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Serum Testosterone Levels After Cardiac Transplantation

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Abstract

BACKGROUND—Men undergoing heart transplantation during the early 1990s had declines in testosterone associated with rapid bone loss. It is unclear whether low testosterone still occurs in an era of lower prednisone doses, whether cyclosporine A (CsA) contributes, whether hypothalamic-pituitary-gonadal (HPG) suppression or direct testicular effects are responsible, and whether low testosterone influences bone loss in men receiving therapy to prevent osteoporosis.

METHODS—We measured serum testosterone, estradiol, sex hormone binding globulin, gonadotropins and bone density and recorded prednisone and CsA doses and levels for the first two years after transplantation in a more recently transplanted cohort of 108 participants in a trial comparing alendronate and calcitriol for prevention of post-transplant osteoporosis.

RESULTS—Total and free testosterone levels were lowest during the first month (257±131 and 6.2±3 ng/dl respectively) and normalized by two months. Gonadotropins were low in the majority, suggesting HPG suppression. Low total testosterone persisted in 14% at one and 18% at two years. Prednisone was the major predictor of serum testosterone. We detected no adverse effect of CsA and no relationship between serum testosterone and bone density change.

CONCLUSIONS—Low serum testosterone levels still occur in the early post-transplant period, probably related to HPG suppression by prednisone rather than direct testicular effects of CsA. They are not associated with bone loss in men receiving therapies to prevent osteoporosis. At later time-points, low testosterone levels are common and apparently related to primary gonadal dysfunction, suggesting that long-term male heart transplant recipients should be evaluated for hypogonadism.

Keywords

total testosterone; free testosterone; sex hormone binding globulin; gonadotropins; prednisone; cyclosporine A; cardiac transplantation

Introduction

Relatively few studies have evaluated serum testosterone levels in heart transplant recipients. Several studies from the early 1990s reported low serum testosterone at various times after transplantation, particularly early time points (1–4). In a study of the natural history of bone loss and fracture after heart transplantation in the early 1990s, we measured

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serial serum testosterone levels in 52 men before and for three years after grafting (5). They experienced a transient decline in serum testosterone immediately after transplantation, but levels returned to the normal range by three months and remained there for the duration of the study. Lower testosterone levels were associated with more rapid bone loss (5).

Although these studies have provided data on the time course of changes in serum testosterone levels after heart transplantation, the pathogenesis of the low testosterone levels has never been addressed in detail. Low serum testosterone levels could result from suppression of hypothalamic-pituitary secretion of luteinizing hormone (LH), the gonadotropin hormone responsible for stimulating testicular androgen synthesis. Such central suppression of the hypothalamic-pitutitary-gonadal (HPG) axis occurs in the setting of major illness or surgery (6–8) and high prednisone doses (9–12). Low testosterone levels could also result from direct effects upon the testis itself. In this regard, rodent studies suggest that Cyclosporine A lowers testosterone both by suppressing the HPGaxis and reducing LHproduction (13), and by directly inhibiting testicular testosterone synthesis, which was associated with corresponding elevations in gonadotropins (14). Also unclear is whether similar changes occur in men transplanted more recently when prednisone doses are typically lower than in the early 1990s, the proportion of men in whom low serum testosterone levels persist and whether transient hypogonadism is associated with bone loss in men receiving therapy to prevent osteoporosis.

To address these questions, we prospectively measured serum total testosterone levels, sex hormone binding globulin (SHBG), the gonadotropins LH and follicle stimulating hormone (FSH), in a new and larger cohort of men who were participating in a study comparing the efficacy of antiresorptive drug alendronate and calcitriol, the active metabolite of vitamin D, for prevention of bone loss during the first two years after heart transplantation. Although the bone density and fracture data from that study have been published (15), the data on serum testosterone levels in this report are new and provide additional information on the pathogenesis of low testosterone levels and their prevalence in the long-term heart transplant recipient.

Subjects and Methods

Study population

The study population included 108 adult men, aged 18 to 70, who underwent heart transplantation between January 1999 and June 2001 at Columbia University Medical Center or Newark-Beth Israel Medical Center. All participated in a randomized clinical trial comparing alendronate (10 mg/day) and calcitriol (0.5 μg/day) for prevention of bone loss during the first post-transplant year (15). The study also included a small nonrandomized reference group who received only calcium and vitamin D. The 108 men described herein were a subset of 149 men from the primary study who survived for at least 12 months and had at least 3 measurements of serum testosterone. Exclusion criteria were those of the primary study and included cancer, primary hyperparathyroidism, thyrotoxicosis, sarcoidosis, serum creatinine above 2.5 mg/dl, active peptic ulcer disease, nephrolithiasis and previous use of bisphosphonates.

