High frequency of association of rheumatic/autoimmune diseases and untreated male hypogonadism with severe testicular dysfunction

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Received: 10 January 2001 Revisions requested: 16 March 2001 Revisions received: 25 July 2001 Accepted: 7 August 2001 Published: 12 September 2001

Arthritis Res 2001, 3:362-367

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(Print ISSN 1465-9905; Online ISSN 1465-9913)

Abstract
Our goal in the present work was to determine whether male patients with untreated hypogonadism have an increased risk of developing rheumatic/autoimmune disease (RAD), and, if so, whether there is a relation to the type of hypogonadism. We carried out neuroendocrine, genetic, and rheumatologic investigations in 13 such patients and 10 healthy male 46,XY normogonadic control subjects. Age and body mass index were similar in the two groups. Nine of the 13 patients had hypergonadotropic hypogonadism (five of whom had Klinefelter’s syndrome [karyotype 47,XXY]) and 4 of the 13 had hypogonadotropic hypogonadism (46,XY). Of these last four, two had Kallmann’s syndrome and two had idiopathic cryptorchidism.

Eight (61%) of the 13 patients studied had RADs unrelated to the etiology of their hypogonadism. Of these, four had ankylosing spondylitis and histocompatibility B27 antigen, two had systemic lupus erythematosus (in one case associated with antiphospholipids), one had juvenile rheumatoid arthritis, and one had juvenile dermatomyositis. In comparison with the low frequencies of RADs in the general population (about 0.83%, including systemic lupus erythematosus, 0.03%; dermatomyositis, 0.04%; juvenile rheumatoid arthritis, 0.03%; ankylosing spondylitis, 0.01%; rheumatoid arthritis, 0.62%; and other RAD, 0.1%), there were surprisingly high frequencies of such disorders in this small group of patients with untreated hypogonadism \((P<0.001)\) and very low serum testosterone levels \((P=0.0005)\). The presence of RADs in these patients was independent of the etiology of their hypogonadism and was associated with marked gonadal failure with very low testosterone levels.

Keywords: ankylosing spondylitis, hypogonadism, rheumatic diseases, systemic lupus erythematosus, testosterone

Introduction
The clinical observation that sexual dimorphism plays a role in the immune response suggests that the endocrine system is an important factor for the development and maintenance of the response. There is a high frequency of autoimmune diseases in females and an increased immune response to antigenic stimulus. These observations make it evident that sexual dimorphism probably acts on the immune response through its effect upon the thymic-hypothalamic-pituitary-gonadic axis [1].

AS = ankylosing spondylitis; B27 = histocompatibility antigen B27; CREST = calcinosis, Raynaud's phenomenon, esophageal dysfunction, sclerodactyly, telangiectasia; \(E_2 = \text{estradiol-17\beta}\); JRA = juvenile rheumatoid arthritis; RA = rheumatoid arthritis; RAD = rheumatic/autoimmune disease; SLE = systemic lupus erythematosus.
Series of subjects with gonadal dysgenesis, and isolated cases of Klinefelter’s syndrome associated with rheumatic/autoimmune diseases (RAD), suggest a relation between these clinical conditions [2,3]. Among male patients reported to date who have hypogonadism and RAD are individuals with systemic lupus erythematosus (SLE) [4–7], lupus anticoagulant and antiphospholipid syndrome associated [8], scleroderma [9–12], rheumatoid arthritis (RA) [13], ankylosing spondylitis (AS) [14–16], and polymyositis [17], while Turner’s syndrome has been associated with autoimmune thyroiditis [3], juvenile rheumatoid arthritis (JRA) [18], and juvenile-onset inflammatory bowel disease [19]. Only one of these reports included eunuchoid males and female subjects with an abnormal X karyotype [2].

Our goal in the present work was to determine whether male patients with untreated hypogonadism have an increased risk of developing RAD, and, if so, whether there is a relation to the type of hypogonadism.

