Hypothalamic-Pituitary-Gonadal Axis Hormones and Male Rheumatoid Arthritis: Novel Perspectives

The female to male (F:M) incidence ratio in rheumatoid arthritis (RA) is almost 3:1, being exaggerated in child-bearing ages (5:1), as opposed to 2:1 in juveniles and older (50+ years) adults¹. Female preponderance also occurs in systemic lupus erythematosus (SLE; 9:1), particularly in child-bearing years², when its age-specific incidence is highest^{2,3}. In RA, however, the incidence is notably higher in postmenopausal than in premenopausal women. The age-specific gender differential in RA is attributable to adult men having significantly delayed disease onset¹. Such incidence data imply that gonadal hormones may be protective of RA in younger adult men (testosterone), but may predispose to SLE in women (estrogens)^{2,3}.

LONGITUDINAL RESEARCH DESIGN TO STUDY SEX HORMONE AND CLINICAL RELATIONS IN RA

In this issue of *The Journal*, Tengstrand, *et al*⁴ report a longitudinal study of gonadal hormones in early diagnosed (within 1 year of symptoms) male RA. The baseline hormonal data on RA cases were compared to healthy control values. The longitudinal design over a 2-year duration of therapy permitted analyses of the change in hypothalamic-pituitary-gonadal (HPG) hormones as correlated with the change in RA disease activity. At baseline, the main findings were that the younger (< 50 yrs of age) RA males had lower mean serum levels of total testosterone (T) as well as bioavailable T, i.e., free T or non-sex hormone-binding globulin (SHBG)-bound T than the healthy control subjects. The 2-year interval changes revealed an increased total T level from baseline that was associated significantly with decreased disease activity, as measured by Disease Activity Score 28 (DAS28), but without change in serum luteinizing hormone (LH)⁴.

Cross-sectional (or longitudinal) studies cannot indicate whether observed baseline hormonal alterations reflect a primary risk effect or are secondary to disease severity^{4,5}.

Such question of a predisposing risk factor requires prospective analyses of hormone levels, before onset of clinical disease in controlled cohort studies^{6,7} (discussed below).

This commentary addresses some study issues and suggests a broader conceptual framework to interpret the recent results⁴, and raises considerations for further research on gonadal hormones and RA.

EARLIER IDENTIFIED CASES INCLUDED IN THE CURRENT SERIES

The current report⁴ on 41 male patients with early diagnosed RA includes all the 19 early diagnosed cases from a preceding cross-sectional study by this group⁵. That earlier report⁵ indicated a high proportion of hypogonadism in 104 RA cases (31.7%) versus 99 matched healthy controls (7.1%). An issue of “carry-over” effect can be raised regarding such inclusion of the earlier cases in this new report⁴. Statistically, only data from the 22 more recently recruited early disease cases may be considered an independent sample to support the preceding hypothesis of hypo-gonadism in male RA⁵, even though mean hormonal levels were similar in the 2 subgroups⁴.

BASELINE SEX HORMONE FINDINGS IN THE CURRENT⁴ AND PRECEDING⁵ STUDY

Among subjects < 50 years of age in the current report of early RA⁴, the mean (SD) baseline serum total T (nmol/l) level was significantly lower ($p < 0.001$) in the 15 RA [16.2 (3.5)] versus the 88 controls [23.3 (7.5)]. No meaningful difference was found in the earlier study of 20 younger patients with RA [19.6 (8.1)] versus 56 controls [22.8 (8.1)]⁵. However, cases in that report⁵ were not restricted by disease duration, the median being 4.0 yrs (range 0–43) at baseline. In the earlier study⁵, the mean total T level was significantly lower ($p < 0.01$) only in the RA versus control

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males of the 50–59 year age group. The current study⁴ also indicated a lower ($p = 0.02$) mean SHBG level in 14 younger RA males [26 (7)] than the 88 controls [34 (12)], which was unexplained and was not observed in the preceding report⁵. Since serum concentrations of total T and SHBG were positively correlated^{4,5}, part of the significantly lower ($p < 0.001$) baseline total T level in the younger RA males (see above) may have been so influenced, besides the restriction to early disease cases only⁴.

