

Research article

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

F Javier Jiménez-Balderas*, Rosario Tápiá-Serrano†, M Eugenia Fonseca‡, Jorge Arellano§, Arturo Beltrán*, Patricia Yáñez*, Adolfo Camargo-Coronel* and Antonio Fraga*

*Departamento de Reumatología, Hospital de Especialidades, Centro Médico Nacional SXXI IMSS México, DF, México

†Sección de Andrología, Hospital de Especialidades, Centro Médico Nacional SXXI IMSS México, DF, México

‡Laboratorio de Hormonas, Hospital de Especialidades, Centro Médico Nacional SXXI IMSS México, DF, México

§Unidad de Investigación Médica en Inmunología, Hospital de Pediatría, Centro Médico Nacional SXXI IMSS México, DF, México

Correspondence: F Javier Jiménez-Balderas MD, Pregonero #161, Col Fraccionamiento Colina del Sur, CP 01430, México, DF, México. Tel: +52 5 627 69 00, ext 13-15; fax: +52 5 584 00 89; e-mail: fjimenez19@yahoo.com

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**:in press© 2001 Balderas *et al*, licensee BioMed Central Ltd
(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; E₂ = estradiol-17β; 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.

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].

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-17 β (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 \pm standard deviation): respectively, age 25.3 \pm 8.4 years vs 29.5 \pm 7.6 years and body mass index 23.1 \pm 3.3 kg/m² vs 24.2 \pm 3.6 kg/m² ($P = \text{NS}$). The testicular volume was 4.4 \pm 4.3 ml in patients and 43.5 \pm 3.5 ml in controls ($P = 0.001$). Nine of the 13 patients had hypergonadotropic hypergonadism, 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 hypogonadic 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.

Table 1**Clinical, laboratory, and radiologic data for subgroup A: hypergonadotropic hypogonadal male patients with and without rheumatic/autoimmune disease (RAD)**

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 sacroiliitis	AS
6	32	Klinefelter's syndrome; 47,XXY(68%)/46,XY(32%)	Asymptomatic	ESR, 10mm/h; B27 (-)	Normal	None
7	21	Gonadal dysgenesis with mosaicism; 45,X/47,XXY	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

ANA = antinuclear antibodies; APLS = antiphospholipid syndrome; AS = ankylosing spondylitis; B27 = histocompatibility antigen B27; ESR = erythrocyte sedimentation rate; GMN = glomerulonephritis; JRA = juvenile rheumatoid arthritis; LE = lupus erythematosus; SLE = systemic lupus erythematosus. ^aNormal values: anti-DNA, <20 IU/dl; ESR, <15 mm/h; Schober's test, >5 cm. ^bWorld Health Organization [40].

Among the patients, age and body mass index were similar in those with and those without RAD. Serum testosterone and estradiol 17 β 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

Table 2**Clinical, laboratory, and radiologic data for subgroup B: hypogonadotropic hypogonadal male patients, with and without rheumatic/autoimmune disease (RAD)**

Patient no.	Age (years)	Endocrine and genetic diagnosis	Symptoms and disease duration	Laboratory findings ^a	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 cm ^a	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 cm ^a	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. ^aNormal 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.

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% (including RA 0.62%; SLE 0.03%; polymyositis/dermatomyositis 0.04%; JRA 0.03%; AS 0.01%; and other RAD [Sjogren'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 hypogonadism was surprisingly high ($P < 0.001$), suggesting a strong relation between the two conditions (see Supplementary Table 2). The development of RAD only in those patients with severe testicular dysfunction suggests that such dysfunction is one endogenous factor that predisposes to the development of RAD.

The disorder most frequent in our group was the combination 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 population. 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 dermatomyositis. 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 population suggests that the RA and hypogonadism are not related, as has already been suggested [13].

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

Studies in healthy, normogonadic males with RAD have found low serum levels of testosterone and high levels of E_2 in patients with RA, SLE, and Sjogren's syndrome [34,35]. The inflamed tissues of normogonadic patients

with RAD contain intense cellular infiltrates rich in macrophages. These cells have hormonal receptors capable of converting testosterone and androstenedione into estrone and E_2 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 E_2 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 E_2 because the gonadal failure caused a decrease of both hormones, mainly of the testosterone, without showing an increment from its conversion to E_2 . 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, with the subsequent elevation of E_2 . These differences could also explain the low or almost null association of RA and hypogonadism [13]. In both cases, after androgens are given, the clinical picture and the abnormalities of the 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.

