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Commentary

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Testosterone: a natural tonic for the failing heart?

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Introduction

Chronic congestive heart failure (CHF) remains a significant cause of mortality and morbidity in the UK, accounting for 5% of acute hospital admissions and 1% of the total NHS budget.[1] Coronary artery disease (CAD) and hypertension are the most commonly associated conditions. The condition is characterized by left ventricular dysfunction, impaired vascular tone and skeletal muscle abnormalities, producing breathlessness and fatigue. Neuro-hormonal and cytokine activation are self-perpetuating maladaptive responses to the failing heart, which cause further deterioration in cardiac function and increased catabolism.

The mainstay of current therapy includes diuretics and neuro-hormonal manipulation; ACE inhibitors are well established as the most important intervention for improving prognosis, and angiotensin II receptor antagonists offer a good alternative.[2] More recently, reduced mortality has been demonstrated from the use of both beta-blockers and the aldosterone receptor antagonist spironolactone.[3,4] Vasodilators may also provide symptomatic and prognostic benefit. However, the only therapy offering long-term survival is cardiac transplantation, which remains limited by lack of donors and recipient suitability.

There remains, therefore, a need for therapies which alleviate the suffering associated with CHF, as well as reducing mortality. Potential strategies under evaluation include anti-cytokine therapy and inhibitors of neutral endopeptidases, which prevent breakdown of natriuretic peptides. Testosterone therapy has also been proposed as a useful add-on treatment for men with CHF, although there are currently no clinical data to support this.[6] In this article, we review the cardiovascular and neuro-hormonal actions of testosterone, and discuss how androgen therapy may be of benefit to men with chronic heart failure.

Gonadal function in men with CHF

No studies have sought specifically to determine gonadal function in men with heart failure. However, several small studies suggest that these patients may have relatively low androgen levels. A study of 53 men with CHF found that dehydroepiandrosterone (DHEA) levels were significantly lower than in healthy controls.[7] In 17 men with non-ischaemic cardiomyopathy, testosterone levels correlated with cardiac index, and five men with severe left ventricular dysfunction had markedly reduced plasma testosterone, which normalized 2 months after implantation of a ventricular assist device.[8,9] In an animal model of heart failure, hamsters with cardiomyopathy were found to have very low testosterone levels.[10]

These findings are perhaps to be expected given the effect of chronic disease on gonadal function. However, there is also a link between hypotestosteronaemia and stable CAD. Epidemiological data suggest that men with ischaemic heart disease have low androgen levels, and men with proven coronary atheroma have lower testosterone levels than healthy controls.[11,12] In animals, castration promotes atherosclerosis while androgen therapy retards it.[13] Similarly, hypertensive men have relatively

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low androgen levels, which show an inverse correlation with blood pressure.[11] Men with CHF, therefore, are likely to have low testosterone levels, potentially exacerbating the catabolic imbalance.

Effects on cardiovascular function

There are no clinical trial data concerning the effects of testosterone on left ventricular function. In rats, androgen therapy improves coronary blood flow and increases both fractional shortening and peak myocardial oxygen consumption, thereby improving cardiac function.[14] Castration results in reduced ejection fraction and diastolic dysfunction, with alteration of the isoenzyme composition of the myosin heavy chain.[14]

Testosterone therapy has been used to treat men with angina; the beneficial effects on both ischaemia and exercise tolerance have been demonstrated in several studies (see Table 1).

Numerous reports from animal studies have demonstrated the vasodilator properties of androgens in several vascular beds, both *in vitro* and *in vivo* (see Table 2). In humans, testosterone reduces blood pressure and enhances relaxation of brachial arteries; direct injection into coronary arteries produces dilatation and increased coronary blood flow.[39–41] Low circulating levels of testosterone may therefore contribute to the generalized increase in vascular tone found in patients with CHF. A vasodilator effect could be important in relieving pulmonary congestion and improving peripheral perfusion. Androgen therapy could therefore also improve cardiac function by reducing pre-load and after-load and by increasing coronary blood flow.

