

## A RANDOMIZED TRIAL OF TESTOSTERONE THERAPY IN MALES WITH RHEUMATOID ARTHRITIS

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### SUMMARY

Thirty-five male patients, aged 34-79 yr, with definite rheumatoid arthritis (RA) were recruited from out-patient clinics and randomized to receive monthly injections of testosterone enanthate 250 mg or placebo as an adjunct therapy for 9 months. Endpoints included disease activity parameters and bone mineral density (BMD). At baseline, there were negative correlations between the ESR and serum testosterone ( $r = -0.42$ ,  $P < 0.01$ ) and BMD (hip,  $r = -0.65$ ,  $P < 0.01$ ). A total of 29.6% of all patients had at least one vertebral fracture, most having multiple fractures. Back pain, however, was not more prevalent in fracture patients (55% vs 50%). Disease activity was significantly higher in the fracture group (joint score  $P < 0.05$ , rheumatoid factor  $P < 0.01$ ). Thirty patients completed the trial, 15 receiving testosterone and 15 receiving placebo. There were significant rises in serum testosterone, dihydrotestosterone and oestradiol in the treatment group. There was no significant effect of treatment on disease activity overall, five patients receiving testosterone underwent a 'flare'. Differences in mean BMD following testosterone or placebo were non-significant (spine: +1.2% vs -1.1%; femur: -0.3% vs +0.3%). There was no suggestion of a positive effect of testosterone on disease activity in men with RA.

**KEY WORDS:** Rheumatoid arthritis, Male, Disease activity, Bone density, Vertebral fracture, Testosterone.

THERE is *in vitro* evidence to suggest that androgens may play a role in immune and inflammatory pathways, most studies pointing towards an overall immunosuppressive effect [1, 2]. Androgen receptors have been isolated in synovial tissue [3] and levels of testosterone may be low in males with rheumatoid arthritis (RA) [4, 5]. Whether a low androgen status is seen as a secondary response to chronic illness or as a primary phenomenon is unclear, although the recent finding of subnormal levels of dehydroepiandrosterone sulphate in premenopausal women before they develop RA is supportive of the latter concept [6]. Only one published study of testosterone therapy in RA has been published; this was an open study of seven patients that found modest benefits on disease activity after 6 months of treatment [7].

RA has been associated with lower bone density [8-10] and greater risk of vertebral [11] and hip fracture [12] in females, but studies of osteoporosis in males with RA have been scarce. The use of testosterone in the treatment of male osteoporosis has been advocated, partly because hypogonadism is associated with osteoporosis [13], but no randomized studies are available to support a hormonal replacement therapy for the prevention of bone loss in men, as is now well accepted in women. This may be particularly relevant to males with RA, given the association with subnormal androgen levels.

This study was designed primarily to assess the effects of testosterone therapy on disease activity in men with RA. At the same time, it was decided to

include a descriptive account of vertebral fracture prevalence and the short-term response of bone density to testosterone.

### PATIENTS AND METHODS

#### Patients

Forty-seven male RA clinic attenders (aged 34-79 yr) were invited to participate in a 9 month study of the effects of testosterone in RA. Patients were included if they were receiving a stable dose of routine anti-rheumatic therapy [including slow-acting anti-rheumatic drugs (SAARDs) and corticosteroids] and had no contraindications to testosterone therapy. Inactive disease was not an exclusion criterion. Patients were unselected for fracture, low bone mineral density (BMD) or back pain.

Thirty-five patients were included in the trial and randomly allocated to receive testosterone enanthate 250 mg i.m. monthly (Primoteston Depot, Schering Healthcare) or placebo injections. This is a recognized dosage for men with proven hypogonadism [14], providing elevated testosterone levels for at least 3 weeks ( $t_{1/2}$   $224 \pm 18$  h) and guaranteeing compliance. Injections were administered by the clinic nurse, but all assessments were made by clinicians blinded to treatment. Serum levels of testosterone were monitored monthly, on the day of injection. After 6 months, it was noted that serum androgen levels had failed to rise significantly; consequently, testosterone injections were administered fortnightly between months 6 and 9 with resultant substantial elevations in androgen levels. This implies that for the first 6 months of the study, high levels of androgens were achieved for at least the first 2 weeks of each month, which then gradually fell to normal levels by the time of the next injection. During

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the last 3 months of the trial, high androgen levels were maintained throughout.

