Testosterone concentrations in men on chronic glucocorticosteroid therapy

ABSTRACT – To determine whether free (or active) testosterone concentrations are reduced in men receiving glucocorticosteroids for chronic inflammatory diseases, 17 men (mean age 55.5 years) receiving a mean daily dose of 16.3 mg prednisolone, and 13 control patients (mean age 52.2 years) receiving no prednisolone, were studied. Serum testosterone and the testosterone/sex hormone binding globulin (SHBG) ratio were measured. The testosterone/SHBG ratio (a measure of free (active) testosterone) was significantly reduced in patients treated with prednisolone (p = 0.026), thus showing that glucocorticosteroids reduce free testosterone in male patients. This may be an important cause of glucocorticosteroid-induced osteoporosis, and suggests an additional approach to bone prophylaxis and treatment.

Glucocorticosteroid (GC) therapy is a potent cause of osteoporosis and is associated with an increased risk of fractures, especially of vertebral bodies. The relative contributions to GC-induced bone loss of reduced osteoblast function, increased osteoclastic resorption and calcium malabsorption remain uncertain. Osteoblast inhibition is likely to be the dominant factor, but bone resorption may be stimulated by hyperparathyroidism secondary to calcium malabsorption[1–4].

One possible mechanism of GC-induced osteoporosis has received scant attention. Bone mineral content in men is directly related to circulating testosterone concentration[5]. The acute administration of exogenous GC to normal adult men suppresses circulating testosterone concentrations[6,7], as does chronic GC therapy in men with inflammatory diseases[8–11]. This deficiency may be important in the pathogenesis of GC-induced osteoporosis. Sex hormone-binding globulin (SHBG) concentration is a possible confounding variable. There has been a single report that GC therapy may reduce SHBG, thus leading to increased free testosterone, as calculated from the testosterone/SHBG ratio[12]. This effect on SHBG would tend to neutralise the possible adverse effect of GC on testosterone metabolism and, in turn, on bone. Only one of the four studies of GC and testosterone concentrations includes SHBG data[11].

The purpose of the present study was to determine whether free (active) testosterone concentrations are reduced in male patients receiving GC for chronic inflammatory diseases.

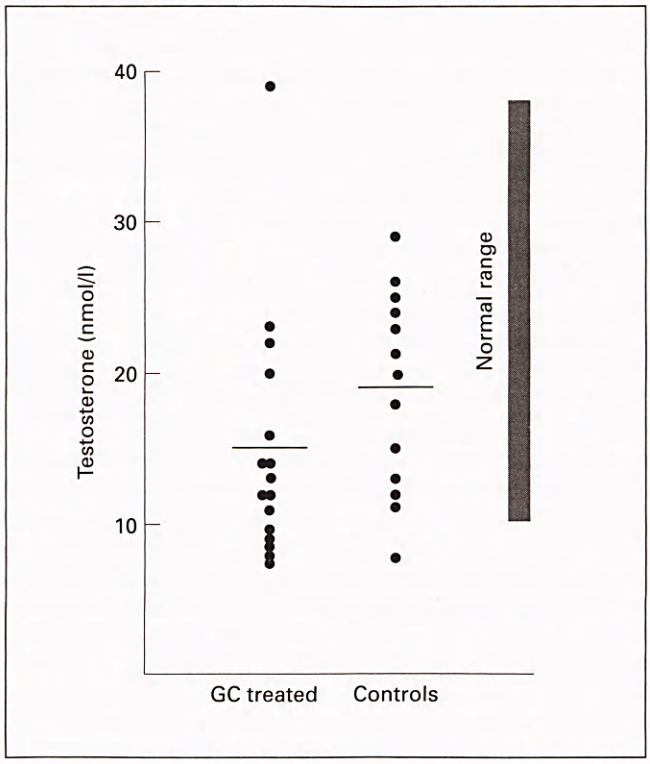
REBECCA C FITZGERALD, MA, MB, MRCP, *Senior House Officer in Rheumatology*
SUSAN J SKINGLE, RGN, *Clinical Investigator*
ADRIAN J CRISP, MA, MD, FRCP, *Consultant Rheumatologist*
Addenbrooke's Hospital, Cambridge

Patients and methods

Thirty male patients were recruited at random from outpatient clinics of the departments of rheumatology, gastroenterology and respiratory medicine: nine had rheumatoid arthritis, six ankylosing spondylitis, and the other 15 had a wide variety of diseases. All patients with rheumatoid arthritis were receiving additional disease-modifying or second-line medication.

