Gonadal Hormones in Men with Rheumatoid Arthritis — From Onset Through 2 Years

BIRGITTA TENGSTRAND, KJELL CARLSTRÖM, and INGIÄLD HAFSTRÖM

ABSTRACT. ***Objective.*** To evaluate changes over a 2-year course in the hypothalamic-pituitary-gonadal (HPG) axis in men with early rheumatoid arthritis (RA) from start of treatment with disease modifying antirheumatic drugs.

Methods. Forty-one men with early RA and with joint symptoms less than 1 year were studied. Mean age at inclusion was 53 years and mean disease duration 6 months. They were followed prospectively for 2 years for disease activity [Disease Activity Score 28 (DAS28)], physical impairment (Health Assessment Questionnaire), total serum testosterone, non-sex hormone-binding globulin-bound testosterone, and luteinizing hormone (LH). A group of 131 healthy, medicine-free men served as controls for baseline hormone concentrations.

Results. The men with RA already had mean testosterone levels lower than controls early in the disease course. Patients older than 50 years also had significantly lower LH levels compared with controls, consistent with mild hypogonadotropic hypogonadism. In patients who responded to treatment at the 2-year followup the testosterone levels increased significantly. A decrease in DAS28 during the 2 years correlated significantly with increased testosterone levels ($r^s = -0.46$, $p = 0.006$). LH levels were low and stable and did not correlate with disease activity.

Conclusion. In early RA, current inflammation seemed to affect the HPG axis, mainly at the gonadal rather than the hypothalamic-pituitary level. Prospective studies are indicated to determine if low HPG activity may be a cause rather than a consequence of a chronic inflammatory state. (First Release March 1 2009; J Rheumatol 2009;36:887–92; doi:10.3899/jrheum.080558)

Key Indexing Terms:
GONADAL HORMONES MEN RHEUMATOID ARTHRITIS
HYPOTHALAMIC-PITUITARY-GONADAL AXIS

Rheumatoid arthritis (RA) is a chronic inflammatory disease that frequently causes joint destruction and deformation and subsequently physical impairment. The course of RA may vary considerably from aggressive to mild forms, and in some patients the disease resolves spontaneously.

It has been shown that some patients with RA have an inappropriate response of the hypothalamic-pituitary-adrenal (HPA) and the hypothalamic-pituitary-gonadal (HPG) axes to inflammatory and stress stimuli[1,2]. Further, male patients with RA have been reported often to have decreased activity in the HPG axis[3-7]. It is not known if this is a cause or a consequence of the perpetuated inflammation in RA and nothing is known about the HPG axis in self-limiting inflammatory joint diseases.

Testosterone has immunosuppressive properties concerning macrophages, T cells, and B cells[8]. Reduced testosterone concentrations thus affect the antiinflammatory ability of the immune system, and a chronic inflammatory state may develop. On the other hand, proinflammatory cytokines suppress the HPG axis[9], and low testosterone levels may be expected in patients with RA, at least if inflammation is active.

Low testosterone levels have also been found in men with other chronic inflammatory diseases, e.g., chronic obstructive pulmonary disease[10], chronic kidney disease[11], and other chronic rheumatic diseases, e.g., systemic lupus erythematosus[12]. In contrast, normal testosterone levels have been found in ankylosing spondylitis[13]. Further, longterm stress conditions as well as acute stress, such as septic shock, are associated with low testosterone levels[14].

Our primary aim was to investigate longitudinally the HPG axis in men with early RA for 2 years, in order to determine if the hypogonadism is correlated with inflammatory activity in rheumatic disease. If sex hormone aberrations are a sequel of inflammation, normalization of hormone levels is to be expected in patients recovering from active disease.

