## ORIGINAL RESEARCH—ENDOCRINOLOGY

# Subjective Sexual Response to Testosterone Replacement Therapy Based on Initial Serum Levels of Total Testosterone

Luis Reyes-Vallejo, MD, Stephen Lazarou, MD, and Abraham Morgentaler, MD

Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA

DOI: 10.1111/j.1743-6109.2006.00381.x

**ABSTRACT**

***Introduction.*** Testosterone replacement therapy (TRT) has been shown to be beneficial for men with hypogonadism. However, it is unknown how well hypogonadal men respond to TRT based on the severity of testosterone deficiency.

***Aim.*** To determine subjective sexual response rates to TRT based on initial serum testosterone values, with particular interest in men with low-normal levels of total testosterone (TT).

***Main Outcome Measures.*** Subjective responses to TRT in the domains of erectile dysfunction, libido, orgasm, and morning erections.

***Methods.*** A retrospective study was performed of 211 men with sexual symptoms of hypogonadism who underwent TRT. All men had either low values of TT (<300 ng/dL) or free testosterone (FT) (<1.5 ng/dL). The cohort was divided into three groups based on initial TT levels: Group 1: 0–200 ng/dL (N = 26; 12.3%); Group 2: 201–300 ng/dL (N = 64; 30.3%); Group 3: 301 ng/dL or greater (N = 121; 57.3%). Improvement in erectile function was determined prior to addition of any other treatment (e.g., phosphodiesterase type 5 inhibitors). The mean follow-up was 9 months (range 3–36 months).

***Results.*** The mean age was 55.2 years. Testosterone gel was used in approximately two-thirds of each group. Improvement in libido was reported in 61.5%, 96.6%, and 29.8% for Groups 1, 2, and 3, respectively ($P < 0.001$). Improvement in erectile function was noted in 46.2%, 45.3%, and 73.6% for Groups 1, 2, and 3, respectively ($P < 0.001$). At time of last follow-up, the percentage of men continuing with TRT was 73.1%, 57.8%, and 58.7% for Groups 1, 2, and 3, respectively ($P$ = nonsignificant).

***Conclusions.*** These preliminary data suggest that men with sexual symptoms of hypogonadism respond well to TRT across a wide range of initial TT values, including men with low-normal TT levels. These men may have low bioavailable levels of testosterone that are not re"ected in TT values. **Reyes-Vallejo L, Lazarou S, and Morgentaler A. Subjective sexual response to testosterone replacement therapy based on initial serum levels of total testosterone. J Sex Med 2007;4:1757–1762.**

***Key Words.*** Sex Steroid Replacement; Male Erectile Disorder; Primary Care Perspective in Treatment of Sexual Dysfunction

### Introduction

The benefits of testosterone replacement have been well established for the treatment of sexual symptoms in hypogonadal men [1–3]. Testosterone replacement therapy (TRT) has been shown to improve erectile quality, libido, and sexual thoughts and feelings [4–7]. Nonsexual symptoms have also shown improvement with TRT in hypogonadal men, including improved mood, muscle mass and strength, reduced fat mass and increased lean body mass, and improvement in bone mineral density [4,5,8,9].

Most of these studies have included only men with reduced values of total testosterone (TT), and have not distinguished response rates based on the severity of the testosterone deficiency. An unanswered question is whether, and to what

extent, a man with more severe hypogonadism is likely to respond to TRT compared with a man with a milder degree of testosterone deficiency. In addition, in clinical practice many men who present with symptoms suggestive of hypogonadism have TT levels that lie above the laboratory reference value indicating low testosterone. This population of men with borderline or low-normal testosterone has not undergone critical evaluation with regard to their potential to benefit symptomatically from TRT.

The diagnostic determination of hypogonadism is complicated in part by the biology of testosterone itself. A substantial proportion of testosterone circulates tightly bound to sex hormone-binding globulin (SHBG). This fraction is considered biologically inactive, yet remains an important contributor to the measurement of TT [10]. This relationship between testosterone and SHBG means that truly hypogonadal men with elevated levels of SHBG may have falsely normal TT levels, especially with aging, which is associated with higher SHBG levels [11].

For this reason, for many years we have routinely obtained the two testosterone assays available through our hospital laboratory, TT and free testosterone (FT). TRT is offered to men seen in our practice presenting with symptoms of hypogonadism if either TT or FT is low.

This study represents a retrospective review of subjective response rates to TRT from our clinical practice, based on initial TT values, and with particular interest in men with low-normal TT levels.

### Patients and Methods

This retrospective study investigated 211 men presenting with a chief complaint of erectile dysfunction, diminished libido, or both, and treated with TRT. The patient population consisted of all men in our clinical practice identified as having received TRT between 2001 and 2005 for whom complete subjective responses were available at follow-up. Men with a history of prostate cancer were excluded. All men had either low values of TT < 300 ng/dL (10.4 nm/L) or FT (<1.5 ng/dL) or clinical symptoms of hypogonadism. Baseline and follow-up blood tests were performed for TT, FT, estradiol (E2), luteinizing hormone (LH), prolactin (PRL), prostate-specific antigen (PSA), and hematocrit (Hct). TT was measured by a Roche electrochemiluminescence assay and FT was measured by Diagnostic Products Corp. radioimmunoassay.

