in patients who have RA or SLE. E_2 is the aromatic product of the gonadal steroid metabolic pathway and the result of peripheral conversion from gonadal androgens (eg, testosterone). There are other upstream precursors of E_2 (eg, DHEAS, progesterone).

Several studies and reviews showed that there are reduced serum concentrations of DHEAS, T, and progesterone in male and female patients who have RA or SLE [12,13]. These data strongly support an accelerated peripheral metabolic conversion of androgen precursors to E_2 (Fig. 1).

Increased estrogen concentrations have been found in the synovial fluids of male and female patients who have RA. There is no explanation for the decreased androgen and increased estrogen levels that are found in the synovial fluids of female and male patients who have RA. An appropriate explanation might originate from recent studies that showed that the inflammatory cytokines (ie, tumor necrosis factor–α [TNF-α], interleukin 1 [IL-1] and IL-6), which are increased in synovitis in patients who have RA, stimulate aromatase activity in peripheral tissues [14,15].

The aromatase enzyme complex is involved in the peripheral conversion of androgens (testosterone and androstenedione) to estrogens (estrone and estradiol, respectively). In tissues that are rich with macrophages, a significant correlation is found between aromatase activity and IL-6 production; aromatase has been found in synoviocytes [16]. Therefore, increased aromatase activity may be induced locally by inflammatory cytokines (ie, TNF-α, IL-1, IL-6). This

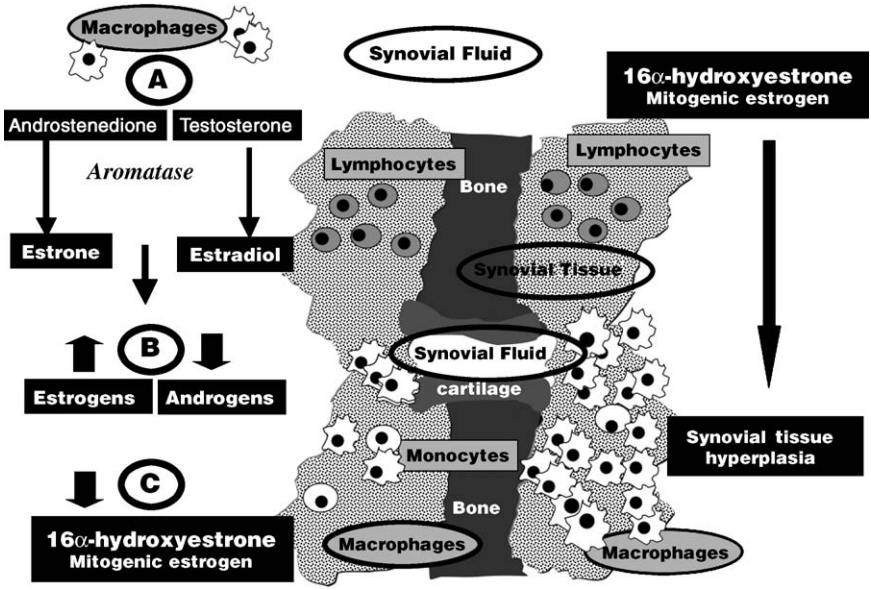

Fig. 1. (*A*) In rheumatoid arthritis synovial fluid, increased formation of estrogens from androgens accounts for the increased local aromatase activity that is induced by proinflammatory cytokines (eg, TNF, IL-1). (*B*) Increased estrogens and decreased androgens in the synovial fluid of male and female patients who have RA. (*C*) Increased formation of hydroxylated estrogens in RA synovial fluid, in particular, increases the mitogen 16α-hydroxyestrone that might induce cell proliferation and synovial tissue hyperplasia.

might explain the altered balance that results in the decreased androgens and increased estrogens that are found in synovial fluids of patients who have RA (see Fig. 1) [17].

The role of local sex hormone concentrations at the inflammatory event may explain some of the modulatory effects that are exerted by hormones on the immune-inflammatory reaction. Men who have RA have low testosterone levels. Moreover, a recent study showed decreased DHEAS and estrone concentrations and increased E_2 levels in male patients who had RA [18].

In the latter study, estrone did not correlate with any disease variable, whereas E_2 did correlate with all measured indices of inflammation. Men who had RA had aberrations in all of the sex hormones that were analyzed, although only estradiol correlated consistently with inflammation [18]. The decreased levels of estrone and DHEAS may depend on a shift in the adrenal steroidogenesis toward the glucocorticoid pathway, whereas an increased conversion of estrone to E_2 could be the cause of increased E_2 levels (effect of the 17 β-hydroxysteroid dehydrogenase) in these patients.