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MATERIALS AND METHODS

Patients. Forty-one male patients, mean (SD) age 53 (16) years, admitted to the Department of Rheumatology at Karolinska University Hospital/Huddinge and diagnosed as having RA were included into the study. Patients were recruited consecutively between June 1997 and February 2006. None refused to participate in the study. All fulfilled the American College of Rheumatology criteria for RA[15] and none reported joint symptoms for longer duration than 12 months, mean disease duration 6 months. All patients were disease-modifying antirheumatic drug (DMARD)-naive. We previously reported hormone levels in a cross-sectional study on men with RA[3]. The 19 men in that study, recruited at disease onset, were also recruited to this longitudinal study.

The local ethics committee approved the study protocol, and informed consent was obtained from all patients.

All but one patient started treatment with DMARD at inclusion. At 0, 1, and 2 years, methotrexate was prescribed to 17, 22, and 22 patients, respectively; sulfasalazine to 16, 6, and 4; other DMARD to 6, 4, and 5; and combinations to 1, 3, and 3. Five patients stopped DMARD treatment before the 12-month control. At inclusion and at 1 and 2 years, 3, 5, and 4 patients were prescribed glucocorticoids. One was treated with cyclosporine at 2 years. Other drugs known to influence testosterone levels were beta-blockers in 5 patients and fenantoin in one.

Disease activity was measured by the Disease Activity Score composite index of 28 joints (DAS28)[16]. This includes number of swollen joints, number of tender joints, patient global assessment of disease activity measured on a visual analog scale (VAS; range 0–100 mm), and the erythrocyte sedimentation rate (ESR), and creates a score ranging from 0 to 10. The EULAR criteria for good response include a reduction of DAS28 with score ≥ 1.2 and a DAS28 value ≤ 3.2[17]. EULAR criteria for remission are defined as DAS28 < 2.6[17].

Patients also completed the Swedish version of the Stanford Health Assessment Questionnaire (HAQ), a self-reporting instrument measuring functional capacity[18]. This disability index comprises 20 questions in 8 subcategories, each consisting of 2 to 3 activities of daily life. The response to each question ranges from 0 (no difficulty) to 3 (unable to perform). Scores range from 0 to 3.0, where a higher score indicates a higher degree of disability[19].

Controls. A volunteer group of 131 healthy, medicine-free men served as controls. Those age < 50 years were medical students or hospital staff; those age ≥ 50 years were admitted to the hospital for minor elective surgery, primarily for minor musculoskeletal disturbances, hernia, and varices. The same control population has been used in 2 of our studies[3,20].

Analytical methods. Venous blood was sampled in the morning, between 8:00 and 10:00 AM, for measurement of serum concentrations of total testosterone, sex hormone-binding globulin (SHBG), luteinizing hormone (LH), albumin, ESR, C-reactive protein (CRP), and rheumatoid factor (RF).

Serum concentrations of testosterone were determined by radioimmunoassay in untreated serum using a commercial kit (Coat-a-Count® Testosterone; Diagnostic Products Corp., Los Angeles, CA, USA). SHBG was determined by time-resolved fluorescence assay (Autodelfia®; Wallac Oy, Turku, Finland). LH was determined by chemiluminescence enzyme immunoassay (Immulite® LH; Diagnostic Products). The values are expressed as U/l of first IRP LH 68/40.

The detection limits and within- and between-assay coefficients of variation for testosterone were 0.1 nmol/l, 6% and 10%, respectively; for SHBG 0.5 nmol/l, 4.9% and 3%; and for LH 0.7 U/l, 6% and 9%.

Serum levels of albumin, ESR, CRP, and RF were determined by routine methods at the Department of Clinical Chemistry, Karolinska University Hospital at Huddinge.

Non-SHBG-bound testosterone (NST; sum of free + albumin-bound testosterone) was used as an index of bioavailable testosterone as proposed by Pardridge[21]. Apparent concentrations of NST were calculated from values for total testosterone, SHBG, and albumin by successive approximation using a computer program based upon an equation system derived from the law of mass action[22].

Statistical methods. Descriptive data are presented as means (SD). Spearman rank order correlations were used for continuous data. Comparisons between 2 groups were performed using t test for unpaired observations or Mann-Whitney U test according to distribution. For comparison of baseline and 2-year data, t test for paired observations or Wilcoxon matched-pairs test was used. Multiple regression analysis was performed, but only 2 independent variables were allowed due to the small number of patients. P values < 0.05 were considered statistically significant. Data at 2 years were available for 38 patients.