References

- Goldsteyn EJ, Fritzer MJ: **Review: the role of the thymus-hypothalamus-pituitary-gonadal axis in normal immune processes and autoimmunity.** *J Rheumatol* 1987, **14**:982-990.
- Vallatton MB, Forbes AP: **Autoimmunity in gonadal dysgenesis and Klinefelter's syndrome.** *Lancet* 1967, **1**:648-651.
- Williams DE, Engel MB, Forbes AP: **Thyroiditis and gonadal dysgenesis.** *New Engl J Med* 1964, **270**:805-810.
- Ortie-Neu C, Le Roy EC: **The coincidence of Klinefelter's syndrome and systemic lupus erythematosus.** *Arthritis Rheum* 1969, **12**:241-246.
- Tsumg SH, Heckman MG: **Klinefelter's syndrome, immunological disorders, and malignant neoplasm.** *Arch Pathol* 1974, **98**:351-354.
- Stern R, Fishman J, Brusman H, Kunkel HG: **Systemic lupus erythematosus associated with Klinefelter's syndrome.** *Arthritis Rheum* 1997, **20**:18-22.
- Lahita RG, Bradlow L, Fishman J, Kunkel HG: **Estrogen metabolism in systemic lupus erythematosus.** *Arthritis Rheum* 1982, **25**:843-846.
- Durand JM, Quiles N, Kaplanski G, Soubeyrand J: **Lupus anticoagulant and Klinefelter's syndrome.** *J Rheumatol* 1993, **20**:920-921.
- O'Donoghue DJ: **Klinefelter's syndrome associated with systemic sclerosis. Post-rheumatic/autoimmune diseases.** *Postgrad Med J* 1982, **58**:575-576.
- Nowlin NS, Zwillich SH, Brick JE, Carson HE: **Male hypogonadism and scleroderma.** *J Rheumatol* 1985, **12**:605-606.
- De Keyser F, Mielants H, Veys EM: **Klinefelter's syndrome and scleroderma.** *J Rheumatol* 1989, **16**:1613-1614.
- Kobayashi S, Shimamoto T, Taniguchi O, Hashimoto H, Hirose S: **Klinefelter's syndrome associated with progressive systemic sclerosis: Report of a case and review of the literature.** *Clin Rheumatol* 1991, **10**:84-86.
- Kobayashi S, Yamamoto S, Tanaka M, Hashimoto H, Hirose S: **Klinefelter's syndrome and rheumatoid arthritis. Report of a case and review of the literature.** *Clin Rheumatol* 1994, **13**:500-503.
- Couloumère J, Ayraud N, Cohen J, Ziegler G: **Syndrôme de Klinefelter associé à une spondylarthrite ankylosante.** *Rheumatologie* 1975, **27**:261.
- Armstrong RD, MacFarlane DG, Panayi GS: **Ankylosing spondylitis and Klinefelter's syndrome: does the X chromosome modify disease expression?** *Br J Rheumatol* 1985, **24**:277-281.
- Parges M, Laroche S, Lassoued S, Pages P, Mazieres B, Arlet J: **Association d'une spondylarthrite B27 positive et d'un syndrôme de Klinefelter [letter].** *Presse Med* 1990, **19**:178.
- Murakami M, Kishino B, Fushimi H, Sakata Y, Matsuyuki Y: **The first report of Klinefelter's syndrome associated with polymyositis.** *J Jap Soc Intern Med* 1988, **77**:60-65.
- Balestrazzi P, Ferraccioli GF, Ambanelli U, Giovannelli G: **Juvenile rheumatoid arthritis in Turner's syndrome.** *Clin Exp Rheumatol* 1968, **4**:61-62.
- Scammell AM: **Juvenile onset inflammatory bowel disease. Is more common in people with Turner's syndrome [letter].** *BMJ* 1994, **309**:606.
- Glass AR, Vigersky RA: **Pituitary-testicular axis.** In *Infertility in the Male*. 2nd edn. Edited by Lipshultz LI, Howards SS. St Louis, MO, USA: Mosby-Year Book; 1991:21-36.
- Longcope C, Baker R, Johnston CC: **Androgen and estrogen metabolism: relationship to obesity.** *Metabolism* 1986, **35**:235-237.
- Klippel JH, Weyand CM, Wortmann RL: **Appendix I: criteria for the classification and diagnosis of the rheumatic diseases.** In *Primer on the Rheumatic Diseases*. Edited by Klippel JH, Weyand CM, Wortmann RL. Atlanta, GA, USA: The Arthritis Foundation; 1997:453-464.
- Matsuda T, Horii Y, Ogura K, Nonomura M, Okada K, Yoshida O: **Chromosomal survey of 1001 subfertile males: incidence and clinical features of males with chromosomal anomalies.** *Hinyokika Kyo* 1992, **38**:803-809.
- Zeuthen E, Nielsen J: **Prevalence of Klinefelter's syndrome (47,XXY) in a general male population.** *J Genet Hum* 1978, **26**:85-97.
- Garson OM, Robson MK, Weste SM, Baikie AG: **Clinical findings in patients with numerical abnormalities of the X chromosome: a three-year survey of consecutive admissions to a general hospital.** *Med J Aust* 1980, **2**:33-35.
- Nielsen J: **Chromosome mosaicism in a population sample.** *Humangenetik* 1975, **29**:155-159.