Skeletal muscle and strength

Fatigue and poor exercise tolerance are central features of the symptoms of heart failure, and may be out of proportion to the degree of left ventricular dysfunction. Patients with CHF suffer loss of skeletal muscle mass with reduced muscle strength and endurance. Muscle fibre type and mitochondrial structure are altered, with reduction in the enzymes of the Krebs cycle and oxidative chain.[42] These features may arise from the catabolic effects of neuro-hormonal and cytokine activity. Also, endothelial function is impaired in CHF, resulting in reduced peripheral vasodilator capacity and muscle hypoperfusion.

Testosterone may counter these deleterious effects both by its vasodilator action and by promoting protein synthesis and blocking the catabolic action of glucocorticoids.[6] The anabolic effects of androgens are well described in healthy men, producing skeletal muscle hypertrophy and increased muscle bulk and strength.[43]

There have been no studies of the effects of androgen therapy on strength and endurance in heart failure. However, several small studies have evaluated testosterone therapy in elderly men; these showed improvement in grip and leg strength as well as an increase in lean body mass.[44–46]

Testosterone deficiency is likely to contribute to the weakness and fatigue of CHF which constitute a major aspect of the morbidity. Androgen therapy could potentially improve patient well-being by combating this.

Neuro-hormonal activity

In recent years, advances in our understanding of the role hormones play in the progression, morbidity

Table 1 Studies of testosterone therapy for men with angina

Author	*n*	Dose	Duration	Outcome
Hamm[15]	7	25 mg im 1–12 times a month	1–11 months	Reduced frequency of angina
Walker[16]	9	10–25 mg im 1–4 times a week	12 weeks	Increase in exercise tolerance in 7
Levine[17]	16	25 mg im 3 times a week	4 weeks	Subjective improvement in 8
Sigler*[18]	20	25 mg im twice a week	NS	Increased exercise duration
Lesser*[19]	92	25 mg im weekly	12 weeks	Subjective improvement in 85
Jaffe*[20]	50	200 mg im weekly	8 weeks	Reduced post-exercise ST depression
Wu*[21]	62	40–120 mg po daily	4 weeks	Fewer angina symptoms. Reduced ischaemia on Holter monitor
Rosano*[22]	14	2.5 mg iv	Single dose	Increased time to 1mm ST depression. Increased exercise duration
Webb*[23]	14	2.3 mg iv	Single dose	Increased time to 1mm ST depression
English*[24]	46	5 mg patch daily	12 weeks	Increased time to 1mm ST depression

*Placebo controlled trial. NS, not stated; im, intramuscular; iv, intravenous.

and mortality of CHF have directed modern therapy at reducing hormonal activity. Patients have varying degrees of hormonal activation which results in a catabolic/anabolic imbalance, ranging from a rise in the cortisol/DHEA ratio to elevation of circulating catecholamines, cortisol, aldosterone and plasma renin activity.[7] Levels of anabolic factors, including testosterone and insulin-like growth factor-1 (IGF-1), are depressed, and insulin resistance may develop.[47,48]

Although the effects of androgens on hormonal activation in CHF have not been studied, it would seem logical to oppose excess catabolism with anabolism. Testosterone has been found to increase IGF-1 levels and reduce hyperinsulinaemia and insulin resistance.[39,49] In addition, in animal experiments, the increased release of atrial natriuretic peptide (ANP) which results from cardiac overload is reduced by testosterone, an effect which may have positive prognostic implications.[50]

Cytokine activation

It is now recognized that cytokine activation is likely to play an important role in the progression of cardiac failure. The 'cytokine hypothesis' of heart failure is perhaps a natural progression of the neurohumoral theory and is based on the known actions of several cytokines.[51] Circulating levels of tumour necrosis factor (TNF) and interleukin-6 (Il-6) are elevated in CHF and independently predict mortality.[52] The levels correlate adversely with several prognostic markers, including NYHA class, exercise tolerance and myocardial oxygen consumption, as well as plasma levels of ANP, catecholamines, endothelin-1 and angiotensin II.[52–54]

TNF is produced mainly by macrophages, but also by the myocardium in CHF. It impairs synthesis and promotes catabolism of skeletal muscle, and reduces testosterone production. It causes endothelial dysfunction and impairs production of NO by endothelium.[55] Administration causes left ventricular dysfunction and heart failure in humans; anti-TNF therapy may improve cardiac function.[56,57] Cytokines therefore appear to mediate many of the pathophysiological processes of heart failure.