Methods
The clinical criteria of male hypogonadism refers to failure of testicular function resulting in decreased production or absence of male sex hormones and impaired spermatogenesis, whether this failure is secondary to hypothalamic and pituitary dysfunction or is primary testicular failure [20].

From 60 patients who fulfilled the previous hypogonadism criteria who were seen at the outpatient Andrology Clinic, Mexico City, Mexico, from July 1998 to May 2000, 13 who were not receiving hormone substitution were selected for this study.

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Ten normogonadic healthy male hospital staff with similar age and body mass index [21] constituted the control group for testicular size and hormone levels.

All the patients gave their informed consent. They and the control subjects were given a neuroendocrine, genetic, and clinic evaluation, including a physical exam, in addition to computed tomography of the sella turcica and karyotyping of peripheral leukocytes. The presence of secondary sexual characteristics and testicular volume (normal value >20 ml) were noted.

In the patients, the rheumatologic evaluation included a search for the presence of diagnostic criteria for SLE, RA, AS, psoriatic arthritis, JRA, polymyositis/dermatomyositis, scleroderma/CREST (calcinosis, Raynaud’s phenomenon, esophageal dysfunction, sclerodactyly, telangiectasia), and Behçet’s syndrome [22]. Venous blood (20 ml) was extracted to determine the erythrocyte sedimentation rate (Wintrobe method, mm/h), lupus erythematosus cells, rheumatoid factor (normal value <20 IU/ml), antinuclear antibodies by immunofluorescence test (rat kidney substrate), anti-DNA (radioimmunoassay), and Ro, La, Sm, and Scl-70 by nephelometry to disclose autoimmune phenomena and/or inflammatory serum subclinical abnormalities. The histocompatibility antigen B27 (B27) was determined by Terasaki’s joint-to-thyroid function test (Cis bio international Groupe ORIS Cedex-France) using radioimmunoassay. Serum levels of testosterone (double-antibody radioimmunoassay technique), estradiol-17β (E2) (International CIS Sorin, Paris, France; double-antibody radioimmunoassay kit), follicle-stimulating hormone, luteinizing hormone, and prolactin (Diagnostic Products Co, Los Angeles, CA, USA; double-antibody radioimmunoassay kit) (in duplicate) were determined in patients and controls. Coefficients of intra-assay and interassay variations were, respectively, as follows: testosterone, 6.0 and 10.4%; E2, 5.0 and 8.5%; follicle-stimulating hormone, 3.1 and 7.7%; luteinizing hormone, 7.0 and 7.9%; and prolactin, 4.4 and 8.6%. X-rays were made of the lumbosacral spine, sacroiliac joints, and affected peripheral joints and were interpreted blind. Affected tissues were biopsied as appropriate for the clinical signs.

Fisher’s exact test and the Mann–Whitney U test were used for statistical analysis (computer package Epi-Info, Version 6.00; Centers for Disease Control and Prevention, USA, World Health Organization, Geneva, Switzerland). The significance limit was set at $P < 0.05$.

Results
Age and body mass index were similar in patients and controls (mean ± standard deviation): respectively, age 25.3 ± 8.4 years vs 29.5 ± 7.6 years and body mass index 23.1 ± 3.3 kg/m² vs 24.2 ± 3.6 kg/m² ($P = \text{NS}$). The testicular volume was 4.4 ± 4.3 ml in patients and 43.5 ± 3.5 ml in controls ($P = 0.001$). Nine of the 13 patients had hypergonadotropic hypogonadism, five of whom had Klinefelter’s syndrome (47,XXY). The other four of the 13 patients had hypogonadotropic hypogonadism (46,XY); two of this group had Kallmann’s syndrome and two had idiopathic cryptorchidism.