### Assessments

Parameters of disease activity were monitored monthly and included a swollen joint count (JTS), Ritchie articular index (AI), visual analogue pain scale (VPS), early morning stiffness (EMS), rheumatoid factor (RF), ESR and C-reactive protein (CRP). A Health Assessment Questionnaire (HAQ) was completed at study entry and on completion. Questionnaires for recalled back pain were included and patients were considered to have significant back pain if they had experienced pain for at least 1 month during the previous year that had required analgesia. Smoking and alcohol consumption were also evaluated.

BMD of the lumbar spine (BMDLS) and femoral neck (BMDF) was assessed using dual-energy X-ray absorptiometry (DEXA, Hologic QDR1000/W). Short-term precision at these sites was 0.9 and 1.5%, respectively. Measurements were made at entry and on completion of the study. Z-scores have been used for comparison and give the number of s.d.s of the recorded BMD from an age-matched reference population provided by the absorptiometer manufacturers.

Plain lateral radiographs of the thoracic and lumbar spine were examined by two independent observers, including a radiologist. A fracture was defined as a reduction in height of >20% in antero-posterior or central-anteroposterior dimensions. A further analysis used a previously described semi-automated method of defining a fracture as a reduction in at least two of the four computed measurements by >2 s.d. from a reference population [15]. A fracture was recorded if described by both independent observers and the computer algorithm.

Sex hormone measurements included serum testosterone (T), dihydrotestosterone (DHT), dehydroepiandrosterone sulphate (DHEAS) and oestradiol (E2), using standard radioimmunoassay techniques.

### Statistics

Data were normally distributed and comparison of baseline data was made using Student's *t*-test and  $\chi^2$ . Since sample sizes were small, Wilcoxon analyses were also used, but did not differ from the *t*-test and results from the latter analyses are described. Longitudinal analyses of BMD were carried out on patients completing the study using Student's *t*-test and analyses of covariance to correct for confounding variables. Correlations between variables used Pearson's correlation coefficient.

## RESULTS

### Baseline

Table I gives the baseline characteristics of all the study patients.

**Hormonal status.** Mean baseline androgen levels in

the whole group were mostly within the normal reference range for our laboratory. The number of patients with levels of T, DHT and DHEAS below the lower limit of normal were 4 (11%), 8 (23%) and 20 (57%), respectively. There were significant negative correlations between T and ESR ( $r = -0.42$ ,  $P < 0.01$ ) and CRP ( $r = -0.40$ ,  $P < 0.01$ ) (Fig. 1).

**Bone mass and fracture.** Thirty-five patients started the study and five withdrew on account of concurrent illness or change of address. Of the remaining 30 patients, 27 had vertebral X-rays available for analysis. Eight patients had a total of 21 thoracic or lumbar vertebral fractures; all but one patient having multiple fractures. Table II lists the group characteristics by the presence of fractures. There were no significant differences between the groups in age, disease duration or weight. Disease activity parameters tended to be higher in the fracture group, differences being significant for the swollen joint count and rheumatoid factor. Bone density, and Z-scores, were lower in the fracture group at both sites, but differences were not significant, possibly due to small cohort sizes. Intergroup differences in BMD could be explained by the greater disease activity in the fracture group; there were negative correlations between ESR, swollen joint count and BMD, particularly at the hip (Table III).

Chronic back pain was common in the overall group and was no more frequent in the fracture group. A total of 89% of the group were current or ex-smokers and all the fracture patients were smokers (mean pack-years = 33). There were negative correlations between the number of pack-years and BMDLS ( $r = -0.52$ ,  $P < 0.01$ ) and androgen levels (DHT  $r = -0.60$ ,  $P < 0.01$ ). Alcohol consumption was not generally high and was similar in both groups. Fracture patients had a non-significantly higher cumulative steroid dose.