The immune-modulatory properties of androgens have been well described. In various disease models (though not in heart failure), androgens have been found to significantly suppress macrophage production of cytokines both *in vitro* and *in vivo* (see Table 3). In man, androgen levels correlate negatively with plasma cytokine levels and gonadotropin therapy suppresses the high level seen in hypogonadal men.[72]

These findings suggest another important mechanism by which androgen therapy could improve outcome in men with CHF.

Table 2 Animal studies of effects of androgens on vascular tone

Author	Vessel	Model	Effect on vascular tone
Greenberg[25]	Dog femoral	*in vivo*	↑
Mosnarova[26]	Rabbit aorta, renal, femoral	*in vivo*	↓
Schror[27]	Guinea pig coronary	*in vitro*	↑
Adams[28]	Monkey coronary	*in vivo*	↓
Farhat[29]	Pig coronary	*in vitro*	↑
Yue[30]	Rabbit coronary, aorta	*in vitro*	↓
Perusquia[31]	Rat aorta	*in vitro*	↓
Costarella[32]	Rat aorta	*in vitro*	↓
Chou[33]	Dog coronary	*in vivo*	↓
Hutchinson[34]	Rabbit aorta	*in vitro*	↑
Farrukh[35]	Ferret pulmonary	*in vitro*	↓
Honda[36]	Rat aorta	*in vitro*	↓
Teoh[37]	Pig coronary	*in vitro*	↑
Crews[38]	Pig coronary	*in vitro*	↓

Table 3 Effects of androgens on cytokine activity

Model	Androgen	Effect
Rat macrophage[58]	T	Trend to↓TNF production
Mouse macrophage[59]	T	↓ LPS-induced TNF ↑ LPS-induced Il-10
Human monocytes[60]	T	↓ Il-6 production
Human monocytes[61 a]	T	↓ Il-6 production
Human monocytes[62 b]	T	↓ Il-1 production
Human gingival fibroblasts[63]	T	↓ Il-6 production
Human osteoblasts[64]	T	↓ Il-6 production
Mouse cells[65]	DHT	↓ γ-interferon, Il-4
Mice with autoimmune disease[66*]	DHT	↓ γ-interferon ↑ Il-10
Obese rats[67*]	DHEA	↓ TNF
Mice[68]	DHEA	↓ Il-1 ↓ LPS-induced TNF
Mouse macrophages[69]	DHEA	↓ LPS-induced TNF, Il-1, Il-6
Human monocytes[70]	DHEA	↓ Il-6 production
Mice[71*]	Castrated	↑ LPS-induced TNF

[a]Patients with systemic lupus erythematosus; [b]patients with rheumatoid arthritis and healthy subjects; **in vivo.* LPS, lipopolysaccharide; T, testosterone; DHT, dihydrotestosterone; DHEA, dehydroepiandrosterone.

Conclusion

Patients with chronic heart failure suffer considerable morbidity as well as early mortality. They exhibit altered structure and function of cardiac and skeletal muscle and excessive activation of catabolic hormones and inflammatory cytokines. Men with CHF have relatively low androgen levels, which may contribute to the pathophysiological process. Androgen replacement therapy could potentially ameliorate symptoms by improving cardiac and vascular function and increasing strength and endurance. It may also redress the catabolic/anabolic imbalance of chronic CHF and suppress the cytokine activation which leads to progression of the disease. Clinical trials are needed to evaluate the effects of androgen therapy for chronic congestive heart failure.