RESULTS

Due to different age distributions in patient and control groups, analyses were performed in 2 age groups (Table 1). Patients younger than 50 years had lower testosterone, NST, and SHBG concentrations compared with controls. In patients aged ≥ 50 years testosterone and NST were lower compared with controls, although only borderline significances were reached. Patients aged ≥ 50 years on average had significantly lower LH levels than controls. The low LH levels were not associated with higher testosterone levels that were to be expected (Table 1).

At baseline the patients with RA had active disease as assessed by DAS28 mean 5.5 (SD 1.1) and HAQ mean 1.0 (SD 0.5), and 29 out of 41 of the patients had erosive disease. All patients but 3 showed decreased inflammatory activity after 2 years. At that timepoint, 22 of the 38 patients still in the study were responders by the EULAR criteria. Both the responder and the nonresponder groups showed significantly reduced DAS28 and HAQ after 2 years (Table 2).

All patients were recruited from disease onset and followed for 2 years. In a previous cross-sectional study men with RA were studied irrespective of disease duration[3]. All men in that study that were recruited at disease onset (N = 19) also participated in this longitudinal study. These men were older (mean age 59 vs 46 yrs; p = 0.042) but did not differ significantly in testosterone (14.7 vs 16.1 U/l), NST (9.0 vs 10.4 U/l), LH (3.9 vs 4.0), or DAS at baseline (5.2 vs 5.4).

Baseline characteristics and levels of sex hormones were similar between patients that later responded versus patients that did not respond to treatment and could thus not predict the response (Table 1).

As shown in Table 2, mean testosterone levels increased in the responder group but were unchanged in the nonresponders, and differed significantly between the 2 groups at the end of study (Figure 1). Also, SHBG increased, resulting in unchanged mean testosterone/SHBG ratios in responders but lower mean testosterone/SHBG ratios in nonresponders at 2 years. The changes in NST levels reflected the changes in testosterone and testosterone/SHBG levels, but were not significant for any group. The reduced inflammatory activity did not affect LH, which remained low during the observation period.

As response to therapy does not exclude a low or moderate degree of inflammation, we further separated patients in remission according to the EULAR criteria versus patients not in remission at 2 years. The results were similar to those for responders versus nonresponders. Patients in remission had

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Table 1. Baseline hormone concentrations in patients and controls. Values are given as means (SD).

Group	Patients	N	Controls	N	p
Age < 50 yrs					
Age	36.3 (6.1)	15	34.8 (7.9)	88	0.18
Testosterone	16.2 (3.5)	15	23.3 (7.5)	88	< 0.001
SHBG	26 (7)	14	34 (12)	88	0.020
T/SHBG	0.64 (0.16)	15	0.73 (0.26)	88	0.19
NST	11.2 (2.5)	15	14.9 (4.5)	88	0.004
LH	3.3 (1.7)	15	4.1 (2.0)	16	0.28
Age ≥ 50 yrs					
Age	61.3 (6.1)	25	59.4 (5.3)	43	0.51
Testosterone	15.0 (4.9)	25	17.6 (5.8)	43	0.06
SHBG	38 (14)	25	36 (11)	43	0.46
T/SHBG	0.43 (0.16)	25	0.49 (0.18)	43	0.17
NST	9.0 (2.9)	25	10.4 (3.1)	43	0.07
LH	4.3 (3.3)	24	6.2 (2.1)	21	< 0.001

SHBG: sex hormone-binding globulin; T/SHBG: testosterone/SHBG ratio; NST: non-SHBG testosterone; LH: luteinizing hormone.

Table 2. Disease activity and hormone levels at baseline and at 2 years in all patients, responders and non-responders; baseline values divided in those who later respond versus no response.