All patients received prednisone and calcineurin inhibitors, predominantly cyclosporine A. Intravenous methylprednisolone was administered intraoperatively and during the first 24 hours, followed by oral prednisone (50 mg/day) tapered rapidly to 30 mg/day by two weeks and 5–10 mg/day by six months. Prednisone was not discontinued in any subject. Rejection was managed with high-dose oral or intravenous glucocorticoids. Trough whole blood cyclosporine A levels were maintained between 250–300 ng/ml for the first six months, 200–250 ng/ml for the second six months and 150–200 ng/ml for the second year.

Study design

The initial evaluation was performed during the first month after transplantation (mean, 21 days). Serial measurements of renal and hepatic function, total testosterone, SHBG, LH, FSH and estradiol (E2) were obtained at defined intervals for the next two years. Prednisone and Cyclosporine A doses were recorded and whole blood Cyclosporine A levels were measured at each visit. Bone density was measured by dual energy x-ray absorptiometry (Hologic, QDR-4500) at baseline and every 6 months for two years.

Measurements

Fasting serum was obtained in the morning and stored at −70° until the end of the study. All samples from each individual were analyzed in the same assay. Gonadal hormone and gonadotropin measurements were performed in the laboratory of Dr. Christopher Longcope. Total testosterone was measured by radioimmunoassay using Coat-a-Count kits (Diagnostic Products Corp., Los Angeles, CA). The intra-and inter-assay coefficients of variation (CVs) were 5.8% and 9.0% respectively. Estradiol was measured by radioimmunoassay using Coat-a-Count kits (Diagnostic Products Corp., Los Angeles, CA). Intra-and inter-assay CVs were 2% and 8%. LH was measured by chemiluminescence using the automated Immulite system (Diagnostic Products Corp., Los Angeles, CA). Intra-and inter-assay CVs were 5.5% and 9.5%. FSH was measured by chemiluminescence using the automated Immulite system (Diagnostic Products Corp., Los Angeles, CA). Intra-and inter-assay CVs were 5.1% and 6.4%. SHBG was measured by chemiluminescence using the automated Immulite system (Diagnostic Products Corp., Los Angeles, CA). Intra- and inter-assay CVs were 4.5 and7.9%, respectively. Free testosterone was calculated using the Rosner formula (16). Percent Free Estradiol was calculated using the Sodergard formula (17). Renal and hepatic function were measured by autoanalyzer (Technicon Instruments) in the laboratories of New York-Presbyterian Hospital.

Statistical Analysis

Using mixed linear model analysis, multiple regression and chi-square analysis, the trends in hormone levels over time, the prediction of testosterone and bone density levels, and the proportion of samples with hormone concentrations outside the normal range, respectively, were evaluated. The normal range of total testosterone was defined by the laboratory normal range (250–1100 ng/dl). To address the relationship between age and serum testosterone, we also used age-specific lower limit of normal thresholds from the Massachusetts Aging Study, also assayed in Dr. Longcope's laboratory (18). Thelower limit of normal testosterone for each age group in the Massachussetts Aging Study corresponds to the 2.5th percentile of the data (18).

Results

Characteristics of the study population

The baseline characteristics of the subjects are shown in Table 1. Mean age was 54 ± 10 years and the majority was Caucasian. Most required transplantation for ischemic or dilated cardiomyopathy.

Serum Total and Free Testosterone Levels

At baseline (mean 21 days after transplantation), mean total and free serum testosterone were at the very low end of the normal range. Total testosterone measured 257±131 ng/dl (normal, 250–1100 ng/dl) and free testosterone measured 6.2±3 ng/dl (normal, 5–21 ng/dl). Both total and free testosterone increased significantly by two months, remaining above

baseline and well within the normal range for the remainder of the study (Table 2 and Figure 1).

At baseline, total testosterone levels were subnormal in 63% of men while only 33% of men had low free testosterone levels (Figure 2A). Thereafter, the proportion of men with low total testosterone levels declined progressively to 33% by 2 months and 21% by 6 months. Notably, however, low total serum testosterone levels were present in 14% of the men by one year and 18% by two years. Ten percent of men had low free testosterone levels at all times after baseline (Figure 2A).

Serum testosterone levels decline with increasing age. Our study subjects were generally over age 50. As normal ranges for these assays were established in men of all ages, measures contributed by younger men could increase the lower normal limit and lead us to overestimate the proportion with low testosterone levels. When we compared our subjects to healthy older men of comparable age participating in the Massachusetts Aging Study and assayed in the same laboratory (23), fewer had low serum testosterone (48% at baseline, 20% at two months, and 9–12% at other time points). The pattern was similar for both total and free testosterone (Figure 2B). However, even after considering the effect of age, approximately 10% of the subjects had persistently and frankly low serum total testosterone at one and two years.