References

1. Cowie MR. The epidemiology of heart failure—an epidemic in progress. In: Coats A, ed. *Controversies in the management of heart failure*. London, Churchill Livingstone, 1997:11–24.
2. Pitt B, Poole-Wilson PA, Segal R, Martinez FA, Dickstein K, Camm AJ, Konstam MA, Riegger G, Klinger GH, Neaton J, Sharma D, Thiyagarajan B. Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomised trial—the Losartan Heart Failure Survival Study ELITE II. *Lancet* 2000; **355**:1582–7.
3. The Cardiac Insufficiency Bisoprolol Study II (CIBIS II): a randomised trial. *Lancet* 1999; **353**:9–13.
4. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J, Wittes J. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomised aldactone evaluation study investigators. *N Engl J Med* 1999; **341**:709–17.
5. Cohn JN, Archibald DG, Ziesche S, Franciosa JA, Harston WE, Tristani FE, Dunkman WB, Jacobs W, Francis GS, Flohr KH. Effect of vasodilator therapy on mortality in chronic congestive heart failure: results of a Veterans Administration Cooperative Study. *N Engl J Med* 1986; **314**:1547–52.
6. Shapiro J, Christiana J, Frishman WH. Testosterone and other anabolic steroids as cardiovascular drugs. *Am J Ther* 1999; **6**:167–74.
7. Anker SD, Chua TP, Ponikowski P, Harrington D, Swan JW, Kox WJ, Poole-Wilson PA, Coats AJS. Hormonal changes and catabolic/anabolic imbalance in chronic heart failure and their importance for cardiac cachexia. *Circulation* 1997; **96**:526–34.
8. Tappler B, Katz M. Pituitary-gonadal dysfunction in low-output cardiac failure. *Clin Endocrinol* 1979; **10**:219–26.
9. Noirhomme P, Jaquet L, Underwood M, El Khoury G, Goenen M, Dion R. The effect of chronic mechanical circulatory support on neuroendocrine activation in patients with end-stage heart failure. *Eur J Cardiothorac Surg* 1999; **16**:63–7.
10. Otenweller JE, Tapp WN, Creighton D, Natelson BH. Aging, stress and chronic disease interact to suppress plasma testosterone in Syrian hamsters. *J Gerontol* 1988; **43**:M175–80.
11. English KM, Steeds R, Jones TH, Channer KS. Testosterone and coronary heart disease: is there a link? *Q J Med* 1997; **90**:787–91.
12. English KM, Mandour O, Steeds RP, Diver MJ, Jones TH, Channer KS. Men with coronary artery disease have lower levels of androgens than men with normal coronary angiograms. *Eur Heart J* 2000; **21**:890–4.
13. Alexandersen P, Haarbo J, Byrjalsen I, Lawaetz H, Christiansen C. Natural androgens inhibit male atherosclerosis. A study in castrated, cholesterol-fed rabbits. *Circ Res* 1999; **84**:813–19.
14. Scheuer J, Malhotra A, Schaible TF, Capasso J. Effects of gonadectomy and hormonal replacement on rat hearts. *Circ Res* 1987; **61**:12–19.
15. Hamm L. Testosterone propionate in the treatment of angina pectoris. *J Clin Endocrinol* 1942; **2**:325–8.
16. Walker TC. Use of testosterone propionate and estrogenic substance in treatment of essential hypertension, angina pectoris and peripheral vascular disease. *J Clin Endocrinol* 1942; **2**:560–8.
17. Levine SA, Likoff WB. The therapeutic value of testosterone propionate in angina pectoris. *N Engl J Med* 1943; **229**:770–2.
18. Sigler LH, Tulgan J. Treatment of angina pectoris by testosterone propionate. *N Y State J Med* 1943; **43**:1424–8.
19. Lesser MA. Testosterone propionate therapy in one hundred cases of angina pectoris. *J Clin Endocrinol* 1946; **6**:549–57.
20. Jaffe MD. Effect of testosterone cypionate on postexercise ST segment depression. *Br Heart J* 1977; **39**:1217–22.
21. Wu S-Z, Weng X-Z. Therapeutic effects of an androgenic preparation on myocardial ischemia and cardiac function in 62 elderly male coronary heart disease patients. *Chin Med J* 1993; **106**:415–18.
22. Rosano GMC, Leonardo F, Pagnotta P, Pelliccia F, Panina G, Cerquetani E, Della Monica PL, Bonfigli B, Volpe M, Chierchia SL. Acute anti-ischemic effect of testosterone in men with coronary artery disease. *Circulation* 1999; **99**:1666–70.
23. Webb CM, Adamson DL, De Zeigler D, Collins P. Effect of acute testosterone on myocardial ischaemia in men with coronary artery disease. *Am J Cardiol* 1999; **83**:437–9.
24. English KM, Steeds RP, Jones TH, Diver MJ, Channer KS. Low dose transdermal testosterone therapy improves angina threshold in men with chronic stable angina. *Circulation* 2000: in press.
25. Greenberg S, George WR, Kadowitz PJ, Wilson WR. Androgen-induced enhancement of vascular reactivity. *Can J Physiol Pharmacol* 1974; **52**:14–22.
26. Mosnarova A, Stecova A, Huzulakova I, Motesicka M. The influence of one month sex hormones administration on the isolated rabbit vessels reactivity. *Acta Physiol Hung* 1994; **82**:251–6.
27. Schror K, Morinelli TA, Masuda A, Mathur R, Halushka PV, Matsuda K. Testosterone treatment enhances thromboxane A2 mimetic induced coronary artery vasoconstriction in guinea pigs. *Eur J Clin Invest* 1994; **24**:50–2.
28. Adams MR, Williams JK, Kaplan JR. Effects of androgens on coronary artery atherosclerosis and atherosclerosis related impairment of vascular responsiveness. *Arterioscler Thromb Vasc Biol* 1995; **15**:562–70.