There were a total of 11 of 30 patients taking corticosteroids. BMD in this group was significantly lower at the spine compared with the remaining 19 RA

TABLE I  
Baseline characteristics and hormone levels in 35 males with rheumatoid arthritis

	Mean (s.d.)	Range (median)	Reference range
Age (yr)	60.8 (9.7)	34–79 (62)	
Disease duration (yr)	11.7 (8.9)	2–44 (10)	
Articular index (0–84)	9.4 (5.9)	0–22 (8)	
HAQ (0–3)	1.1 (0.8)	0–2.8 (1.1)	
ESR (mm/h)	21.1 (19)	1–81 (13)	
CRP (mg/l)	38.1 (27.9)	5–115 (30)	
Testosterone (nmol/l)	15.9 (6.5)	5–35.5 (15.5)	9.0–35.0
DHT (nmol/l)	1.8 (0.9)	0.4–4.0 (1.8)	1.0–2.6
DHEAS ( $\mu$ mol/l)	2.7 (2.6)	0.2–13.7 (2.1)	2.8–12.0
Oestradiol (pmol/l)	85.6 (46.7)	21–178 (73)	<175
Patients receiving steroids (n)	11		
Daily dose prednisolone (mg)	3.1 (3.6)	1.0–12.5 (3.3)	
Cumulative dose (g)	1.88 (2.1)	0.9–3.3 (1.7)	

HAQ, Health Assessment Questionnaire; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; DHT, dihydrotestosterone; DHEAS, dehydroepiandrosterone sulphate.

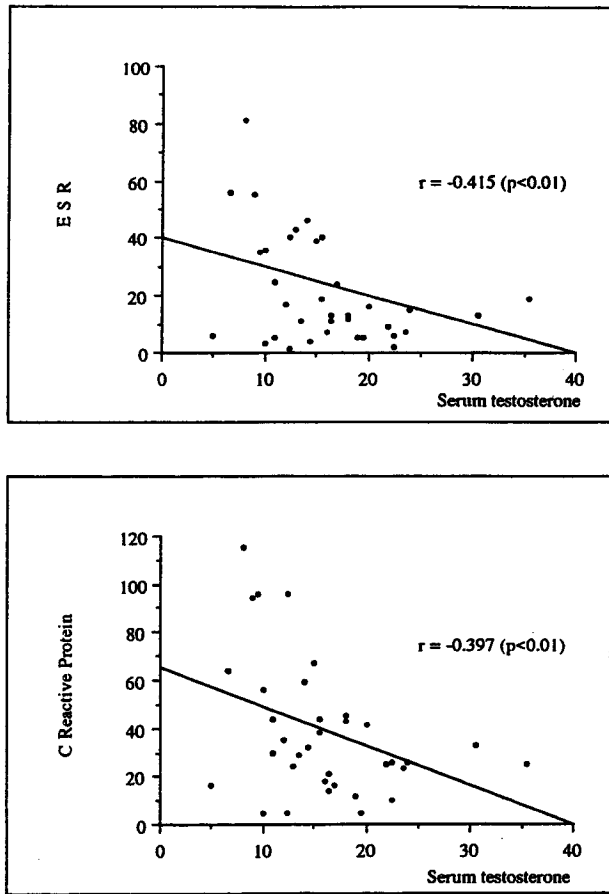


FIG. 1.—Correlation between serum testosterone, ESR and C-reactive protein in males with rheumatoid arthritis.

patients (LS: 0.91 vs 1.02 g/cm,  $P = 0.03$ ; F: 0.75 vs 0.80,  $P = 0.2$ ). The Z-scores in the non-steroid and steroid groups were  $-0.03$  and  $-0.55$ , respectively, for the spine and  $+0.11$  and  $-0.40$ , respectively, for the femoral neck. However, the two groups were not readily comparable since steroid users were older (66.6 vs 59.1 yr,  $P = 0.02$ ), lighter (70.9 vs 77.1 kg, NS) and had more active disease (AI: 12.7 vs 7.2,  $P = 0.01$ ; ESR: 14.2 vs 25.7,  $P = 0.07$ ). Following adjustments for these differences, BMD was similar in both groups.

Androgen levels tended to be lower in the fracture group, although this was only significant in the case of DHEAS and could be partly explained by a weak association between disease activity and DHEAS ( $r = -0.38$ ,  $P = 0.05$ ). There were no significant correlations between any sex hormones and bone density (Table III).