Eight out of the 13 male hypogonadal patients also had RAD independently of the cause of their hypogonadism. Of these, four had B27 + AS, two had SLE (in one case associated with anti-phospholipid antibodies), one had JRA, and one had juvenile dermatomyositis (Tables 1 and 2). We did not find adult RA, scleroderma, scleroderma/CREST, psoriatic arthritis, or Behçet’s syndrome.
Among the patients, age and body mass index were similar in those with and those without RAD. Serum testosterone and estradiol 17β levels were lower in those with RAD, but only the difference in testosterone was highly significant (1.0 ± 0.7 vs 2.7 ± 1.2 ng/ml, \( P = 0.0005 \)) (see Supplementary Table 1).

### Table 1

| Patient no. | Age (years) | Endocrine and genetic diagnosis | Symptoms and disease duration | Laboratory findings \(^a\) | X-rays | RAD |
|------------|------------|---------------------------------|------------------------------|--------------------------|-------|-----|
| 1          | 33         | Klinefelter’s syndrome; 47,XXY  | Mucocutaneous rash with Raynaud’s phenomenon; 2 years | ANA +; anti-DNA, 100 IU/dl; LE cells +; ESR, 25 mm/h; B27 (−); GMN, IIB WHO \(^b\) | Normal | SLE |
| 2          | 18         | Klinefelter’s syndrome; 47,XXY  | Multiple venous thrombosis, mucocutaneous rash, symmetrical polyarthritis; 6 weeks | ANA +; anti-Ro +; La +; anti-DNA, 30 IU/dl; ESR, 32 mm/h; B27 (−); skin biopsy compatible with SLE; serum antiphospholipid + IgG | Normal | SLE and APLS |
| 3          | 20         | Klinefelter’s syndrome; 47,XXY/sexual chromatin X(90%) | Lumbar pain, morning stiffness, Achilles tendinitis; 6 months; Schober’s test, 4 cm \(^a\) | ESR, 5 mm/h; B27 (+) | Ankylosis of sacroiliac joints | AS |
| 4          | 20         | Testicular damage with hyperprolactinemia; 46,XY | Symmetrical arthritis of knees; 15 years; Schober’s test, 6 cm \(^a\) | ESR, 51 mm/h; LE cells +; B27 (−); synovial biopsy; rheumatoid arthritis | Normal | JRA |
| 5          | 44         | Bilateral orchidectomy due to carcinoma of testicle; 47,XY | Chronic lumbar and hip pain, knee arthritis, acute intermittent uveitis, Achilles tendinitis; 6 years; Schober’s test, 4 cm \(^a\) | ESR, 50 mm/h; B27 (+) | Bilateral sacroilitis | AS |
| 6          | 32         | Klinefelter’s syndrome; 47,XXY(88%)/46,XY(32%) | Asymptomatic | ESR, 10mm/h; B27 (−) | Normal | None |
| 7          | 21         | Gonadal dysgenesis with mosaicism; 45,X/47,XY | Asymptomatic | ESR, 15mm/h; B27 (−) | Normal | None |
| 8          | 17         | Bilateral cryptorchidism, orchidectomy; 46,XY | Asymptomatic | ESR, 15mm/h; B27 (−) | Normal | None |
| 9          | 31         | True hermaphrodite; 46,XY | Asymptomatic | ESR, 41mm/h; B27 (−) | Normal | None |

\(^a\)Normal values: anti-DNA, <20 IU/dl; ESR, <15 mm/h; Schober’s test, >5 cm. \(^b\)World Health Organization [40].

Among the patients, age and body mass index were similar in those with and those without RAD. Serum testosterone and estradiol 17β levels were lower in those with RAD, but only the difference in testosterone was highly significant (1.0 ± 0.7 vs 2.7 ± 1.2 ng/ml, \( P = 0.0005 \)) (see Supplementary Table 1).

### Discussion

As far as we know, this is the first report of an intentional search for RAD in male patients with untreated hypogonadism.

Usually, males with hypogonadism diagnosed in infancy or in youth are those who have a complete hypogonadic clinical picture. Some individuals, however, exhibit an incomplete clinical picture and may reach adulthood without having their condition diagnosed. Their condition may come to light during tests of sterility in a couple, or during epidemiological studies [23–26], which have established the frequency of male patients with hypogonadism.