Relationship of Serum Gonadotropin and Serum Testosterone Levels

In order to address the pathogenesis of the decline in serum testosterone, we measured serum LH and FSH (Table 2). If low serum testosterone resulted from central suppression of the HPG axis, one would expect low LH and FSH levels. If a direct effect on the testis was the cause, LH and FSH levels should be elevated. Mean serum FSH and LH levels were lowest during the first month when serum testosterone was at its nadir, suggesting suppression of the HPG axis predominated at this point. FSH and LH increased significantly at 2 and 6 months. Although mean levels were well within the normal range at every point, the proportion of men with elevated levels increased progressively from 15% at baseline to 29% at 6 months. While this could suggest primary gonadal dysfunction, it is equally plausible that this pattern could represent recovery of the HPG axis. At 24 months, 14% of the men had elevated gonadotropins (Figure 3), comparable to the 18% and 10% with low total and free serum testosterone levels, suggesting that primary gonadal dysfunction may be the issue at later times. Total serum estradiol rose over time, likely because of the significant increase in SHBG, as percent free estradiol did not increase.

Contribution of Prednisone and CsA to Serum Testosterone Levels

Daily prednisone dose declined from 29±13 mg at baseline to 4±3 mg at 24 months (Table 2). Daily prednisone dose correlated inversely with total testosterone at two months ($r = -0.32$; $p=0.002$) and six months ($r = -0.27$; $p=0.006$), but to free testosterone only at two months ($r = -0.26$; $p=0.008$). CsA levels also declined significantly from 246±114 ng/dl at baseline to 195±93 at 24 months. CsA level was directly related to total ($r = +0.30$; $p=0.003$) and free testosterone ($r = +0.24$; $p=0.03$) at 12 months. By multiple regression analysis, daily prednisone dose ($r^2=0.07$ $p = 0.0004$) and SHBG ($r^2= 0.43$ $p <0.0001$) were the major determinants of total testosterone at all time points, while the major determinants of free testosterone were daily prednisone ($r^2= 0.11$ $p <0.0001$) and age ($r^2=0.12$ $p <0.0001$). The underlying illness (dilated vs. ischemic cardiomyopathy) did not influence serum testosterone at baseline or thereafter.

Relationship Between Serum Testosterone and BMD

All subjects were participants in a larger trial comparing effects of alendronate and calcitriol on rates of bone loss during the first year after heart transplantation (15). Neither age-adjusted total or free testosterone levels, nor estradiol differed over time by treatment group (alendronate versus calcitriol; p=0.78, p=0.47, and p=0.35 respectively). At one year, lumbar spine BMD declined by 0.7% in the alendronate group, 1.6% in the calcitriol group and 3.2% in the reference group. At the total hip, BMD declined by 1.5% in the alendronate group, 2.3% in the calcitriol group and 4.6% in the reference group. By multiple regression analysis, we found no relationship between rates of bone loss during the first year and serum total or free testosterone.

Discussion

In this study, the majority of men transplanted at our center between 1999 and 2001 had low serum total testosterone levels at some point during the first two years. This was most common and severe immediately after grafting and resolved by 6 months in most. As FSH and LH levels were also at their nadir then, low serum testosterone appeared to be due to central suppression of the HPG axis rather than to a direct testicular effect. Although recent major surgery likely influenced the baseline measures, prednisone was also a major contributor. We found no evidence of any adverse effect of CsA on serum testosterone. Although low serum testosterone has been associated with higher rates of post-transplant bone loss in older studies (4,5), we found no evidence of such an effect, probably because most were taking calcitriol or alendronate. This observation provides reassurance that both therapies are effective in preventing post-transplant bone loss regardless of gonadal status, and is consistent with another study that reported that alendronate increased BMD in men regardless of gonadal status (19). It is noteworthy that a substantial proportion of men had frankly low serum testosterone levels at one and two years. As hypogonadism is associated with troubling symptoms and decreased quality of life, our results suggest that long-term male heart transplant recipients should be evaluated for hypogonadism.

Our study lacked a control group of normal men and therefore we cannot ascertain whether hypogonadism was more common in our patients that in men of comparable age. Harman et al. (20) reported low serum testosterone levels, defined as < 325 ng/dl, in 12% and 19% of healthy men in their 50s and 60s respectively. Similarly, we found that 14–18% of heart transplant recipients still had low serum testosterone levels at one and two years. However, our lower normal limit was considerably lower (250 ng/dl), suggesting that biochemical hypogonadism may not be more common in men who have had a heart transplant than in normal men of the same age (18).

Serial gonadotropins suggest that the pathogenesis of low serum testosterone levels differ according to time post-transplantation. Immediately after transplantation, low testosterone was associated with normal or low gonadotropin levels in most, a pattern consistent with hypothalamic suppression rather than primary testicular dysfunction. Large doses of prednisone suppress the HPG axis (6,9–11), as does major surgery (6,8), (21). However, some men (14%) had elevated gonadotropins, consistent with another study that suggests that both primary and secondary hypogonadism can occur (7). By 2 and 6 months, there were significant increases in serum testosterone, FSH and LH, a pattern consistent with recovery of HPG function. Lower prednisone doses were probably a very significant factor in this recovery, since prednisone was a major determinant of both total and free testosterone at all times. At 1 and 2 years however, 14% and 18% respectivelyof the study population had low serum testosterone and 17% and 14% had elevated gonadotropins. This pattern is more likely to reflect primary gonadal dysfunction as the surgery was relatively distant and prednisone doses were much lower.