The baseline mean bioavailable T level was also significantly lower in the younger RA versus control subjects, both in the current⁴ and in the previous⁵ report ($p = 0.004$ and $p < 0.05$, respectively). In that earlier report⁵, bioavailable T was significantly lower in the RA versus control subjects in all 3 age groups: 30–49 ($p < 0.05$), 50–59 ($p < 0.01$), and 60–69 years ($p < 0.05$).

Baseline mean LH levels in the current report⁴ were significantly lower ($p < 0.001$) in 24 older (50+ yrs) RA [4.3 (3.3)] than in 21 control [6.2 (2.1)] subjects, but not in the younger RA versus their control counterparts. From the reported data on mean serum T and LH levels⁴, we calculated crude ratios (mean T/LH), in order to explore HPG physiological relations in the RA versus control subjects. A proper analysis should be based upon the ratios of individual subjects. Ratios were derived from values at baseline for the RA and control subjects, and at 2 years, for the total RA patients, and for those who had response versus nonresponse to therapy. The baseline mean T/LH ratios appeared comparable for the RA versus control groups, being greater for younger (5.1 vs 6.9) than for older (3.8 vs 3.0) subjects, which might be expected physiologically. At 2 years, the ratio for all 38 RA cases was 4.4, with subgroup means being 4.5 for the 22 responders and 6.0 for the 16 non-responders to therapy. Further physiological investigation of HPG axis responsiveness in RA versus control subjects appears warranted.

LONGITUDINAL CHANGES IN HORMONAL LEVELS FROM ONSET TO 2 YEARS FORWARD

The current report⁴ provides comparative baseline and 2-year data on 38 RA patients and the subgroups of 22 who responded fully to therapy and 16 considered nonresponders, by predefined criteria. Both subgroups actually improved clinically, but to different degrees. The mean total T level increased only among the 22 responders ($p < 0.05$) from baseline [15.8 (5.5)] to 2 years [17.7 (5.8)]⁴. At 2 years, the mean total T level was significantly higher ($p = 0.023$) in the responders than in nonresponders⁴. The mean SHBG levels increased significantly ($p < 0.01$) between baseline and 2-year assessments in both subgroups, without a difference between them at either assessment⁴. Of interest, “The blood samples (concerning SHBG) were analyzed at separate time” (Tengstrand B, personal communication).

The current report⁴ shows a scatter plot of changes

between the baseline and 2-year values in DAS28 versus total T levels of the individual patients. The correlation was negative and overall significant ($p = 0.006$), being stronger for older ($p = 0.009$) versus younger ($p = 0.0233$) men, but the difference is not significant. Change in DAS28 was not correlated significantly with changes in bioavailable T or LH levels, irrespective of age⁴.

BIOLOGICAL STUDIES SUPPORTING TESTOSTERONE SUPPRESSION OF INFLAMMATION

Testosterone has been reported to have immune suppressive effects^{4,8–11}. In the mouse, T reduces macrophage expression of toll-like receptor 4, a trigger for inflammation and innate immunity⁸. Testosterone has been shown to suppress interleukin 2 (IL-2), IL-4, and IL-10 production by human leukocytes *in vitro*, while estradiol stabilized or increased immune stimuli-induced secretion of these and other cytokines⁹. Testosterone also stimulated apoptosis of human bone marrow-derived macrophages by a mechanism involving caspase-3, caspase-8, and poly(ADP-ribose) polymerase¹⁰. However, one study found opposing effects of T and dihydrotestosterone (DHT) in microglia, the central nervous system macrophage-like cell¹¹. DHT acted as an antiinflammatory agent, depressing both nitric oxide and TNF- α levels. However, T treatment of microglia and peritoneal macrophages increased nitric oxide levels, indicative of a proinflammatory effect¹¹. Determination of circulating DHT level as well as total T and bioavailable T may be important in future studies.