At present, it is considered that the frequency of male patients with hypogonadism in the general male population is somewhere between 0.04 and 1% [23,24] and that the most frequent genetic alteration found in these persons is that causing Klinefelter’s syndrome, whose prevalence is of the order of 0.02 to 0.09% in healthy populations [23–26] and 0.2 to 41.3% in populations with certain mental or behavioral problems [27–29].

Our study was performed in a smaller group of male patients with hypogonadism to those that have been reported previously, for two reasons. First, the patients were studied in an andrology clinic for infertility and thus are not an unselected sample of the general population. Second, their hypogonadism had not been diagnosed or treated previously. Although it is arguable that our series of patients, not being a representative sample, is unsuitable for evaluation of the frequency of RAD in patients with hypogonadism, we investigated RAD only in those who had not been treated for their hypogonadism, to avoid...
the possibility that androgen replacement had interfered
with the development of RAD [30,31].

Because the clinical picture of RAD in some of the
patients was severe, with clear systemic and articular
symptoms, their RAD had been diagnosed elsewhere.
However, other patients with hypogonadism who also had
JRA and AS had only a few articular symptoms, so slight
that the RAD had gone unnoticed until we looked for it.

Considering that the frequency of RAD in Mexico City,
where our study was performed, is about 0.83% (includ-
ing RA 0.62%; SLE 0.03%; polymyositis/dermatomyositis
0.04%; JRA 0.03%; AS 0.01%; and other RAD [Sjögren’s
syndrome, mix connective tissue disease, etc.], 0.1%) [32],
the relatively large number of cases of RAD in this
very small group of male patients with untreated hypogo-
nadism was surprisingly high (P<0.001), suggesting a
strong relation between the two conditions (see Supple-
mentary Table 2). The development of RAD only in those
patients with severe testicular dysfunction suggests that
such dysfunction is one endogenous factor that predis-
poses to the development of RAD.

The disorder most frequent in our group was the combi-
nation of B27 with AS. The frequency of patients with B27
(all of whom also developed AS) was very high (30.7%),
leading to the conclusion that the risk that males with
hypogonadism will develop AS is higher than that of a
healthy Mexican mestizo (about 4%, P = 0.001) [33]. We
cannot explain this association at present.

The frequency of SLE in male patients with hypogonadism
was higher than would be expected in the general popula-
tion. Despite the increased odds ratio for the development
of SLE in such patients, the confidence interval was very
wide, suggesting that other factors in addition to hormonal
and genetic alterations affect the development of SLE in
these patients.

Our group of patients includes, as far as we know, the first
case of hypogonadism associated with juvenile dermato-
myositis. The development of dermatomyositis and JRA
was higher in our patients than in the general population
(P = 0.006 and P = 0.004, respectively; Supplementary
Table 2). Nevertheless, the confidence interval was not
calculable; therefore we conclude that these associations
are coincidental. The fact that frequency of RA was no
higher in our group of patients than in the general popula-
tion suggests that the RA and hypogonadism are not
related, as has already been suggested [13].

Because the group of patients we studied was so hetero-
geneous (hypogonadism due to various causes, and vari-
ous RAD), we can conclude only that the hypogo-
nadism itself (regardless of its particular etiology) and the
very low serum testosterone levels are associated with the
increased frequency of RAD.