Our study provides some insight into whether CsA adversely affects gonadal or HPG function in humans. CsA directly inhibited testosterone biosynthesis in rat Leydig cells, as well as several adrenal enzymes involved in testosterone biosynthesis (14,22). However, another rodent study showed that CsA lowers serum testosterone levels by suppressing the HPGaxis and LHproduction (13). In contrast, we did not find an adverse effect of CsA on total or free testosterone levels, and in fact observed a positive relationship between whole blood trough CsA levels and testosterone at some points. Our results are thus consistent with findings from two smaller kidney transplant studies (23) (24) and suggest that CsA, at doses currently used in transplant regimens, does not adversely affect gonadal function. The positive association between CsA and serum testosterone at some points is intriguing, may even suggest a beneficial effect on gonadal function and deserves further evaluation.

In previous prospective longitudinal studies, we and others have found that low serum testosterone was related to higher rates of bone loss in men after cardiac transplantation (25,26). In this study, we did not detect such a relationship, likely because the men were receiving either calcitriol or alendronate for prevention of bone loss (15). Neither medication is known to affect sex hormone concentrations.

The high prevalence of men with low serum testosterone levels at one and two years post-transplantation, suggests that it is important to assess gonadal status in long-term heart transplant recipients. Unfortunately, the diagnosis of male hypogonadism is not straightforward. Symptoms (depression, decreased libido, erectile dysfunction, anemia, reduced muscle and bone mass) are nonspecific and overlap with other common ailments. Biochemical diagnosis is also difficult, as it is not clear which testosterone assay to use, whether total or free testosterone is more accurate, which lower limit of normal is most appropriate, and whether the diagnosis should be made in the context of age and health status.

There are few studies on testosterone replacement after cardiac transplantation. Steif et al. found testosterone replacement was associated with improvement of sexual function and mood in hypogonadal cardiac transplant recipients (26). In our opinion, treatment considerations should vary according to the proximity to transplantation. Our data suggest that therapy of hypogonadism that occurs shortly after transplantation is not required, as it is usually transient and not associated with rapid bone loss in patients on effective treatments for osteoporosis. In contrast, therapy should be considered for long-term cardiac transplant recipients with permanent hypogonadism, as they may have troubling symptoms that respond to testosterone therapy (improved sexual function and quality of life, increased lean body mass, decreased body fat). On the other hand, the potential risks of testosterone therapy, including the possibility of stimulating the growth of an occult prostate cancer and the potential for immune system modulation (27), are not trivial. In this regard, there is a recent case report of acute cardiac allograft rejection that developed after initiation of testosterone replacement therapy (28). Referral to an endocrinologist may be helpful, with regard to both diagnosis and treatment.

This study has several limitations. Availability of information on symptoms of hypogonadism would have more clearly defined the clinical relevance of the biochemical measurements. As pre-transplant serum testosterones were not available, it is possible that low serum testosterone levels might have antedated transplantation, as has been reported in men with congestive heart failure (29) (26). However, in our previous study, mean serum testosterone levels were normal prior to transplantation (489 ng/dl; nl, 300–1200), and only below normal at one month post-transplantation (19). Thus we believe it most likely that the low levels we observed in this study were a post-transplant phenomenon.

In summary, we found that low serum testosterone levels were most common and severe in the early post-transplant period. In the majority, low serum testosterone levels were associated with low FSH and LH, suggesting the mechanism was suppression of the HPG axis related to high prednisone doses and recent major surgery. Although serum testosterone levels normalized in the majority, they remained low in a substantial proportion of the study population at the one and two year points. As gonadotrophins were elevated at that time point, primary gonadal dysfunction was the more likely mechanism. We found no evidence that CsA adversely affected serum testosterone or gonadotropin levels or that serum testosterone influenced the response to osteoporosis therapy. The high prevalence of low serum testosterone observed at one and two years after heart transplantation, and the adverse effect of hypogonadism on health and quality of life, suggest that long-term male heart transplant recipients should be evaluated for hypogonadism. Further studies are needed to assess the clinical implications of low testosterone levels in cardiac transplant recipients and the risks and benefits of testosterone replacement.