Characteristic	All, n = 38	Responders, n = 22	Nonresponders, n = 16	p†
Age baseline, yrs	54.2	54.5	53.8	0.87
DAS baseline	5.34	5.43	5.26	0.67
DAS 2 years	2.76 (1.3)***	1.89 (0.6)***	3.91 (0.9)**	0.000
HAQ baseline	1.0	1.0	1.0	0.98
HAQ 2 years	0.46 (0.4)***	0.32 (0.4)***	0.63 (0.5)**	0.049
Testosterone baseline	15.4 (4.4)	15.8 (5.5)	14.9 (3.3)	0.54
Testosterone 2 years	15.9 (5.2)	17.7 (5.8)*	13.9 (3.5)	0.023
SHBG baseline	34 (15)	37 (19)	31 (10)	0.25
SHBG 2 years	43 (22)***	46 (27)**	38 (17)**	0.83
T/SHBG baseline	0.51 (0.2)	0.49 (0.21)	0.51 (0.16)	0.16
T/SHBG 2 years	0.44 (0.24)	0.49 (0.29)	0.39 (0.11)*	0.47
NST baseline	9.76 (3.1)	9.84 (3.6)	9.51 (2.1)	0.76
NST 2 years	9.10 (3.1)	9.67 (3.7)	8.46 (1.8)	0.44
LH baseline	3.9 (2.8)	4.5 (3.4)	3.3 (1.4)	0.10
LH 2 years	4.2 (3.7)	4.9 (4.5)	3.3 (2.0)	0.11

For definitions see Table 1.

increased average testosterone levels (p = 0.015), whereas LH levels were unchanged compared to patients not in remission.

Baseline DAS28 did not correlate with data for any of the hormones analyzed. However, decreased DAS28 data during the 2 years correlated significantly with increased testosterone levels (r_s = –0.46, p = 0.006; Figure 2). Further analyses showed that correlation was stronger for men age ≥ 50 years (r_s = –0.52, p = 0.009) compared to younger men (r_s = –0.37, p = 0.233). Multivariate analysis showed that change in DAS28 but not age correlated with change in testosterone. There were also negative correlations between changes in DAS28 and changes in NST and testosterone/SHBG, but these changes were not significant (r_s = –0.30 and r_s = –0.24, respectively). No correlation was found between changes in DAS28 and changes in LH levels irrespective of age group.

Excluding the few patients undergoing glucocorticoid treatment, 5–7.5 mg of prednisolone did not affect the findings. The 3 patients already in treatment with glucocorticoids at RA diagnosis did not respond later, according to the EULAR criteria. Four patients were treated with glucocorticoids at the end of the study, 2 responders and 2 nonresponders. There were no significant differences in testosterone or LH levels, or in age, between patients with and those without glucocorticoids during the study. However, the 4 patients treated with glucocorticoids at the end of the study all had decreased testosterone concentrations during the study.

DISCUSSION

Our study shows that men with RA already had mean testosterone levels lower than those of controls early in the disease