29. Farhat MY, Wolfe R, Vargas R, Foegh ML, Ramwell PW. Effect of testosterone treatment on vasoconstrictor response of left anterior descending artery in male and female pigs. *J Cardiovasc Pharmacol* 1995; **25**:495–500.
30. Yue P, Chatterjee K, Beale C, Poole-Wilson PA, Collins P. Testosterone relaxes rabbit coronary arteries and aorta. *Circulation* 1995; **91**:1154–60.
31. Perusquia M, Hernandez R, Morales MA, Campos MG, Villalon CM. Role of endothelium in the vasodilating effect of progestins and androgens on the rat thoracic aorta. *Gen Pharmacol* 1996; **27**:181–5.
32. Costarella CE, Stallone JN, Rutecki GW, Whittier FC. Testosterone causes direct relaxation of rat thoracic aorta. *J Pharmacol Exp Ther* 1996; **277**:34–9.
33. Chou TM, Sudhir K, Hutchison SJ, Ko E, Amidon TM, Collins P, Chatterjee K. Testosterone induces dilation of canine conductance and resistance arteries in vivo. *Circulation* 1996; **94**:2614–19.
34. Hutchison SJ, Sudhir K, Chou TM, Sievers RE, Zhu BO, Sun YP, Deedwania PC, Glantz SA, Parmley WW, Chatterjee K. Testosterone worsens endothelial dysfunction associated with hypercholesterolaemia and environmental tobacco smoke exposure in male rabbit aorta. *J Am Coll Cardiol* 1997; **29**:800–7.
35. Farrukh IS, Peng W, Orlinska U, Hoidal JR. Effect of dehydroepiandrosterone on hypoxic pulmonary vasoconstriction: a Ca^{2+} activated K^{+} channel opener. *Am J Physiol* 1998: **274**:L186–95.
36. Honda H, Unemoto T, Kogo H. Different mechanisms for testosterone-induced relaxation of aorta between normotensive and spontaneously hypertensive rats. *Hypertension* 1999; **34**:1232–6.
37. Teoh H, Quan A, Leung SWS, Man RY. Different effects of 17beta-estradiol and testosterone on the contractile responses of porcine coronary arteries. *Br J Pharmacol* 2000: **129**:1301–8.
38. Crews JK, Khalil RA. Antagonistic effects of 17β-estradiol, progesterone and testosterone on Ca^{2+} entry mechanisms of coronary vasoconstriction. *Arterioscler Thromb Vasc Biol* 1999; **19**:1034–40.
39. Marin P, Holmang S, Jonsson L, Sjostrom L, Kvist H, Holm G, Lindstedt G, Bjorntorp P. The effects of testosterone treatment on body composition and metabolism in middle-aged obese men. *Int J Obes* 1992; **16**:991–7.
40. Ong PJL, Patrizi G, Chong WCF, Webb CM, Hayward CS, Collins P. Testosterone enhances flow-mediated brachial artery reactivity in men with coronary artery disease. *Am J Cardiol 2000,* **85**:269–72.
41. Webb CM, McNeill JG, Hayward CS, De Zeigler D, Collins P. Effects of testosterone on coronary vasomotor regulation in men with coronary heart disease. *Circulation* 1999; **100**:1690–6.
42. Drexler H, Riede U, Munzel T, Konig H, Funke E, Just H. Alterations of skeletal muscle in chronic heart failure. *Circulation* 1992; **85**:1751–9.
43. Bhasin S, Storer TW, Berman N, Callegari C, Clevenger B, Phillips J, Bunnell TJ, Tricker R, Shirazi R, Casaburi R. The effects of supraphysiological doses of testosterone on muscle size and strength in normal men. *N Engl J Med* 1996; **335**:1–7.
44. Sih R, Morley JE, Kaiser FE, Perry HM, Pareick P, Ross C. Testosterone replacement in older hypogonadal men: a 12-month randomised controlled trial. *J Clin Endocrinol* 1997; **82**:1661–7.