Acknowledgments

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References

1. Muchmore JS, Cooper DK, Ye Y, Schlegel V, Pribil A, Zuhdi N. Prevention of loss of vertebral bone density in heart transplant patients. J Heart Lung Transplant 1992;11 (5):959. [PubMed: 1420245]
2. Muchmore JS, Cooper DK, Ye Y, Schlegel VT, Zuhdi N. Loss of vertebral bone density in heart transplant patients. Transplant Proc 1991;23 (1 Pt 2):1184. [PubMed: 1989181]
3. Ramirez G, Narvarte J, Bittle PA, Ayers-Chastain C, Dean SE. Cyclosporine-induced alterations in the hypothalamic hypophyseal gonadal axis in transplant patients. Nephron 1991;58 (1):27. [PubMed: 1906995]
4. Sambrook PN, Kelly PJ, Fontana D, et al. Mechanisms of rapid bone loss following cardiac transplantation. Osteoporos Int 1994;4 (5):273. [PubMed: 7812075]
5. Shane E, Rivas M, McMahon DJ, et al. Bone loss and turnover after cardiac transplantation. J Clin Endocrinol Metab 1997;82 (5):1497. [PubMed: 9141540]
6. Becker, KL. Principles and Practice of Endocrinology and Metabolism. 3. Philadelphia, PA: Lippincott Willimas & Wilkins; 2001.
7. Spratt DI, Bigos ST, Beitins I, Cox P, Longcope C, Orav J. Both hyper- and hypogonadotropic hypogonadism occur transiently in acute illness: bio- and immunoactive gonadotropins. J Clin Endocrinol Metab 1992;75 (6):1562. [PubMed: 1464665]
8. Woolf PD, Hamill RW, McDonald JV, Lee LA, Kelly M. Transient hypogonadotropic hypogonadism caused by critical illness. J Clin Endocrinol Metab 1985;60 (3):444. [PubMed: 3919042]
9. MacAdams MR, White RH, Chipps BE. Reduction of serum testosterone levels during chronic glucocorticoid therapy. Ann Intern Med 1986;104 (5):648. [PubMed: 3083749]
10. Ringstrom SJ, Schwartz NB. Cortisol suppresses the LH, but not the FSH, response to gonadotropin-releasing hormone after orchidectomy. Endocrinology 1985;116 (1):472. [PubMed: 3917253]
11. Ringstrom SJ, Schwartz NB. Differential effect of glucocorticoids on synthesis and secretion of luteinizing hormone (LH) and follicle stimulating hormone (FSH). J Steroid Biochem 1987;27 (1–3):625. [PubMed: 2826893]
12. Veldhuis JD, Lizarralde G, Iranmanesh A. Divergent effects of short term glucocorticoid excess on the gonadotropic and somatotropic axes in normal men. J Clin Endocrinol Metab 1992;74 (1):96. [PubMed: 1727834]

13. Sikka SC, Bhasin S, Coy DC, Koyle MA, Swerdloff RS, Rajfer J. Effects of cyclosporine on the hypothalamic-pituitary-gonadal axis in the male rat: mechanism of action. Endocrinology 1988;123 (2):1069. [PubMed: 3396498]
14. Seethalakshmi L, Flores C, Carboni AA, Bala R, Diamond DA, Menon M. Cyclosporine: its effects on testicular function and fertility in the prepubertal rat. J Androl 1990;11 (1):17. [PubMed: 2312396]
15. Shane E, Addesso V, Namerow PB, et al. Alendronate versus calcitriol for the prevention of bone loss after cardiac transplantation. N Engl J Med 2004;350 (8):767. [PubMed: 14973216]
16. Rosner W. Errors in the measurement of plasma free testosterone. J Clin Endocrinol Metab 1997;82 (6):2014. [PubMed: 9177424]
17. Sodergard R, Backstrom T, Shanbhag V, Carstensen H. Calculation of free and bound fractions of testosterone and estradiol-17 beta to human plasma proteins at body temperature. J Steroid Biochem 1982;16 (6):801. [PubMed: 7202083]
18. Mohr BA, Guay AT, O'Donnell AB, McKinlay JB. Normal, bound and nonbound testosterone levels in normally ageing men: results from the Massachusetts Male Ageing Study. Clin Endocrinol (Oxf) 2005;62 (1):64. [PubMed: 15638872]
19. Orwoll E, Ettinger M, Weiss S, et al. Alendronate for the treatment of osteoporosis in men. N Engl J Med 2000;343 (9):604. [PubMed: 10979796]
20. Harman SM, Metter EJ, Tobin JD, Pearson J, Blackman MR. Longitudinal effects of aging on serum total and free testosterone levels in healthy men. Baltimore Longitudinal Study of Aging. J Clin Endocrinol Metab 2001;86 (2):724. [PubMed: 11158037]
21. Spratt DI, Cox P, Orav J, Moloney J, Bigos T. Reproductive axis suppression in acute illness is related to disease severity. J Clin Endocrinol Metab 1993;76 (6):1548. [PubMed: 8501163]
22. Seethalakshmi L, Flores C, Malhotra RK, et al. The mechanism of cyclosporine's action in the inhibition of testosterone biosynthesis by rat Leydig cells in vitro. Transplantation 1992;53 (1): 190. [PubMed: 1310171]
23. Ishikawa A, Ushiyama T, Suzuki K, Fujita K. Serum testosterone levels after renal transplantation. Transplant Proc 1996;28 (3):1952. [PubMed: 8658958]
24. Samojlik E, Kirschner MA, Ribot S, Szmal E. Changes in the hypothalamic-pituitary-gonadal axis in men after cadaver kidney transplantation and cyclosporine therapy. J Androl 1992;13 (4):332. [PubMed: 1399835]
25. Stempfle HU, Werner C, Echtler S, et al. Prevention of osteoporosis after cardiac transplantation: a prospective, longitudinal, randomized, double-blind trial with calcitriol. Transplantation 1999;68 (4):523. [PubMed: 10480411]
26. Stief J, Gaertner R, Uberfuhr P, Theisen K, Stempfle HU. Post-transplantation hypogonadism: A reflection of sex steroids deficiency due to previous congestive heart failure or an immunosuppressive side effect? J Bone Miner Res 2004;19 (Suppl 1):S476.
27. Ansar Ahmed S, Penhale WJ, Talal N. Sex hormones, immune responses, and autoimmune diseases. Mechanisms of sex hormone action. Am J Pathol 1985;121 (3):531. [PubMed: 3907369]
28. Schofield RS, Hill JA, McGinn CJ, Aranda JM. Hormone therapy in men and risk of cardiac allograft rejection. J Heart Lung Transplant 2002;21 (4):493. [PubMed: 11927227]
29. Tappler B, Katz M. Pituitary-gonadal dysfunction in low-output cardiac failure. Clin Endocrinol (Oxf) 1979;10 (3):219. [PubMed: 455737]