BIOLOGICAL RELATIONS OF AGING AND INFLAMMATION

Aging is proposed to activate inflammatory pathways^{12–16}. Also, inflammation is a core causal pathway of RA¹² as well as a contributor to some of its comorbid diseases and mortality, such as cardiovascular¹⁷. Interpretation of such generalized data is complex and has multiple limitations^{15,18}. Nevertheless, we suggest areas for future research on (1) aging-related pathways in RA; (2) the directionality of such inferred etiologic pathways (vectors); and (3) determining their mechanisms and interactions.

The somatic systems that influence risk of developing RA are broad in scope, and include (1) hormonal, (2) immunological, and (3) vascular (“H-I-V” — the hormonal-immunological-vascular triad)¹⁹. In turn, these biological systems are complex and are influenced by their own interactions as well as by their genetic control mechanisms and behavioral and environmental factors^{15,18,19}. Within such a holistic framework of RA, a relevant question might be whether or not this disease is importantly induced by underlying determinants of accelerated biological aging, more than is currently recognized. Specifically, might genetic and behavioral/environmental-related mechanisms that actively

induce aging^{13,15,16} also be important pathways for risk of developing RA¹², besides accelerating its mortality? Better understanding of pathways in biological aging¹²⁻¹⁶ may help to dissect the complex web of interacting susceptibility factors for RA^{18,19}.

LIFESPAN TRAJECTORIES AND CAUSAL PATHWAYS IN AGING AS RELATED TO RA

Bioavailable T decreases in normal aging^{4,20} and RA risk is significantly elevated in older versus younger males¹. Might these outcomes have shared commonalities and be dependent upon underlying processes that importantly advance biological aging? Notably, patients with RA have premature mortality¹⁷. The estimated standardized mortality ratios in RA subject inception cohorts are reported to be circa 1.3, in both clinic and community/population based samples¹⁷. The attributed causes of death among persons with RA have been proportionately stable over several decades and are similar to the general population¹⁷. The few exceptions in proportionate mortality include excesses from infection and pulmonary and renal comorbidities¹⁷.

Might genetic and somatic mechanisms that importantly control natural lifespan also be underlying pathways that influence the risk of adult RA? If so, such relations may help to explain the associated premature mortality in RA. Accordingly, increased mortality in RA (e.g., cardiovascular) could be, to some degree, a coassociated ("confounding") outcome of enhanced aging, rather than strictly a process of RA leading to such premature mortality.

Similarly, some degree of lower serum T and free T levels (if not also LH) in RA males could potentially be coassociated outcomes of underlying aging determinants. Further research can also address to what degree observed low serum T and bioavailable T levels result from inflammatory or other severity features of RA (secondary) as opposed to being a possible primary predisposing risk relation, which was not evident in a previous cohort study⁶.

WEB OF CAUSATION OF RA AND PROSPECTS OF PROSPECTIVE PREDICTIVE STUDIES

Prospective cohort studies of presymptomatic RA and control subjects can uncover alterations that predict the subsequent onset of disease. Multivariate analyses can further identify independent predictors that may be suspected to contribute to disease. Importantly, even strong independent predictors may not necessarily be disease determinants, since they may themselves be markers that reflect effects of unrecognized causal pathways or confounder biases.

An analysis of 54 preclinical RA and 216 control subjects was performed by principal components technique²¹. An independent component was identified that could be labeled as "Youthful (vs older)." The major variables in this component were patient age (the strongest correlate) and adrenal androgen levels (androstenedione and dehydroepiandrosterone sulfate).

This age-related component independently predicted membership in the study groups, i.e., older associated with RA, and explained 11.5% (± 0.05 SD) of the variance. Such preliminary data suggest that age-related variables could potentially predict the later development of onset of RA²¹.

Whether alterations in HPG hormones can contribute to RA risk in men or be a consequence of its disease pathways remains unresolved^{4-6,18,19,21}. The most recent study⁴ further suggests the hypothesis that mild primary hypo-gonadotropic hypogonadism may occur in RA⁵. We raise novel considerations that might link the complex pathways of accelerated biological aging determinants, RA risk, its premature mortality, and HPG axis hormonal alterations, which may deserve further longitudinal and prospective study.

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