45. Urban RJ, Bodenburg YH, Gilkison C, Foxworth J, Coggan AR, Wolfe RR, Ferrando A. Testosterone administration to older men increases skeletal muscle strength and protein synthesis. *Am J Physiol* 1995: **269**:E820–6.
46. Tenover JS. Effects of testosterone supplementation in the aging male. *J Clin Endocrinol Metab* 1992; **75**:1092–8.
47. Niebauer J, Pflaum C-D, Clark AL, Strasburger CJ, Hooper J, Poole-Wilson PA, Coats AJS, Anker SD. Deficient insulin-like growth factor 1 in chronic heart failure predicts altered body composition, anabolic deficiency, cytokine and neurohormonal activation. *J Am Coll Cardiol* 1998; **32**:393–7.
48. Swan JW, Walton C, Godsland IF, Clark AL, Coats AJS, Oliver MF. Insulin resistance in chronic heart failure. *Eur Heart J* 1994; **15**:1528–32.
49. Hobbs CJ, Plymate SR, Rosen CJ, Adler RA. Testosterone administration increases insulin-like growth factor-1 levels in normal men. *J Clin Endocrinol Metab* 1993; **77**:776–9.
50. Deng Y, Kaufman S. The influence of reproductive hormones on ANF release by rat atria. *Life Sci* 1993; **53**:689–96.
51. Seta Y, Shan K, Bozkurt B, Oral H, Mann DL. Basic mechanisms in heart failure: the cytokine hypothesis. *J Card Fail* 1996; **2**:243–9.
52. Tsutamoto T, Hisanaga T, Wada A, Maeda K, Ohnishi M, Fukai D, Mabuchi N, Sawaki M, Kinoshita M. Interleukin-6 spillover in the peripheral circulation increases with the severity of heart failure, and the high plasma level of interleukin-6 is an important prognostic predictor in patients with congestive heart failure. *J Am Coll Cardiol* 1998; **31**:391–8.
53. Anker SD, Clark AL, Kemp M, Salsbury C, Teixera MM, Hellewell PG, Coats AJS. Tumour necrosis factor and steroid metabolism in chronic heart failure: possible relation to muscle wasting. *J Am Coll Cardiol* 1997; **30**:997–1001.
54. Torre-Amione G, Kapadia S, Benedict C, Oral H, Young JB, Mann DL. Proinflammatory cytokine levels in patients with depressed left ventricular ejection fraction: a report from the Studies of Left Ventricular Dysfunction (SOLVD). *J Am Coll Cardiol* 1996; **27**:1201–6.
55. Yoshizumi M, Perrella MA, Burnett JCJ, Lee M-E. Tumor necrosis factor downregulates endothelial nitric oxide synthase mRNA by shortening its half-life. *Circ Res* 1993; **73**:205–9.
56. Hegewisch S, Weh H-J, Hossfeld DK. Tumour necrosis factor-induced cardiomyopathy. *(Letter) Lancet* 1990: **335**:294–5.
57. Deswal A, Bozkurt B, Seta Y, Parilti-Eiswirth S, Hayes FA, Blosch C, Mann DL. Safety and efficacy of a soluble P75 tumor necrosis factor receptor (Enbrel, etanercept) in patients with advanced heart failure. *Circulation* 1999; **99**:3224–6.
58. Chao T-C, Van Alten PJ, Greager JA, Walter RJ. Steroid sex hormones regulate the release of tumor necrosis factor by macrophages. *Cell Immunol* 1995; **160**:43–9.
59. D'Agostino P, Milano S, Barbera C, Di Bella G, La Rosa M, Ferlazzo V, Farruggio R, Miceli DM, Miele M, Castagnetta L, Cillari E. Sex hormones modulate inflammatory mediators produced by macrophages. *Ann N Y Acad Sci* 1999; **876**:426–9.
60. Kanda N, Tsuchida T, Tamaki K. Testosterone inhibits immunoglobulin production by human peripheral blood mononuclear cells. *Clin Exp Immunol* 1996; **106**:410–15.