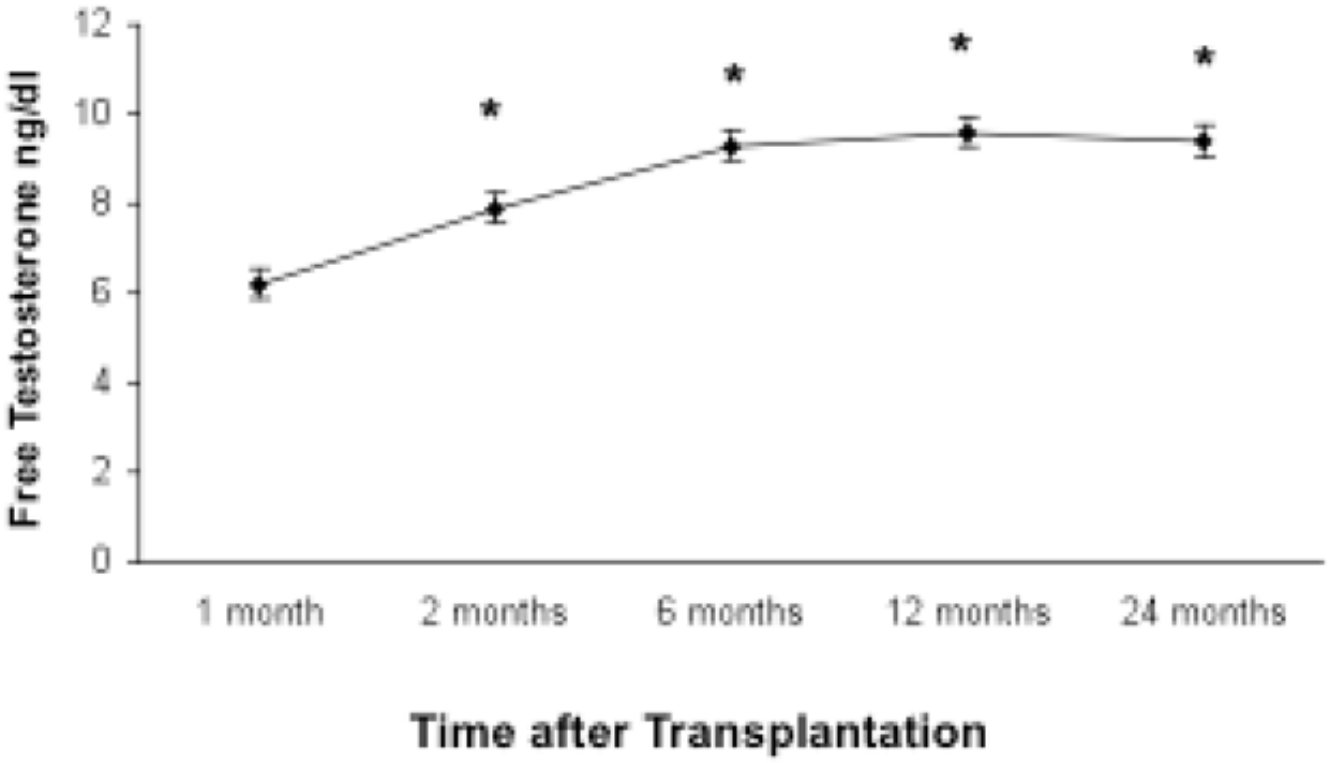

FIG 1.
Free testosterone following cardiac transplantation. * $p < 0.05$ compared to 1 month.