27. Márquez-Monter H, Santiago-Payán H, Kofman-Alfaro S: **Sex chromatin survey in mentally handicapped children in Mexico.** *J Med Genet* 1968, **5**:40-44.
28. Zavala C, Mora G, Lisker R: **Estudios cromosómicos en una prisión mexicana.** *Rev Invest Clin* 1970, **22**:251-256.
29. Schroder J, de la Chapelle A, Hakola P, Virkkunen M: **The frequency of XYY and XXY men among criminal offenders.** *Acta Psychiatr Scand* 1981, **63**:272-276.
30. Kocar IH, Yesilova Z, Ozata M, Turan M, Sengul A, Ozdemir I: **The effect of testosterone replacement treatment on immunological features of patients with Klinefelter's syndrome.** *Clin Exp Immunol* 2000, **121**:448-452.
31. Bizzarro A, Valentini G, Di Martino G, DaPonte A, De Bellis A, Iacono G: **Influence of testosterone therapy on clinical and immunological features of autoimmune diseases associated with Klinefelter's syndrome.** *J Clin Endocrinol Metab* 1987 Jan, **64**:32-36.
32. Jiménez-Balderas FJ, Katona G: **Frecuencia de las enfermedades reumáticas en el servicio de consulta externa del Hospital General, SSA de la Ciudad de México.** *Rev Med Hosp Gral* 1973, **32**: 73-92.
33. Arellano J, Vallejo M, Jiménez J, Mintz G, Kretschmer RR: **HLA-B27 and ankylosing spondylitis in the Mexican Mestizo population.** *Tissue Antigens* 1984, **23**:112-116.
34. Cutolo M, Straub R: **Recent aspects of gonadal hormones and neurotransmitter interactions with synovial cells in rheumatoid arthritis.** *Ann Rheum Dis* 2000, **59**:657-661.
35. Cutolo M, Wilder R: **Different roles for androgens and estrogens in the susceptibility to autoimmune rheumatic diseases.** *Rheum Dis Clin North Am* 2000, **26**:825-839.
36. Straub RH, Zeuner M, Antiniou E, Schölmerich J, Lang B: **Dehydroepiandrosterone sulfate is positively correlated with soluble interleukin 2 receptor and soluble intercellular adhesion molecule in systemic lupus erythematosus.** *J Rheumatol* 1996, **23**:856-861.
37. Purohit A, Ghilchick MW, Duncan L, Wang DY, Singh A, Walker MM, Reed MJ: **Aromatase activity and interleukin-6 production by normal and malignant breast tissues.** *J Clin Endocrinol Metab* 1995, **80**:3052-3058.
38. Cutolo M, Balleari E, Giusti M, Intra E, Accardo S: **Androgen replacement therapy in male patients with rheumatoid arthritis.** *Arthritis Rheum* 1991, **34**:1-5.
39. Bebo BF Jr, Zelinka-Vincent E, Adamus G, Amundson D, Vandenberg AA, Offner H: **Gonadal hormones influence the immune response to PLP 139-151 and the clinical course of relapsing experimental autoimmune encephalomyelitis.** *J Neuroimmunol* 1998, **84**:122-130.
40. Appel GB, Cohen DJ, Pirani CL, Meltzer JI, Estes D: **Long-term follow-up of patients with lupus nephritis. A study based on the classification of the World Health Organization.** *Am J Med* 1987, **83**:877-885.

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

B27 = histocompatibility antigen B27; CI = confidence interval; OR = odds ratio; – = not calculable. ^aFisher exact test. ^bReference [32]. ^cReference [33]. *Other RAD = Sjögren's syndrome, mix connective tissue disease, scleroderma, rheumatic fever, reactive arthritis etc.