Bioavailable testosterone in men with rheumatoid arthritis—high frequency of hypogonadism

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Abstract

Objectives. To study bioavailable testosterone (T) in men with rheumatoid arthritis (RA) by determining non-sex hormone-binding globulin (SHBG)-bound T (NST) under standardized conditions and to investigate if NST is related to disease variables.

Methods. Basal serum concentrations of total T, SHBG and luteinizing hormone (LH) were measured in 104 men with RA, and the levels of NST as well as the quotient T/SHBG were calculated. The data were compared with those of 99 age-matched healthy men. The results were analysed separately for the age groups 30–49, 50–59 and 60–69 yr.

Results. The RA men had lower NST levels than the healthy men in all age groups. T levels and the T/SHBG ratio were lower only in the age group 50–59 yr. SHBG did not differ significantly. LH was significantly lower in the patients than in the controls. Thirty-three of the 104 patients were considered to have hypogonadism compared with seven of the 99 healthy men. The only clinical variable apart from age that had a significant impact on NST was the Stanford Health Assessment Questionnaire (HAQ).

Conclusion. Men with RA had lower levels of bioavailable T and a large proportion were considered hypogonadal. The low levels of LH suggested a central origin of the relative hypoandrogenicity.

KEY WORDS: Rheumatoid arthritis, Men, NST, Testosterone, HAQ, Disease activity.

Previous studies indicate that men with rheumatoid arthritis (RA) have lower levels of serum testosterone (T) than healthy men [1–4] as well as compared with men with osteoarthritis [2] and ankylosing spondylitis [1, 4]. These findings have led to the hypothesis that low T levels may have a pathogenic role in RA [5], a hypothesis strengthened by the fact that the mean age for the start of the disease in men is just above 60 yr, when the level of bioavailable T has decreased substantially [6]. On the other hand, there are reports indicating that low levels of T are correlated with disease activity [1, 7] as well as influenced by treatment with prednisone [8] and sulphasalazine [9] and, thus, a result and not a partial cause of RA.

In circulation, T is strongly bound to sex hormone-binding globulin (SHBG), loosely bound to albumin and a minor amount (1% in males) is free. The free T (fT) or, alternatively, the sum of free and albumin-bound fractions [non-SHBG-bound T (NST)], is considered bioavailable [10]. The levels of fT and NST are strongly affected by age [11], body mass index [11] and the circadian rhythm of T [12]. In several previous studies on androgen status and RA, these factors have not been taken into consideration. This prompted us to undertake the present study on the pituitary–testicular axis in men with RA and to relate the findings to clinical manifestations and to current treatment of the disease.

Patients and methods

Patients and controls
One hundred and four male patients, aged 30–69 yr, with RA according to the American College of Rheumatology criteria [13] were enrolled into the study. The patients were attending the Rheumatology Department at Huddinge University Hospital, a referral clinic for a population of 800000 inhabitants, and were consecutively asked to participate in the study. Only one patient declined. Clinical data are shown in Table 1. Most of the patients were, thus, on disease-modifying anti-rheumatic drugs (DMARDs), but 19 of the patients had early RA where DMARDs and/or glucocorticoids had not been introduced when the examinations were...
immunoassay in untreated serum using a commercial kit (LH), albumin, ESR, C-reactive protein (CRP) and concentrations of total T, SHBG, luteinizing hormone (LH). The values are expressed as 1st International Reference Preparation LH 68/40.

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

The patients also completed the Swedish version of the Stanford Health Assessment Questionnaire (HAQ), a self-reporting instrument measuring functional capacity [15]. This disability index was comprised of 20 questions, divided into eight subcategories, each consisting of two to three activities of daily life. The response to each question ranged from 0 (no difficulty) to 3 (unable to perform). The created score for the disability index ranged from 0 to 3, where a higher score indicated a higher degree of disability [16].

Biochemical analysis
Venous blood was sampled in the morning, between 8.00 and 10.00 a.m., for the measurement of serum concentrations of total T, SHBG, luteinizing hormone (LH), albumin, ESR, C-reactive protein (CRP) and rheumatoid factor (RF).