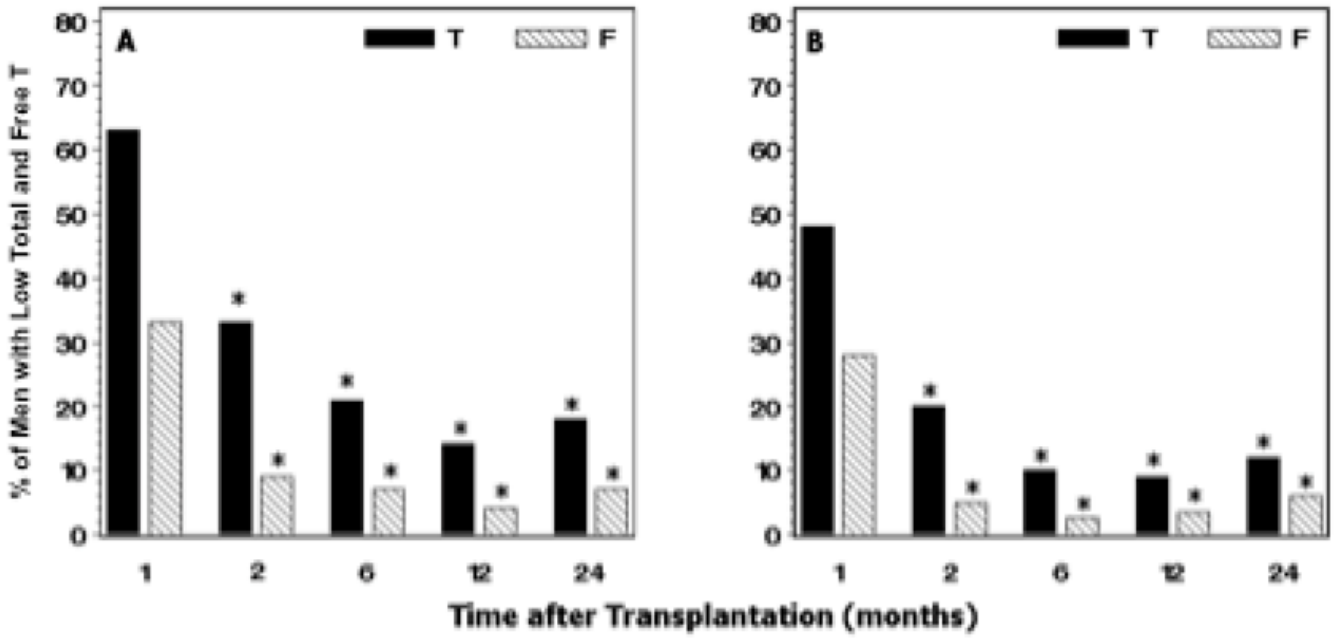

FIG 2.

Panel A: Percentage of men with low total (solid) and free (cross hatched) testosterone using laboratory normal values (lower limit of normal for total testosterone 250 ng/dl and free testosterone 5 ng/dl); Panel B: Percentage of men with low total (solid) and free (cross hatched) testosterone and using age adjusted normal values. Lower limit of normal for total testosterone 251, 216, 196 and 156 ng/dl and free testosterone 5.3, 4.2, 3.7, and 2.2 ng/dl for men in their 40s, 50s, 60s and 70s respectively (18). * $p < 0.05$ compared to 1 month.