Studies in healthy, normogonadal males with RAD have
found low serum levels of testosterone and high levels of
E2 in patients with RA, SLE, and Sjögren’s syndrome
[34,35]. The inflamed tissues of normogonadal patients

Table 2

| Patient no. | Age (years) | Endocrine and genetic diagnosis | Symptoms and disease duration | Laboratory findings | X-rays | RAD |
|------------|------------|--------------------------------|-----------------------------|--------------------|--------|-----|
| 1          | 23         | Kallmann’s syndrome; 46,XY     | Intermittent lumbar and hip pain, symmetrical ankle arthritis; 10 years; Schober’s test, 4.5 cm² | ESR, 3 mm/h; B27 (+) | Bilateral sacroiliitis | AS |
| 2          | 34         | Kallmann’s syndrome; 46,XY     | Intermittent lumbar pain and morning stiffness; 10 years; Schober’s test, 4.5 cm² | ESR, 7 mm/h; B27 (+) | Ankylosis of sacroiliac joints | AS |
| 3          | 17         | Idiopathic hypogonadotropic MPHG; 46,XY; bilateral cryptorchidism | Photosensitive skin heliotrope rash, alopecia, proximal muscle weakness with atrophy, Gottron’s papules; 11 years; arthritis of MCP and PIP joints | ESR, 53 mm/h; CK, 182 U/ml; C3, 115 mg/dl; C4, 76 mg/dl; ANA + speckled pattern; anti-DNA, 26 IU/ml; B27 (-); muscle biopsy: myositis | Muscle calcinosis | JDM |
| 4          | 20         | Idiopathic hypogonadotropic MPHG with hyperprolactinemia; 46,XY; bilateral cryptorchidism; bilateral orchidectomy | Asymptomatic | ESR, 16 mm/h; B27 (-) | Normal | None |

ANA = antinuclear antibodies; AS = ankylosing spondylitis; B27 = histocompatibility antigen B27; CK = creatine kinase; ESR = erythrocyte sedimentation rate; JDM = juvenile dermatomyositis; MCP = metacarpophalangeal; MPHG = male patient with hypogonadism; PIP = proximal interphalangeal. *Normal values: anti-DNA, <20 IU/dl; C3, 80–120 mg/dl; C4, 12–20 mg/dl; creatine kinase, 0–95 U/ml; ESR, <15 mm/h; Schober’s test, >5 cm.
with RAD contain intense cellular infiltrates rich in macrophages. These cells have hormonal receptors capable of converting testosterone and androstenedione into estrone and E2 by means of aromatase [36–38]. An increase in the activity of aromatase induced locally could explain the drop in androgen levels and the increase in estrogens observed in patients with RA [38]. However, in our group of patients, serum testosterone and E2 were both decreased. Therefore, in our hypogonadic male patients, the main cause of the testosterone decrease was not due to an increase in its conversion to E2 because the gonadal failure caused a decrease of both hormones, mainly of the testosterone, without showing an increment from its conversion to E2. Although the effects of low serum testosterone levels on the immune system have been little studied, Bebo et al [39] have shown that orchidectomy in mice can diminish the flow of CD4+ activated in serum testosterone levels on the immune system have shown that orchidectomy in mice can diminish the flow of CD4+ activated in immune system, with the subsequent elevation of E2. These cells have hormonal receptors (mainly in RA) the decrease of testosterone serum levels is explain the drop in androgen levels and the increase in estrogens observed in patients with RA [38]. However, in our group of patients, serum testosterone and E2 were both decreased. Therefore, in our hypogonadic male patients, the main cause of the testosterone decrease was not due to an increase in its conversion to E2 because the gonadal failure caused a decrease of both hormones, mainly of the testosterone, without showing an increment from its conversion to E2. Although the effects of low serum testosterone levels on the immune system have been little studied, Bebo et al have shown that orchidectomy in mice can diminish the flow of CD4+ activated in experimental autoimmune encephalomyelitis [39]. In humans, before treatment with androgens, patients who have Klinefelter’s syndrome but not RAD have very diminished levels of testosterone associated with high levels of IgG, IgA, IgM, IL-2, and IL-4 and with an absolute increase of CD3+, CD4+, and the CD4+/CD8+ ratio [30]. In patients who have both Klinefelter’s syndrome and RAD, the diminished level of testosterone is associated with low percentages of OKT3+ and OKT8+ and with an increase of the OKT4/OKT8 ratio [31]. On the basis of our findings and of the reports cited, we conclude that lack of testosterone increases humoral and cellular immunity. When androgens are given, these abnormalities are reversed and the clinical picture improves [30,31].