Serum concentrations of T were determined by radio-immunoassay in untreated serum using a commercial kit obtained from Diagnostic Products Corp. (Los Angeles, CA, USA; ‘Coat-a-Count® I125, Testosterone). SHBG was determined by time-resolved fluorescence assay using a commercial kit (Autodelfia®) obtained from Wallac Oy (Turku, Finland). LH was determined by chemiluminescence enzyme immunoassay using commercial kits obtained from Diagnostic Products Corp. (Immulite® LH). The values are expressed as 1st International Reference Preparation LH 68/40.

There are several methods to estimate fT or bioavailable T in serum [17]. We used NST as an index of bioavailable T, as proposed by Partridge [10]. Apparent concentrations of NST were calculated from values for total T, SHBG and albumin by successive approximation using a computer program based on an equation system derived from the law of mass action [18]. Those individuals who had NST values below the two-tailed 95% confidence interval in the control population were considered hypogonadal. The cut-off levels were: for individuals 30–49 yr: 8.1 nmol/l; 50–59 yr: 7.7 nmol/l; 60–69 yr: 6.5 nmol/l.

In clinical practice the simple ratio between T and SHBG is frequently used as an index of bioavailable T rather than calculated NST or fT [19]. For comparative purposes the T/SHBG ratio was also included in the calculations.

The presence and titre of RF were determined using the classical Waaler–Rose haemagglutination method. The assay was calibrated against the international reference RF preparation WHO 64/1.

Statistics
NST was transformed by logarithm to obtain a normal distribution and then a multiple regression analysis was performed to calculate the impact of the appropriate variables on NST. Other statistical calculations were performed with non-parametric tests.

Results
Our RA patients were a heterogeneous population with respect to age and disease duration and they exhibited great variations in inflammatory activity as well as in their degree of functional impairment (HAQ; Table 1).

Within the three different age groups, T and the T/SHBG ratio were lower in the RA patients than in the controls only in men aged 50–59 yr. No differences in SHBG were found between patients and controls. NST levels were significantly lower in the patients than in the controls in all three age groups (Table 2).

The frequency of hypogonadism, as judged by NST values, was far more pronounced and significantly higher in the patients than in the controls. Thus, 33 of the 104 patients were hypogonadal compared with seven of the 99 controls (P < 0.001).
Table 2. Androgen data for the patients with RA and for the healthy controls, given for the separate age groups

<table>
<thead>
<tr>
<th>Age group 30–49 yr</th>
<th>Patients with RA</th>
<th>Healthy controls</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>20</td>
<td>56</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>44.2</td>
<td>39.8</td>
<td></td>
</tr>
<tr>
<td>T (nmol/l)</td>
<td>19.6 (8.1)</td>
<td>22.8 (8.1)</td>
<td>NS</td>
</tr>
<tr>
<td>SHBG (nmol/l)</td>
<td>35.2 (20.1)</td>
<td>36.1 (11.4)</td>
<td>NS</td>
</tr>
<tr>
<td>T/SHBG</td>
<td>0.61 (0.2)</td>
<td>0.67 (0.2)</td>
<td>NS</td>
</tr>
<tr>
<td>NST (nmol/l)</td>
<td>11.6 (4.7)</td>
<td>14.5 (4.8)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Percentage hypogonadal</td>
<td>15</td>
<td>5</td>
<td>NS</td>
</tr>
</tbody>
</table>