In patients who had SLE, aromatase activity that was evaluated in skin and subcutaneous tissue was increased when compared with control subjects

[19]. Aromatase activity varied inversely with disease activity and the patients had decreased androgen and increased estrogen serum levels [19]. Therefore, tissue aromatase activity correlated with estrogen levels in patients who had SLE.

These data suggest that abnormal regulation of aromatase activity (ie, increased activity) may explain, in part, the abnormalities of peripheral estrogen synthesis (ie, increased availability of E_2 and possible metabolites) in SLE, as well as the altered serum sex hormone levels and ratio (ie, decreased androgens and DHEAS) (see Fig. 1).

In a recent study, the urinary excretion of hydroxyestrogens (ie, 16α-hydroxyestrone and 2-hydroxyestrogens) also reflected their production in tissues because no hydroxylase activity is found in the urine [20,21]. Peripheral estrogen hydroxylation is increased in men and women who have SLE and the estrogenic hydroxylated metabolites increase B cell differentiation and activate T cells [22].

The role of estrogen metabolites

The elevated serum levels of 16α-hydroxyestrone show that men—who have SLE—and women had elevations of 16α-hydroxyestrone and estriol [23], the feminizing estrogens. These data suggest abnormal patterns of E_2 metabolism, which may lead to increased estrogenic activity in patients who have SLE. Levels of catechol or 2-hydroxylated estrogens were not elevated, and, in some cases, were depleted significantly.

A similar phenomenon is found in the synovial fluids of patients who have RA; 16α-hydroxyestrone/4-hydroxyestradiol levels were significantly increased when compared with controls (see Fig. 1) [17,20]. In these studies, molar ratios of free estrogen:free androgen also were increased significantly.

Two important facts must be noted. The total serum levels of E_2 are not outside of normal physiologic ranges in patients, of either sex, who have RA or SLE [24–26]. Gender, therefore, may not influence these phenomena and the gonadal production of the sex hormones probably is not responsible for the observed metabolic findings. Most of the measured metabolites are converted in peripheral tissues, which largely occurs independent of gender. The phenomenon seems to be dependent on the inflammatory state of the tissues. Common mechanisms that are apparent in patients who have RA or SLE indicate that these phenomena are not disease specific.

Furthermore, estradiol may play a pro- or anti-inflammatory role in chronic inflammatory diseases that could be related to decreased and increased concentrations, respectively. It is possible that this phenomenon might depend on dose-related rates of peripheral E_2 conversion to pro- or anti-inflammatory metabolites, such as 16α-hydroxyestrone or the catechol (ie, 2-hydroxyestrogens), respectively [27].

Possible mechanisms of immunomodulation by sex hormones: the clinical evidence

Macrophages release cytokines (eg, TNF-α, IL-1, IL-6) that modulate the symptoms of many diseases, most importantly RA. Macrophage release of these cytokines can be modulated by estrogen in different ways. Fcγ receptor type IIIA (CD16a) is a receptor that is expressed on macrophages that selectively bind IgG molecules, an important factor in RA. Binding of CD16 by anti-CD16 monoclonal antibodies stimulates macrophage cytokine release. Estrogen also can modulate proinflammatory cytokine release from activated monocytes or macrophages, in particular through the modulation of CD16 expression [28].

Recent studies also showed that 16α-hydroxyestrone is a steroid that is more potent than E_2 in the induction of proliferative activities [27]. More recently, cultured human myeloid monocytic cells, which differentiate into activated macrophages, were evaluated with regard to the effects of E_2 and testosterone on cell proliferation and apoptosis. The effects were evaluated by looking at necrosis factor–κB (NF-κB) activity, as a complex of molecules that modulate cellular activation. Testosterone exerted proapoptotic effects and reduced macrophage proliferation, whereas E_2 induced the opposite effects by interfering with NF-κB activities. Therefore, these results might support the hypothesis of sex hormone modulation of cell growth and apoptosis. The next obvious step is to test the effects of 16α-hydroxyestrone and 2-hydroxyestrogen on the same cells.