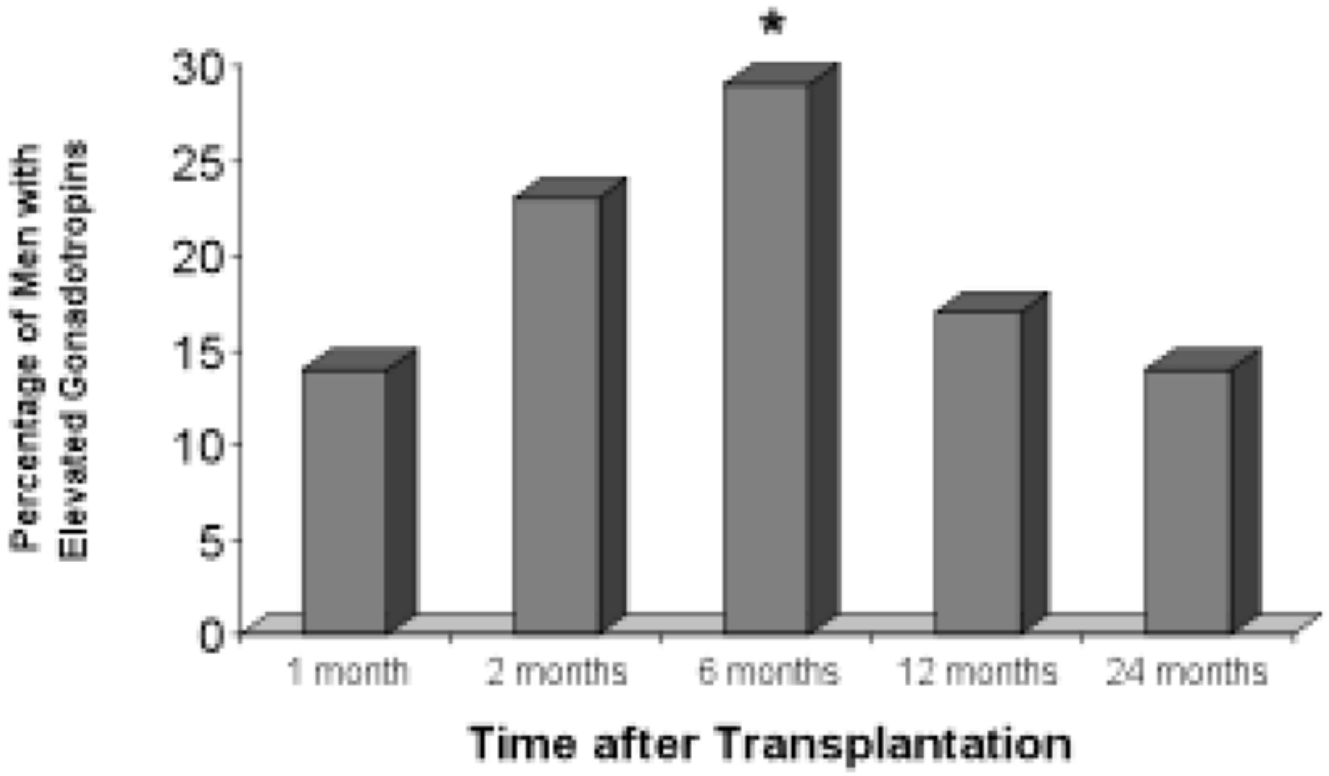

FIG 3.
Percentage of men with elevated gonadotrophins following cardiac transplantation. * p< 0.05 compared to 1 month.

Table 1

Baseline Characteristics of Study Subjects

	n	108
	Age (yrs)	54 ± 10
	BMI (kg/m^2)	25.4 ± 3.7
Ethnicity		
	Caucasian	76 (70%)
	African American	17 (16%)
	Hispanic	10 (9%)
	Asian	1 (1%)
	Other	4 (4%)
Diagnosis		
	Ischemic	64 (60%)
	Congenital	3 (3%)
	Valvular	7 (6%)
	Dilated	33 (31%)
	Hypertrophic	1 (1%)
	Days after Transplant (1 month)	22 ± 13

Table 2

Characteristics and biochemical measurements in 108 men followed for 2 years after cardiac transplantation.

Parameter	1 month	2 months	6 months	12 months	24 months
n	108	108	108	108	108
Age (yrs)	54 ± 10	55 ± 10	55 ± 10	55 ± 10	56 ± 10
BMI (kg/m^2)	25.4 ± 3.7	26.1 ± 3.7	27.7 ± 4.5*	28.3 ± 4.7*	28.5 ± 4.6*
Total Testosterone (250–1100 ng/dl)	257 ± 131	332 ± 154*	378 ± 143*	409 ± 152*	383 ± 166*
Free Testosterone (5–21 ng/dl)	6.2 ± 3	7.9 ± 3*	9.3 ± 3*	9.6 ± 3*	9.4 ± 4*
SHBG (20–70 nmol/L)	27 ± 12	29 ± 14	31 ± 13*	33 ± 13*	33 ± 14*
LH (0.8–7.6 mIU/ml)	4.5 ± 3.1	5.4 ± 3.7	6.3 ± 6.6*	5.4 ± 5.7	5.2 ± 7.7
FSH (0.7–11 mIU/ml)	4.2 ± 4.2	7.4 ± 6.9*	7.3± 7.3*	5.7 ± 7.9	5.2 ± 7.7
Estradiol (10–50 pg/ml)	27 ± 12	29 ± 14	38 ± 29*	40 ± 18*	37 ± 17*
Free Estradiol (%)	2.0 ± 0.3	1.8 ± 0.2*	1.8 ± 0.2*	1.7 ± 0.2*	1.7 ± 0.2*
Prednisone dose (mg/d)	29 ± 13	18 ± 8*	9 ± 6*	7 ± 6*	4 ± 3*
Cyclosporine dose (mg/d)	395 ± 128	403 ± 149	337 ± 158*	267 ± 161*	259 ± 111*
Cyclosporine level (ng/dl)	246 ± 114	301 ± 88*	255 ± 78	215 ± 84*	193 ± 93*
Serum creatinine (mg/dl)	1.4 ± 0.5	1.6 ± 0.5	1.8 ± 0.6*	1.8 ± 0.6*	1.6 ± 0.4*

Results are mean ± SD.

* $p < 0.05$ compared to the one month value.