### Trial

Fifteen patients each completed testosterone therapy and placebo, respectively. Three patients withdrew from the placebo arm (hypertension, cerebrovascular accident, change of address) and two from the testosterone arm (recurrence of osteomyelitis, pneumonia). Table IV gives baseline characteristics in the

TABLE II  
Characteristics, disease activity, hormone levels and bone density of fracture and non-fracture groups

	Fractures	No fractures	P
Number (mean, s.d.)	8	19	
Age (yr)	64.5 (6.7)	60.1 (10.2)	NS
Disease duration (yr)	11.6 (5.7)	11.2 (10.3)	NS
Weight (kg)	74.3 (9.0)	75.9 (11.6)	NS
Articular index (0–84)	11.5 (5.1)	7.7 (4.8)	NS
JTS (0–28)	3.4 (2.1)	1.4 (1.3)	0.04
EMS (mins)	51.9 (47.2)	36.4 (39.2)	NS
ESR (mm/h)	27.3 (21.8)	13.3 (11.7)	NS
CRP (mg/l)	42.4 (28.8)	30.5 (20.3)	NS
Rheumatoid factor (inverse ratio)	3920 (1758)	1315 (1645)	0.004
HAQ (0–3)	1.28 (0.87)	0.96 (0.74)	NS
Testosterone (nmol/l)	14.9 (8.3)	16.9 (6.3)	NS
DHT (nmol/l)	1.5 (0.8)	2.02 (0.93)	NS
DHEAS ( $\mu$ mol/l)	1.8 (1.2)	3.24 (2.03)	0.04
Oestradiol (pmol/l)	74.8 (58.9)	92.8 (42.5)	NS
Back pain (%)	50%	55%	NS
Smoking (pack-years)	33	23	NS
Total cumulative steroid dose (g)	8.01 (12.36)	1.65 (3.60)	NS
BMDLS (g/cm <sup>2</sup> )	0.94 (0.13)	0.99 (0.13)	NS
BMDF (g/cm <sup>2</sup> )	0.74 (0.17)	0.80 (0.11)	NS
Z-score LS	-0.37	-0.19	NS
Z-score F	-0.66	+0.2	NS

DHT, dihydrotestosterone; DHEAS, dehydroepiandrosterone sulphate; JTS, swollen joint score; EMS, early morning stiffness; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; BMDLS, bone mineral density lumbar spine; BMDF, bone mineral density femoral neck.

testosterone and placebo arms, and responses to treatment. Patients allocated to testosterone were lighter ( $P = 0.05$ ) and tended to be older (NS). As discussed in the methods section, there were significant rises in all hormone levels, except DHEAS, during the last 3 months of testosterone therapy.

**Disease activity.** None of the inflammatory indices showed any significant change during the study in either group. Results were unchanged when assessing

TABLE III  
Correlations between variables and bone density in males with rheumatoid arthritis

	BMDLS	BMDF
Age	$r = -0.23$	-0.29
Disease duration	0.16	0.01
Weight	0.47*	0.15
Articular index	-0.10	-0.31
Swollen joint score	-0.23	-0.53*
ESR	-0.45*	-0.65*
Rheumatoid factor titre	-0.17	-0.18
HAQ	-0.01	-0.33
Testosterone	-0.08	0.08
Dihydrotestosterone	0.23	0.30
DHEAS	0.09	0.12
Oestradiol	0.25	0.25
Cumulative steroid dose	-0.06	-0.14

Values given are Pearson correlation coefficients.

BMDLS, bone density lumbar spine; BMDF, bone density proximal femur; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; DHEAS, dehydroepiandrosterone sulphate.

\* $P < 0.01$ .

TABLE IV  
Disease activity and bone density in testosterone and placebo groups at trial entry and after 9 months

Month of trial	Placebo (n = 15)		Testosterone (n = 15)		Effect of treatment
	0	9	0	9	
Age (yr)	59.4 (7.0)		64.2 (10.3)		
Disease duration (yr)	11.4 (5.3)		11.4 (12.2)		
Weight (kg)	78.4 (8.1)		70.8 (11.9)*		
AI (0-84)	10.1 (5.3)	8.8 (6.9)	8.3 (6.0)	10.5 (5.9)	NS
JTS (0-28)	1.9 (1.6)	0.8 (1.1)	2.4 (2.1)	1.4 (1.7)	NS
VPS (mm)	46.4 (21.8)	39.8 (34.3)	36.9 (27.6)	34.3 (23.0)	NS
EMS (min)	45.0 (44.9)	30.0 (37.2)	31.8 (33.2)	61.4 (98.0)	NS
ESR (mm/h)	16.3 (16.9)	15.5 (12.4)	20.9 (16.2)	22.2 (21.4)	NS
RF (inverse ratio)	1740 (1900)	796 (1368)	2345 (2293)	1781 (2189)	NS
HAQ (0-3)	1.1 (0.8)	1.0 (0.8)	1.0 (0.8)	1.0 (0.6)	NS
T (nmol/l)	15.6 (5.3)	13.6 (3.9)	16.6 (7.9)	31.1 (10.6)	P < 0.001
DHT (nmol/l)	1.8 (0.8)	2.9 (1.2)	1.9 (0.9)	7.0 (3.1)	P < 0.001
DHEAS ( $\mu$ mol/l)	2.6 (1.6)	2.6 (1.8)	2.4 (2.3)	4.0 (2.8)	P = 0.1
E2 (pmol/l)	83.6 (48.5)	82.6 (58.8)	80.7 (45.4)	183.4 (105)	P < 0.001
BMDLS (g/cm <sup>2</sup> )	1.0 (0.1)	1.0 (0.1)	0.95 (0.1)	0.96 (0.15)	NS
BMDF (g/cm <sup>2</sup> )	0.80 (0.13)	0.81 (0.14)	0.76 (0.12)	0.76 (0.13)	NS