<table>
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<tr>
<th>Age group 50–59 yr</th>
<th>Patients with RA</th>
<th>Healthy controls</th>
<th>P value</th>
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</thead>
<tbody>
<tr>
<td>n</td>
<td>34</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>55.5</td>
<td>55.1</td>
<td></td>
</tr>
<tr>
<td>T (nmol/l)</td>
<td>14.9 (5.1)</td>
<td>18.6 (6.0)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>SHBG (nmol/l)</td>
<td>32.9 (13.2)</td>
<td>34.7 (12.9)</td>
<td>NS</td>
</tr>
<tr>
<td>T/SHBG</td>
<td>0.49 (0.2)</td>
<td>0.56 (0.2)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>NST (nmol/l)</td>
<td>8.9 (2.5)</td>
<td>11.4 (3.0)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Percentage hypogonadal</td>
<td>35</td>
<td>9</td>
<td>&lt; 0.05</td>
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<table>
<thead>
<tr>
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<th>Healthy controls</th>
<th>P value</th>
</tr>
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<td>n</td>
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<td>20</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>64.9</td>
<td>64.2</td>
<td></td>
</tr>
<tr>
<td>T (nmol/l)</td>
<td>14.1 (4.9)</td>
<td>16.6 (5.6)</td>
<td>NS</td>
</tr>
<tr>
<td>SHBG (nmol/l)</td>
<td>41.9 (16.1)</td>
<td>40.2 (16.1)</td>
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<td>T/SHBG</td>
<td>0.36 (0.1)</td>
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<tr>
<td>NST (nmol/l)</td>
<td>7.6 (2.5)</td>
<td>9.2 (2.8)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Percentage hypogonadal</td>
<td>36</td>
<td>10</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>

P values refer to differences between the patients and the controls. Values are means (standard deviation). NS, not significant.

Data for LH in the controls were available in 37 of the 99 subjects. The median serum LH in the total patient material was 4.0 U/l (range 0.7–25) compared with 5.1 U/l (range 1.7–11) in the controls. This difference was statistically significant (P < 0.01). There were three patients with very high levels of LH (15, 17 and 25 U/l). The mean value of LH with these three patients excluded was 3.6 U/l (range 0.7–11). The mean age of the controls where LH values were available was 51.4 ± 11.3 yr, compared with 58.0 ± 8.5 yr for the total patient material.

Serum total T and SHBG showed significant positive correlations in patients and controls in the total material as well as in the different age groups (P < 0.01 for all age groups, r = 0.51, 0.67 and 0.43, respectively).

In the multiple regression analysis, age had the largest impact on NST in the RA patients (P < 0.001) as well as in the healthy men. In the patients, the only other variable with a statistically significant association to NST was the HAQ (P < 0.05).

The inflammatory activity measured as DAS28 did not show any statistically significant impact directly on NST, but was indeed the variable that had the largest influence on the HAQ (r = 0.59, P < 0.001). Neither ESR, CRP nor swollen joints were significantly correlated to NST.

Treatment with glucocorticoids, sulphasalazine or methotrexate did not influence NST, nor did smoking habits, body mass index, the presence of RF or disease duration (data not shown). The NST levels in the patients with beta-blockers did not differ from those in patients not taking beta-blockers, nor did the LH levels.

Discussion

This study showed that men with RA had lower levels of bioavailable T expressed as NST compared with healthy age-matched controls and that frank hypogonadism was quite common. Thus, 33 of the 104 examined patients were considered hypogonadal, which was significantly more than in the control population.

The finding of lower NST levels in RA men than in healthy age-matched controls confirms previous studies on bioavailable T [1, 3, 4, 20]. Corresponding significant differences in total T and the T/SHBG ratio were found only for one age group. This illustrates the still often overlooked fact that total T is not a good marker of androgenic activity. Concerning the T/SHBG ratio, this is an excellent marker for bioavailable T in women, but less good in adult men. A key assumption for the derivation of the T/SHBG ratio is that the binding capacity of SHBG greatly exceeds the concentration of its ligand T. This is not the case in adult men where T concentrations are close to the binding capacity of SHBG [19].

Serum LH was significantly lower in the patients than in the controls. This is in contrast to the reports by Gordon et al. [1] who found higher levels of LH and follicle stimulating hormone in patients than in controls, but within the normal range, and Spector et al. [3] who found comparable LH levels in patients and controls, in the presence of subnormal levels of fT. These latter studies were comprised, however, of small patient numbers, partly of other patient groups as controls and used a different method to analyse LH.