Seventeen patients (mean age 55.5 years) were taking an oral daily dose of at least 5 mg prednisolone (mean daily dose 16.3 mg). None of the 13 control patients (mean age 52.2 years) had received any oral prednisolone or other form of GC therapy for at least one year. The two groups did not differ statistically in their mean age or distribution of diseases. It is unlikely

Fig 1. *Range and mean values of testosterone concentrations (nmol/l) in men treated with glucocorticoids (GC) and in a control group of men.* There was no statistical difference between them when the single high concentration in the GC-treated group was included (p = 0.08).



that non-prednisolone treatments, such as non-steroidal anti-inflammatory drugs, might have affected the results. It was not possible to control for disease activity, but it is likely that the GC-treated patients originally had more active disease than the untreated control group. Patients with renal, liver or relevant endocrine diseases were excluded from the study, as were all patients receiving drugs known to influence sex hormone concentrations.

Serum testosterone (normal range 10–38 nmol/l) and SHBG concentrations (normal range 15–55 nmol/l) were measured on a single occasion by radioimmunoassay. The testosterone/SHBG ratio ('androgen index') was calculated to ascertain free (or active) testosterone status. Results were analysed by non-parametric Mann-Whitney U tests and the Spearman rank correlation test.

Results

The mean serum testosterone concentrations in the GC-treated and control groups were 14.9 nmol/l and 18.7 nmol/l, respectively, but this difference did not achieve statistical significance ($p = 0.08$) (Fig 1), nor was there a significant difference between their mean SHBG concentrations (39.7 nmol/l and 34.6 nmol/l, respectively; $p = 0.95$). However, the mean testosterone/SHBG ratio in the GC-treated group ($r = 0.501$) was significantly lower than the ratio in the control group ($r = 0.666$; $p = 0.026$) (Fig 2). There was a weak, but significant inverse correlation between prednisolone dose and the testosterone/SHBG ratio ($r = -0.368$; $p = 0.045$).

Discussion

Free testosterone concentrations are reduced in men receiving GC therapy. We could not confirm the one previous report that GC therapy suppresses SHBG concentration[12]. Our data are consistent with those of Morrison *et al* [11] who concluded that GC had no significant effect on SHBG. There is some evidence that GC therapy suppresses gonadotrophin-releasing hormone secretion by the hypothalamus[8] and may also directly suppress gonadal hormone secretion[6,7,13]. Reduced serum testosterone concentrations have been reported in Cushing's syndrome, the endogenous counterpart to pharmacological GC therapy[14,15].

Our study sheds no further light on the mechanism of suppression of free testosterone concentration by GC; follicle-stimulating hormone (FSH) and luteinising hormone (LH) levels were all within the normal range in the 10 patients in whom they were measured. It has been reported that men with rheumatoid arthritis not treated by GC have normal total testosterone levels but elevated FSH and LH, whereas patients treated with GC have reduced testosterone levels with only slight elevation of FSH and LH compared with a normal control group[10]. It seems likely

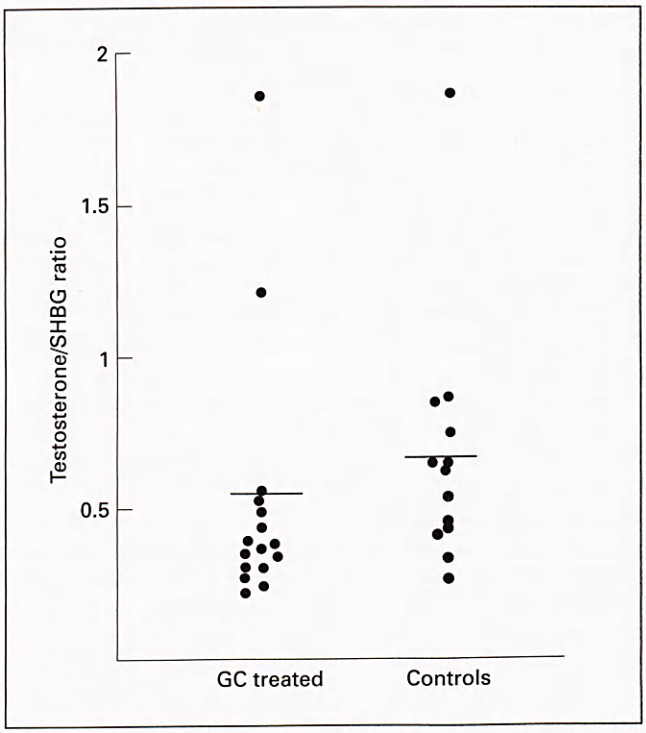


Fig 2. *Range and mean values of testosterone/sex hormone-binding globulin (SHBG) ratio in men treated with glucocorticoids (GC) and in a control group of men.* There was a statistically significant difference between the two groups ($p = 0.026$).

that GC has inhibitory effects at more than one level of the hypothalamic-pituitary-testicular axis.