AI, articular index; JTS, swollen joint count; VPS, visual analogue pains core; EMS, early morning stiffness; ESR, erythrocyte sedimentation rate; RF, rheumatoid factor; HAQ, Health Assessment Questionnaire; T, testosterone; DHT, dihydrotestosterone; DHEAS, dehydroepiandrosterone sulphate; E2, oestradiol; BMDLS, bone density spine; BMDF, bone density femoral neck.

\*Difference between groups  $P = 0.05$ .

only patients with low basal androgen levels. Responses were unchanged during the final 3 months when testosterone dose frequency was doubled. Five patients suffered a flare, as defined by the following arbitrary criteria: increase in AI > 6, increase in ESR > 30%, increase in CRP > 50%. All five patients were receiving testosterone and flares tended to occur early in the trial. None of these patients withdrew from the study, they did not differ from the others at baseline, either clinically or hormonally, and did not experience greater or lesser hormonal changes with treatment.

**Bone density.** Following adjustment for age and weight, BMD changes were +1.2% (S.D. 6.1) and -0.30% (S.D. 3.9) in the testosterone group at the spine and femur, respectively, compared with -1.1% (S.D. 6.4) and +0.3% (S.D. 3.1) in the placebo group. The differences between groups were not significant. Increments in BMDLS did not correlate with increments in androgen levels (T,  $r = 0.15$ ; DHT,  $r = 0.19$ , DHEAS,  $r = 0.09$ ), but there was a weak correlation between changes in BMDLS and E2 ( $r = 0.43$ ,  $P = 0.05$ ). There was no effect of treatment when patients were divided by steroid use, fracture status or baseline hormone levels.

## DISCUSSION

This study failed to show any overall effect of testosterone on disease activity in male RA, although five patients deteriorated. Secondary findings of the study addressed skeletal status and demonstrated a vertebral fracture prevalence of almost 30%. Fractures (and BMD) were associated with disease activity and smoking, but not with steroid usage nor with an increased frequency of back pain.

Our subjects had androgen levels that were within the normal reference range for our laboratory,

although > 50% had low DHEAS levels. This is at variance with other studies that reported subnormal levels of testosterone in male RA [4, 5] when compared with an age-matched control group. The lack of a control group in our study may partly account for these results. However, despite normal testosterone levels, there was a strong negative correlation between the ESR and T, and a weaker correlation with DHEAS. This corroborates the findings of some, but not all, studies [5, 16]. This may be the result of a direct effect of systemic inflammation on androgen synthesis [17], but could alternatively represent a primary defect in RA that may result in favourable alterations in immune mechanisms for RA pathogenesis. The recent report of low DHEAS levels up to 18 yr before the onset of RA would support the latter viewpoint [6] and suggest a possible beneficial effect of testosterone therapy.

To our knowledge, this is the first published double-blind, randomized trial of testosterone in males with RA. We were unable to demonstrate a beneficial effect of testosterone on disease activity and five patients actually flared. This is at variance with the open, uncontrolled study of Cutolo *et al.* [7] which reported a 60% overall clinical improvement. Their study differed to ours in many respects: they used oral testosterone undecanoate in patients who were biochemically hypogonadal and not receiving steroids or SAARDs. They did not report oestrogen levels, but the increase in oestradiol seen in our group, due to peripheral aromatization of testosterone, may have interfered with any potential hormonal immunomodulation. This study used testosterone as an adjunct therapy—any future study of testosterone should evaluate patients with more active disease and who are receiving limited anti-rheumatic medications.