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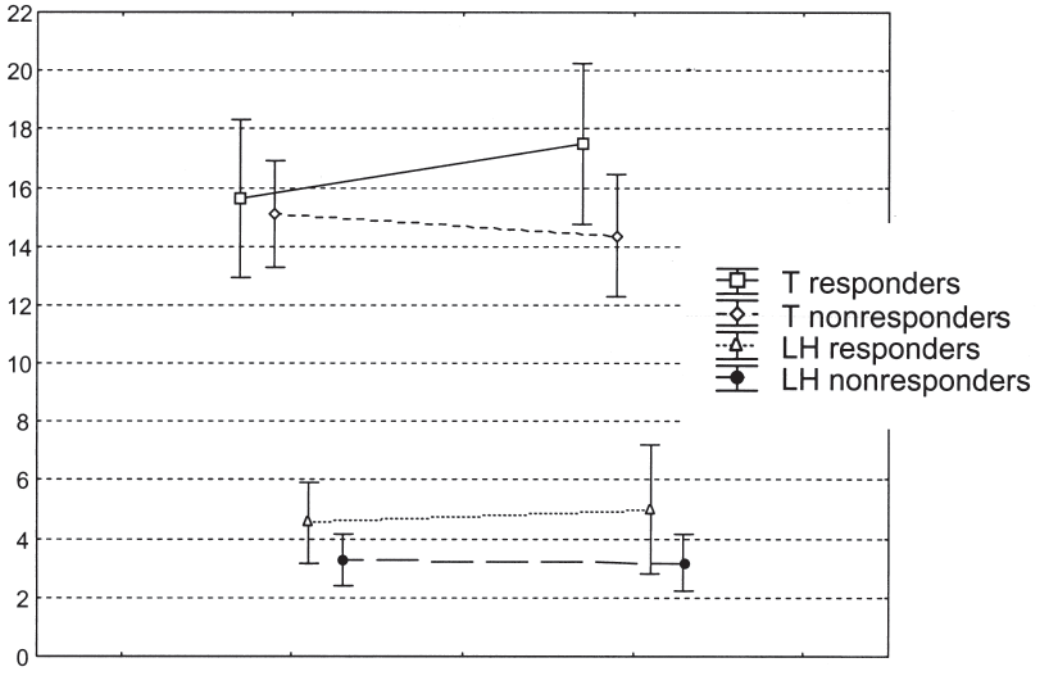

Figure 1. Testosterone (T) and luteinizing hormone (LH) at diagnosis and after 2 years. Data are means (95% confidence interval) of nmol/l for testosterone and U/l for LH. Patients are divided in 2 groups, those who were responders according to the EULAR criteria after 2 years (n = 22) and nonresponders (n = 16). The only significant difference is the testosterone levels at 2 years (see Table 2).

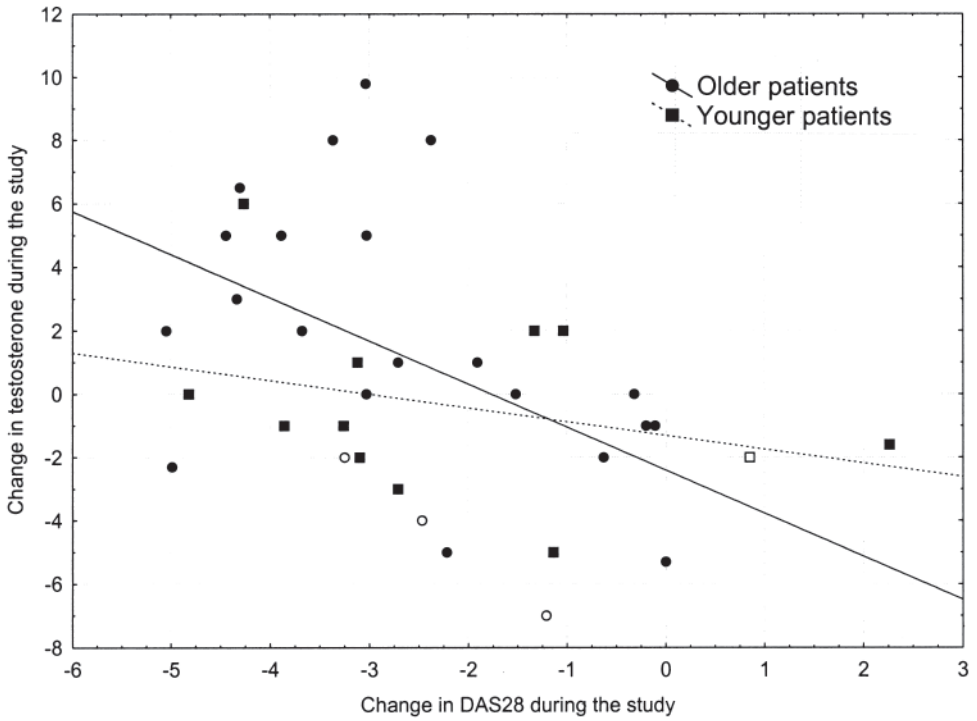

Figure 2. Correlation between change in DAS28 and change in testosterone levels during the study. For men age ≥ 50 years, r = –0.52, p = 0.0090. For men age < 50 years, r = –0.37, p = 0.233. Patients on treatment with glucocorticoids are marked with open circles and squares.