Bone mineral content in men with Klinefelter's syndrome has been shown to be directly related to circulating testosterone concentration[5], and testosterone replacement therapy in hypogonadal men increases bone mass[16,17]. It therefore seems reasonable to give testosterone supplementation to patients receiving GC whose testosterone levels are below the normal range (5/17 in the present study), but there are no satisfactory data yet to support testosterone supplementation in patients whose levels are in the lower range of normal.

Acknowledgements

We thank Dr P R Raggatt, Department of Clinical Biochemistry, Addenbrooke's Hospital, for measurements of serum testosterone, and Dr M J Wheeler, Department of Chemical Pathology, St Thomas's Hospital, London, for measurements of sex hormone-binding globulin.

References

1 Chavassieux P, Pastoureau P, Chapuy MC, Delmas PD, Meunier PJ. Glucocorticoid-induced inhibition of osteoblastic bone formation in ewes: a biochemical and histo-morphometric study. *Osteoporosis Int* 1993;**3**:97–102.

2 Meunier PJ. Is steroid induced osteoporosis preventable? *New Engl J Med* 1993;**328**:1781–2.
3 Spector TC, Sambrook PN. Steroid osteoporosis. *Br Med J* 1993;**307**:519–20.
4 Sambrook PN. Osteoporosis in rheumatoid arthritis: what is the role of antirheumatic therapy? *Lancet* 1994;**344**:3–4.
5 Foresta C, Ruzza G, Mioni R, Meneghello A, Baccichetti C. Testosterone and bone loss in Klinefelter syndrome. *Horm Metab Res* 1983;**15**:56–7.
6 Doerr P, Pirke KM. Cortisol-induced suppression of plasma testosterone in normal adult males. *J Clin Endocrinol Metab* 1976;**43**:622–9.
7 Schaison G, Durand F, Mouszowicz I. Effect of glucocorticoids on plasma testosterone in men. *Acta Endocrinol (Copenhagen)* 1978;**89**:126–31.
8 MacAdams MR, White RH, Chipps BE. Reduction of serum testosterone levels during chronic glucocorticoid therapy. *Ann Intern Med* 1986;**104**:648–51.
9 Reid IR, Ibbertson HK, France JT, Pybus J. Plasma testosterone concentration in asthmatic men treated with glucocorticoids. *Br Med J* 1985;**291**:574.
10 Martens HF, Sheets PK, Tenover JS, Dugowson CE, *et al.* Decreased testosterone levels in men with rheumatoid arthritis: effect of low dose prednisolone therapy. *J Rheumatol* 1994;**21**:1427–31.
11 Morrison D, Capewell S, Reynolds SP, Thomas J, *et al.* Testosterone levels during systemic and inhaled corticosteroid therapy. *Respir Med* 1994;**88**:659–63.
12 Vermeulen A, Verdonck L, Van der Strueten M. Capacity of the testosterone-binding globulin in human plasma and influence of specific binding of testosterone and its metabolic clearance rate. *J Clin Endocrinol* 1969;**29**:1470–80.
13 Hsueh AJ, Erickson GF. Glucocorticoid inhibition of FSH induced estrogen production in cultured rat granulosa cells. *Steroids* 1978;**32**:639–48.
14 McKenna TJ, Lorber D, Lacroix A, Rabin D. Testicular activity in Cushing's disease. *Acta Endocrinol (Copenhagen)* 1979;**91**:501–10.
15 Luton JP, Thieblot P, Valcke JC, Mahoudeau JA, Bricaire H. Reversible gonadotrophin deficiency in male Cushing's disease. *J Clin Endocrinol Metab* 1977;**45**:488–95.
16 Finkelstein JS, Klibanske A, Neer RM, Greenspan RL, *et al.* Osteoporosis in men with idiopathic hypogonadotropic hypogonadism. *Ann Intern Med* 1987;**106**:354–61.
17 Baran DT, Bergfeld MA, Teitelbaum SL, Avioli LV. Effect of testosterone therapy on bone formation in an osteoporotic hypogonadal male. *Calcif Tiss Res* 1978;**26**:103–6.

Address for correspondence: Dr A J Crisp, Department of Rheumatology, Addenbrooke's NHS Trust, Cambridge CB2 2QQ.