In another study, E_2 increased IgG and IgM production by peripheral blood mononuclear cells in patients who had SLE; this led to elevated levels of polyclonal IgG, including IgG anti-dsDNA, by enhancing B-cell activity by way of IL-10 [19]. These latter results also should be replicated in the presence of 16α-hydroxyestrone and the naturally occurring 2-hydroxylated catechol estrogens. It was recently shown that disease activity in patients who had SLE correlated negatively with urinary concentrations of 2-hydroxylated estrogens [21]. Estrogens are confirmed as one of the risk factors in autoimmunity.

Interesting changes of serum estrogens were found during pregnancy in patients who had SLE and correlated with cytokine variations [29,30]. The major hormonal alteration that was observed was the lack of estrogen and progesterone increase during the second and third trimesters of gestation [29]. The progesterone effects were less than for estradiol. This lack of increase may have been due to placental compromise. A smaller than expected increase of IL-6 in the third trimester and persistently high levels of IL-10 during the entire pregnancy are major alterations in the peripheral circulation of pregnant patients who have SLE [30]. Steroid hormone and cytokine variations may result in a decreased humoral immune response that probably is related to a change in the estrogen/androgen balance. This, in turn, could account for a more immunosuppressive effect that is exerted by cytokines on disease activity as observed during the third trimester in pregnant patients who had SLE [29].

Cyclophosphamide-induced ovarian failure is protective against flares of SLE. A recent study evaluated whether patients who have SLE experience a decrease

in disease activity after the menopause [31]. Differences in disease activity scores (mean and maximum) and the number of visits to a rheumatologist's office were significant only when the fourth year before menopause was compared with the fourth year after menopause. Disease activity was mild during the premenopausal and postmenopausal periods in women who had SLE. A modest decrease, especially in the maximum disease activity, was seen after natural menopause [31].

Effects of exogenous estrogens on autoimmune diseases

The use of various birth control pills in lupus erythematosus has been controversial [31–38]. The SELENA (Safety of Estrogens in Lupus Erythematosus National Assessment) trial ended abruptly because of concerns regarding the use of estrogen and cancer. The original study examined the effects of oral contraceptives on the disease in premenopausal women. A second arm of the study examined the use of such medication in postmenopausal women. The overall belief is that the use of estrogenic steroid hormones exacerbates lupus; there is much preliminary data for that belief. The use of hormone replacement therapy (HRT) is not well-established; many physicians believe that nonsupraphysiologic dosages of estrogen can be used safely in older women. Lupus in older women improves with the menopause. There is much debate as to whether replacement with exogenous estrogen would result in an acute exacerbation. In that regard, the use of androgens (eg, DHEA) in lupus poses a dilemma because a moderate portion of the hormone is metabolized to estradiol and levels may reach HRT levels postmenopausally [39].

The use of estrogen-containing tablets in RA also has been controversial [40–45]. RA improves with estrogen therapy and pregnancy. This also observed in other Th1 disease (eg, multiple sclerosis). There also are data that indicate that use of E_2 improves experimental autoimmune encephalomyelitis through its action on the α receptor of estrogen.

Exogenous natural estrogens

There are natural estrogenic substances that are often suggested as estrogen replacement therapy; these include the phytoestrogens from plants and the mycoestrogens from fungi. The phytoestrogens consist of coumestans, lignans, and isoflavones. Many of these naturally occurring estrogens can have effects on the immune system. They largely found largely in plants and vegetables like clover sprouts, alfalfa sprouts, dry split peas, and other legumes. There are few data to indicate that these naturally occurring exogenous estrogens worsen disease of animals or humans. Some pesticides, such as dichlorodiphenyltrichloroethane and bisphenol A (a plasticizer) can have similar effects to estrogens

because they bind to estrogen receptors. Bisphenol A has had a beneficial effect in lupus of the NZB/W F1 mouse [46].

Summary

Sex hormones can exert local actions (paracrine) in the tissues in which they are formed. An accelerated peripheral metabolic conversion of upstream androgen precursors to E_2. Conversion to more estrogenic metabolites is observed in patients who have RA or SLE. Local effects of sex hormones in autoimmune rheumatic diseases seem to consist mainly of modulation of cell proliferation and cytokine production.

All of these data further suggest caution in exogenous estrogen administration (eg, oral contraceptives, estrogen replacements, induction of ovulation) in patients who have autoimmune diseases and might prospect novel and improved applications of hormonal or antihormonal immunotherapy (eg, antiestrogens, receptor modulators, antagonist metabolites, androgenic compounds).

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