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course (borderline significance in older patients). Patients older than 50 years also had significantly lower average LH levels compared with controls in spite of lower testosterone levels, consistent with mild hypogonadotropic hypogonadism. The age-related heterogeneity in HPG axis data might depend on the disproportionately large young control group, making statistical significance easier to obtain.

SHBG is inversely correlated with inflammation, and is increased in both responders and nonresponders[23]. We found no explanation for the lower SHBG levels in patients younger than 50 years compared with controls.

The patients who after 2 years fulfilled the EULAR criteria for clinical response not only showed improved testosterone levels at 2 years compared with baseline, but also had significantly higher testosterone levels compared with patients with sustained inflammation. As also the nonresponding group showed decreased disease activity, although without fulfilling the EULAR response criteria, the difference between the 2 groups concerning testosterone levels was probably attenuated. We therefore performed correlation analyses between changes in DAS28 and changes in hormone levels that confirmed the findings of increased testosterone but unchanged LH levels with decreasing disease activity.

Our findings indicate a persistently dysfunctional HPG axis at the levels of the hypothalamus and/or the pituitary. The improved testosterone levels may depend on reduced levels of proinflammatory cytokines, which decrease the inhibitory effects on the testes. Further, the conversion of testosterone to estrogen is decreased with less inflammatory activity. The proinflammatory cytokine tumor necrosis factor-α (TNF-α) has an inhibiting effect on testicular testosterone synthesis[24,25] by inhibiting important enzymatic steps in adrenal and gonadal glands[26], and the course of testosterone in our study was therefore expected. Further, TNF-α and other proinflammatory cytokines increase the activity of the aromatase complex, which induces the conversion of androgens to estrogens[27-29].

In contrast to the current report and our previous report of hypogonadotropic hypogonadism in men with RA[3], hypoandrogenism in chronic pulmonary and renal disease is associated with high levels of follicle-stimulating hormone (FSH) and LH[10,30]. The aberrations in the HPG axis in men with chronic renal disease is almost normalized after kidney transplant, i.e., testosterone levels increase and the levels of FSH and LH decrease[30]. The hypogonadism in men with RA thus differs from that in chronic pulmonary and renal disease in being of central genesis, i.e., due to a dysfunction in the hypothalamus and/or the pituitary. Consequently, neither the decrease of inflammation nor changes in testosterone levels affected LH levels in our study.

The increase in testosterone levels we observed as disease activity decreased is in accord with findings by Gordon and coworkers[31]. They followed 10 men admitted to hospital for disease flares. Although the free testosterone levels did not increase during the in-hospital period (median 3 weeks), they were significantly increased at followup after 5–14 months in all men but one. In contrast to our study, the average LH level decreased from baseline to followup.

Improvement of inflammation is thus associated with increased testosterone levels. On the other hand, treatment with testosterone may suppress inflammation, as shown by Cutolo and coworkers[32]. TNF blockers may support the HPG axis, according to Straub and coworkers[26], and hormonal factors may contribute to the better response to methotrexate and TNF-α blockers in men compared to women[33]. Macrophage-like synoviocytes in the rheumatoid synovia express androgen receptors, and probably to a higher extent than in healthy controls[34].

Somewhat surprisingly, in an earlier study analyzing the HPG axis in 18 men with established RA, we found stable levels of testosterone and LH during 2 years' treatment with TNF blockers, independent of inflammatory activity[35]. It may be that the long disease duration in that study (median 5 years, range 1–61) had irreversibly hampered the hormone synthesis.

In summary, decreased disease activity following DMARD therapy in men with early RA improved the HPG axis, mainly at the level of testosterone, but it did not increase LH levels. If the unresponsiveness of LH precedes the disease or is a consequence of longterm inflammation remains to be clarified.

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