If our argument is correct, low serum testosterone levels favor the development of RAD in the hypogonadic male patient, while in the normogonadic male who develops RAD (mainly in RA) the decrease of testosterone serum levels is due to an increase in its metabolism for the activated immune system are ameliorated [30,31,38].

In summary, males who have hypogonadism, regardless of its cause, develop RAD more frequently than the general population, when they have very low serum levels of testosterone.

Acknowledgements

The authors are grateful to Margarita Jiménez of the Department of Statistics and Epidemiology, Hospital de Especialidades, Centro Médico Nacional, for technical assistance, and to Rachel Zonana for review of the document.

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## Supplementary material

### Supplementary Table 1

**Characteristics of male patients with hypogonadism with and without rheumatic/autoimmune disease (RAD)**

| Characteristic                        | Patients with RAD (N = 8) | Patients without RAD (N = 5) | P<sup>a</sup> |
|---------------------------------------|---------------------------|-----------------------------|--------------|
| Age (years)                           | 27.5 ± 9.5                | 22.2 ± 6.2                  | NS           |
| Body mass index                       | 23.4 ± 2.1                | 23.8 ± 4.5                  | NS           |
| Prolactin (ng/ml)                     | 8.8 ± 7.1                 | 18.6 ± 8.9                  | NS           |
| Testosterone (ng/ml)                  | 1.0 ± 0.7                 | 2.7 ± 1.2                   | 0.0005       |
| Estradiol-17β (pg/ml)                 | 10.2 ± 8.9                | 13.5 ± 18.0                 | NS           |
| Estradiol-17β/testosterone            | 9.9 ± 10.3                | 4.8 ± 6.1                   | NS           |

Values for data are mean ± standard deviation. NS = not significant. <sup>a</sup>Mann–Whitney U test.

### Supplementary Table 2

**Comparison of rheumatic/autoimmune diseases (RAD) and B27 frequency in male patients with hypogonadism (MPHG) and in controls (general population in Mexico City)**

| Condition                        | RAD/HGMP (%) | RAD/controls (%) | OR | 95% CI       | P<sup>a</sup> |
|----------------------------------|--------------|------------------|----|--------------|--------------|
| RAD/no RAD                       | 8/5 (61)     | 368/43445<sup>b</sup> (0.83) | 188.89 | 55.9–665.91 | <0.001       |
| Ankylosing spondylitis           | 4/9 (30.7)   | 5/43832<sup>b</sup> (0.01)  | 2697.4 | 531.6–13586.8 | <0.001       |
| Systemic lupus erythematosus     | 2/11 (15.3)  | 15/43822<sup>b</sup> (0.03) | 449.5  | 0–2391.1     | <0.001       |
| Polymyositis/dermatomyositis     | 1/12 (7.6)   | 18/43837<sup>b</sup> (0.04) | 187.2  | –            | 0.006        |
| Juvenile rheumatoid arthritis    | 1/12 (7.6)   | 14/43823<sup>b</sup> (0.03) | –     | –            | 0.004        |
| Rheumatoid arthritis             | 0/13 (0)     | 272/43565<sup>b</sup> (0.62) | 0.0    | 0–63.7       | 0.9          |
| Other RAD*                        | 0/13 (0)     | 44/43793<sup>b</sup> (0.1)  | 0.0    | 0–407.1      | 0.9          |
| B27 (+)/(–)                      | 4/9 (30.7)   | 27/638<sup>c</sup> (4)    | 7.27   | 1.86–26.2    | 0.005        |

B27 = histocompatibility antigen B27; CI = confidence interval; OR = odds ratio; – = not calculable. <sup>a</sup>Fisher exact test. <sup>b</sup>Reference [32]. <sup>c</sup>Reference [33]. *Other RAD = Sjögren’s syndrome, mix connective tissue disease, scleroderma, rheumatic fever, reactive arthritis etc.