Studies of postmenopausal women with RA have shown reductions in BMD, particularly at the hip, using a variety of methodologies [8–10]. In their study of 40 males with RA, Garton and Reid [18] found a reduction in trochanteric, but not spinal, BMD and corticosteroid usage resulted in a non-significant reduction in BMD at all measured sites. Other studies of bone mass in RA have included small numbers of men, most finding reduced bone mass [19, 20]. Although we did not have a normal control group, the Z-scores suggest that bone density is only reduced to a major extent in patients receiving steroids. The data on fracture in male RA are scarce, Butler *et al.* [20] only found fractures in male RA patients taking steroids. If the 30% prevalence rate for fracture in our cohort is compared with the 11% rate found in normal men over 65 yr (using similar criteria) [21], it would appear that men with RA may have an increased risk of vertebral fracture. It should be noted that the clinical relevance of vertebral fracture in this cohort remains unclear since symptomology was similar in both fracture and non-fracture groups—also a finding in Zetterberg's study of back pain and osteoporosis [22]. The high prevalence of fractures in both steroid and non-steroid groups contrasts with the relatively normal Z-scores, which are only low in the steroid group, suggesting that co-factors other than BMD are important in the pathogenesis of fracture in RA.

Reduced BMD was not found in our fracture group, but it is clear that the study size limits the statistical power to detect a significant difference between groups. Contrary to our observations in females, where steroid use was more detrimental than disease activity [8], fracture and BMD in male RA were associated with disease activity rather than steroids. This may partly be explained by the greater disease activity in the male steroid patients compared with non-steroid users, implying that steroid doses received were inadequate to control their RA. Higher doses of steroids may, therefore, have improved disease activity, but at the expense of increased bone loss. Clearly, disease control without the use of steroids is preferable.

It should also be noted that every fracture patient was a heavy cigarette smoker and there was an inverse relationship between BMD and pack-years. Other authors have noted the increased risk of osteoporotic fracture in male smokers [23, 24] and it is possible that the higher prevalence of fracture in our cohort was biased by the large number of smokers. It is clearly important to accurately document smoking habits in studies of bone metabolism.

Although there was a suggestion of a possible effect of testosterone therapy on BMDLS, differences between treatment and placebo groups were not significant. This may represent a type II statistical error due to the small study size and interpretation of these results is difficult. However, our results showed a wide response range, no correlation between serum testosterone levels and BMD either at baseline or longitudinally, and no suggestion of an effect of testosterone on BMD. A true positive effect of

testosterone on bone mass in this cohort seems, therefore, unlikely. There are no published randomized trials of the effect of testosterone on bone density in normal or RA subjects, although it is a suggested therapy for hypogonadal men with osteoporosis [13, 25] and oestrogen replacement in female RA has proven efficacy [26]. A study of transdermal testosterone in normal elderly men showed no alteration in any parameters of bone metabolism [27] despite significant gains in androgen levels. More randomized studies of testosterone therapy on BMD are needed in males, perhaps with higher doses and using testosterone preparations that do not undergo conversion to oestrogens, such as dihydrotestosterone.

In summary, we did not find any favourable effect of testosterone therapy on disease activity in male RA. Vertebral fractures were common and associated with disease activity.

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#### REFERENCES

1. Schuurs AHVM, Verheul HAM. Effects of gender and sex steroids on the immune response. *J Steroid Biochem Mol Biol* 1990;**35**:157–72.
2. Da Silva JAP, Hall GM. The effects of gender and sex hormones on outcome in rheumatoid arthritis. *Baillière's Clin Rheumatol* 1992;**6**:193–219.
3. Cutolo M, Accardo S, Villaggio B *et al.* Evidence for the presence of androgen receptors in the synovial tissue of rheumatoid arthritis patients and healthy controls. *Arthritis Rheum* 1992;**35**:1007–15.
4. Ollier W, Spector T, Silman A. Are certain HLA haplotypes responsible for low testosterone levels in males. *Dis Markers* 1989;**7**:139–43.
5. Spector TD, Perry LA, Tubb G, Silman AJ, Huskisson EC. Low free testosterone levels in rheumatoid arthritis. *Ann Rheum Dis* 1988;**47**:65–8.
6. Masi AT, Chatterton RT, Comstock GW, Malamet RL, Hochberg MC. Decreased serum dehydroepiandrosterone sulphate levels before onset of RA in younger premenopausal women: a controlled prospective study. *Arthritis Rheum* 1994;**37**:S315.
7. 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.
8. Hall GM, Spector TD, Griffin AJ, Jawad ASM, Hall ML, Doyle DV. The effect of rheumatoid arthritis and steroid therapy on bone density in postmenopausal women. *Arthritis Rheum* 1993;**36**:1510–6.