The low LH levels in RA men found in the present study indicate that their lower NST levels are of central origin. Only two of the 33 hypogonadal patients had elevated levels of LH, indicating a primary gonadal insufficiency. The hypothalamic–pituitary–gonadal (HPG) axis in RA men has not been systematically studied. However, previous studies suggest disturbances in the regulation of the hypothalamic–pituitary–adrenocortical (HPA) axis in patients with RA [21]. Whether the mechanisms for disturbance in these hormone regulation systems are similar is unknown. Another possible explanation of the low LH levels might be the known fact that long-term treatment with non-steroidal anti-inflammatory drugs (NSAIDs) depresses the release of gonadotropins [22]. An influence by NSAIDs has also been shown on the HPA axis [23]. Virtually all of our patients were treated with NSAIDs. Furthermore, distinct hypogonadotropic hypogonadism is reported to occur in critically ill patients [24]. However, our patients had a low degree of functional impairment and just moderate levels of disease activity and could not be considered as critically ill.

Although exogenous glucocorticosteroids at high doses can suppress androgen secretion [25, 26], the use of low-dose prednisolone by our patients did not have
any impact on NST. Mateo et al. [20] also did not find any correlation between cumulative glucocorticoid dose and FT levels.

In healthy adult males, serum concentrations of total T and SHBG are positively correlated. This does not reflect an effect of SHBG binding on the T metabolism, but rather the attempt of the organism to maintain constant androgenic/anabolic activity, and a prerequisite for this is an intact HPG axis [27]. Positive correlations between total T and SHBG were found in the controls and also in the patients, despite the lower NST and LH levels in the latter. Thus, even if the activity of the HPG axis was suppressed in RA men, its regulatory mechanisms seemed to be intact.

The HAQ was the only clinical variable that had any association to NST. The functional impairment measured by the HAQ reflects different aspects of the RA disease. In early RA (less than 5 yr), inflammatory activity has a great impact on the HAQ, whereas in established disease (more than 5 yr), tissue damage is more important [28]. This is in agreement with the correlation between the HAQ and disease activity, found here, in a patient population with a mean disease duration of 4 yr. As the HAQ is suggested to reflect disease severity [29], the impact of the HAQ on NST could be interpreted as low NST values being associated with a more severe disease. Another possible explanation is that men with low androgen levels may have a functional impairment secondary to the androgen deficiency [30].

The lack of impact of disease activity on NST is in agreement with some reports, but at variance with others. We used the disease activity index DAS28 as a composite index of disease activity, but also when single variables of inflammation were used, such as swollen joints, ESR and CRP, the results were similar (data not shown). Other reports show correlations with some but not with other variables of inflammatory activity. Thus, Spector et al. [3] found an unexpectedly positive correlation between the Ritchie Articular Index (RAI) and FT levels, whereas Mateo et al. found a negative correlation [20]. Gordon et al. [1], on the other hand, found a significant negative correlation between FT concentrations and laboratory indices such as ESR and haemoglobin, but not with the clinical indices RAI and early morning stiffness. The inconsistency of the results might depend on the relatively rapid variations in inflammatory variables over some time. This explanation is supported by the increase in FT time after improvement in disease activity in patients after a flare in the disease [7].

A large proportion of our patients were, thus, hypogonadal. Low levels of bioavailable T may cause depression, anxiety and insomnia, as well as reduced muscle and bone mass [30, 31]. Osteoporosis has also been demonstrated in men with RA [20]. Furthermore, the deficiency of androgens may affect the severity of the RA, as it is well documented that androgens exert immune-suppressive effects on a variety of immune target cells [32].

In conclusion, we have shown that NST, as a measure of bioavailable T, and LH were low in men with RA, suggesting a hypoandrogenicity of central origin. However, the data cannot answer the question of whether the androgen deficiency is a consequence of the disease or an aetiological factor. Further studies are warranted to solve this issue.

Acknowledgement

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References