61. Kanda N, Tsuchida T, Tamaki K. Testosterone suppresses anti-DNA antibody production in peripheral blood mononuclear cells from patients with systemic lupus erythematosus. *Arthritis Rheum* 1997; **40**:1703–11.

62. Li ZG, Danis VA, Brooks PM. Effect of gonadal steroids on the production of Il-1 and Il-6 by blood mononuclear cells in vitro. *Clin Exp Rheumatol* 1993; **11**:157–62.

63. Gornstein RA, Lapp CA, Bustos-Valdes SM, Zamorano P. Androgens modulate interleukin-6 production by gingival fibroblasts in vitro. *J Periodontol* 1999; **70**:604–9.

64. Hofbauer LC, Ten RM, Khosla S. The anti-androgen hydroxyflutamide and androgens inhibit interleukin-6 production by an androgen-responsive human osteoblastic cell line. *J Bone Miner Res* 1999; **14**:1330–7.

65. Araneo BA, Dowell T, Diegel M, Daynes RA. Dihydrotestosterone exerts a depressive influence on the production of interleukin-4 (Il-4), Il-5 and γ-interferon, but not Il-2 by activated murine T cells. *Blood* 1991; **3**:688–99.

66. Dalal M, Kim S, Voskuhl RR. Testosterone therapy ameliorates experimental autoimmune encephalomyelitis and induces a T helper 2 bias in the autoantigen-specific T lymphocyte response. *J Immunol* 1997; **159**:3–6.

67. Kimura M, Tanaka S-I, Yamada Y, Kiuchi Y, Yamakawa T, Sekihara H. Dehydroepiandrosterone decreases serum tumor necrosis factor-α and restores insulin sensitivity: independent effect from secondary weight reduction in genetically obese Zucker fatty rats. *Endocrinology* 1998; **139**:3249–53.

68. Ben-Nathan D, Padgett DA, Loria RM. Androstenediol and dehydroepiandrosterone protect mice against lethal bacterial infections and lipopolysaccharide toxicity. *J Med Microbiol* 1999; **48**:425–31.

69. Padgett DA, Loria RM. Endocrine regulation of murine macrophage function: effects of dehydroepiandrosterone, androstenediol, and androstenetriol. *J Neuroimmunol* 1998; **84**:61–8.

70. Straub RH, Konecna L, Hrach S, Rothe G, Kreutz M, Scholmerich J, Falk W, Lang B. Serum dehydroepiandrosterone (DHEA) and DHEA sulfate are negatively correlated with serum interleukin-6 (Il-6) and DHEA inhibits Il-6 secretion from mononuclear cells in man in vitro: possible link between endocrinosenescence and immunosenescence. *J Clin Endocrinol Metab* 1998; **83**:2012–17.

71. Spinedi E, Suescun MO, Hadid R, Daneva T, Gaillard RC. Effects of gonadectomy and sex hormone therapy on the endotoxin-stimulated hypothalamo-pituitary-adrenal axis: evidence for a neuroendocrine-immunological sexual dimorphism. *Endocrinology* 1992; **131**:2430–6.

72. Yesilova Z, Ozata M, Kocar IH, Turan M, Pekel A, Sengul A, Ozdemir IC. The effects of gonadotropin treatment on the immunological features of male patients with idiopathic hypogonadotropic hypogonadism. *J Clin Endocrinol Metab* 2000; **85**:66–70.