9. Laan RFJM, Buijs WCAM, Verbeek ALM *et al.* Bone mineral density in patients with recent onset rheumatoid arthritis: influence of disease activity and functional capacity. *Ann Rheum Dis* 1993;**52**:21-6.
10. Sambrook PN, Eisman JA, Champion GD, Yeates MG, Pocock NA, Eberl S. Determinants of axial bone loss in rheumatoid arthritis. *Arthritis Rheum* 1987;**30**:721-8.
11. Spector TD, Hall GM, McCloskey EV, Kanis JA. Risk of vertebral fracture in women with rheumatoid arthritis. *Br Med J* 1993;**306**:558.
12. Cooper C, Coupland C, Mitchell M. Rheumatoid arthritis, corticosteroid therapy and hip fracture. *Ann Rheum Dis* 1995;**54**:49-52.
13. Jackson JA, Kleerekoper M. Osteoporosis in men: diagnosis, pathophysiology and prevention. *Medicine* 1990;**69**:137-52.
14. Kley HK, Herrmann J, Morgner KD, Kruskemper HL. Effects of testosterone oenanthate on plasma concentrations of thyroxine, cortisol, testosterone and hormone binding proteins in patients with hypogonadism. *Horm Metab Res* 1973;**5**:271-4.
15. McCloskey EV, Spector TD, Eyres KS *et al.* The assessment of vertebral deformity: a method for use in population studies and clinical trials. *Osteoporosis Int* 1993;**3**:138-47.
16. Gordon C, Beatal GH, Thomson JA, Sturrock RD. Androgenic status and sexual function in males with rheumatoid arthritis and ankylosing spondylitis. *Q J Med* 1986;**60**:671-9.
17. Semple CG, Gray CE, Beatal GH. Adrenal androgens and illness. *Acta Endocrinol (Copenhagen)* 1987;**116**:155-60.
18. Garton MJ, Reid DM. Bone mineral density of the hip and of the anteroposterior and lateral dimensions of the spine in men with rheumatoid arthritis; effects of low-dose corticosteroids. *Arthritis Rheum* 1993;**36**:222-7.
19. Compston JE, Crawley EO, Evans C, O'Sullivan MM. Spinal trabecular bone mineral content in patients with non-steroid treated rheumatoid arthritis. *Ann Rheum Dis* 1988;**47**:660-4.
20. Butler RC, Davie MWJ, Worsfold M, Sharp CA. Bone mineral content in patients with rheumatoid arthritis: relationship to low dose steroid therapy. *Br J Rheumatol* 1991;**30**:86-90.
21. Drinka PJ, Bauwens SF, DeSmet AA. Atraumatic vertebral deformities in elderly males. *Calcif Tissue Int* 1987;**41**:299-302.
22. Zetterberg C, Mannius S, Mellstrom D, Rundgren A, Astrand K. Osteoporosis and back pain in the elderly. A controlled epidemiologic and radiographic study. *Spine* 1990;**15**:783-6.
23. Seeman E, Melton LJ III, O'Fallon WM, Riggs BL. Risk factors for spinal osteoporosis in men. *Am J Med* 1983;**75**:977-83.
24. De Vernejoul MC, Bielekopf J, Hevre M *et al.* Evidence for defective osteoblastic function. A role for alcohol and tobacco consumption in osteoporosis in middle aged men. *Clin Orthopaed Rel Res* 1983;**179**:107-15.
25. Anderson DC. Osteoporosis in men. *Br Med J* 1992;**305**:489-90.
26. Hall GM, Daniels M, Doyle DV, Spector TD. Effect of hormone replacement therapy on bone mass in rheumatoid arthritis patients treated with and without steroids. *Arthritis Rheum* 1994;**37**:1499-505.
27. Orwoll S, Oviatt S. Transdermal testosterone supplementation in normal men: effects on bone and mineral metabolism. *J Bone Miner Res* 1992;**7**(suppl. 1):913.