**Table 1** Categorization of patient responses

| Variable | Description |
|---|---|
| Erectile dysfunction | |
| None | No erectile difficulty |
| Mild | Rigidity diminished without compromise of sexual ability |
| Moderate | Frequent difficulty achieving or maintaining an adequate erection for intercourse |
| Severe | Inadequate rigidity for intercourse on most occasions |
| Libido | |
| Normal | Normal sexual desire |
| Diminished | Sexual desire diminished but still present |
| Absent | Absent or rare sexual desire |
| Orgasm | |
| Normal | Normal experience of orgasm |
| Abnormal | Difficulty achieving orgasm or diminished intensity |
| Absent | Inability to achieve orgasm on most or all occasions |
| Morning erections | |
| Normal | Regular occurrence of morning/nocturnal erections |
| Diminished | Rare or absent morning/nocturnal erections |

The population was divided into three groups based on initial TT levels: Group 1: 0–200 ng/dL (0–6.9 nmol/L); Group 2: 201–300 ng/dL (6.9–10.40 nmol/L); Group 3: 301 ng/dL ( 10.43 nmol/L) or greater. Clinical response to TRT was based on chart documentation of patient responses to a standardized set of questions in the domains of erectile function, libido, morning erections, and orgasm.

The grading system for responses is detailed in Table 1. Erectile dysfunction was categorized as follows: None, if the patient did not report any erectile difficulty; Mild, if rigidity was diminished without compromise of sexual activity; Moderate, if there was frequent difficulty achieving or maintaining an adequate erection for intercourse; and Severe, if there was inadequate rigidity for intercourse on most occasions. Libido was categorized as Normal, Diminished, or Absent. Orgasm was categorized as Normal, Abnormal if there was difficulty achieving orgasm or if the intensity was diminished, or Absent if the individual was anorgasmic. Morning erections were categorized as Normal if they occurred regularly, and Diminished if they occurred rarely or not at all.

Symptomatic improvement in these four domains was assessed based on the patient s response to a structured set of monitoring questions. Improvement in erectile function was determined prior to addition of any other treatment (e.g., phosphodiesterase type 5 inhibitors).

Statistical analysis was performed using the Student s *t*-test or by paired and cross-tab Pearson chi-square analysis. A *P* value of less than 0.05 was

**Table 2** Demographic description and hormone baseline determination in the total population

| Variable | Value |
|---|---|
| Age (years), mean ± SD | 55.2 ± 9.7 |
| Baseline blood test results, mean ± SD | |
| PSA (ng/dL) | 1.4 ± 1.3 |
| TT (ng/dL) | 350.1 ± 159.4 |
| FT (ng/dL) | 1.14 ± 0.41 |
| Estradiol (pg/mL) | 26.0 ± 9.93 |
| LH (mIU/L) | 4.7 ± 4.36 |
| PRL (ng/mL) | 9.2 ± 8.33 |
| Hct (%) | 42.9 ± 5.22 |
| Associated comorbid conditions, N (%) | |
| Hypercholesterolemia | 66 (31.2) |
| Hypertension | 64 (30.3) |
| Diabetes mellitus | 22 (10.4) |
| Coronary artery disease | 10 (4.7) |
| Depression | 7 (3.3) |
| Other | 20 (9.4) |

considered statistically significant. Statistical analysis was performed using SPSS for Windows version 11.5.0 (Leadtools Technologies Inc. Charlotte, North Carolina).

## Results

A total of 211 men were evaluated with a mean age of 55.2 years (range 30–79 years). The mean follow-up was 9 months (range 3–36 months). Characteristics of the study population are shown in Table 2. One or more comorbidities were present in 138 men, with 81 having one condition, and 47 with two or more. The most common comorbidity was hypercholesterolemia (31.2%), followed by hypertension (30.3%), diabetes mellitus (10.4%), coronary artery disease (4.7%), and depression (3.3%).

The mode of testosterone therapy was transdermal gel in 137 men (64.9%), intramuscular injections of testosterone enanthate in 65 men (30.8%). Eight men used the testosterone patch (3.8%) and only one man (0.5%) used buccal testosterone.

The characteristics of the three study groups are shown in Table 3. There were 26 men in Group 1 (12.3%), 64 in Group 2 (30.3%), and 121 in Group 3 (57.3%). No difference in mean age was noted between the three groups ($P$ = nonsignificant), and there were no significant differences in initial mean blood test results between groups, except for TT levels. The proportion of men in each group using gel and injections were similar, with approximately two-thirds using gel.

Baseline symptoms did not differ between the three groups for any of the four areas we investigated (erectile function, libido, orgasm, morning erections) (Table 4). Ninety-four percent of men presented initially with some degree of erectile dysfunction. Nearly three-quarters of the total study (72.5%) population reported either diminished or absent libido. Approximately half of the study group noted a change in orgasm, consisting of either difficulty achieving one, or reduced intensity of the experience. Slightly more than half of the study group reported that morning erections occurred rarely or not at all.

With TRT there was a significant rise in TT from a mean of 350 ng/dL to 553 ng/dL. Significant increases were also seen for FT, PSA, and Hct, and a significant decline was observed for LH and follicle stimulating hormone (Table 5).

Treatment with TRT resulted in symptomatic benefit in over half the population for the domains of erectile function, orgasm, and libido, with the greatest positive response seen for improvement in orgasm (71.6%). Increased frequency of morning erections was noted in 46% overall.

Different patterns of response rates were noted between groups for specific symptoms (Figure 1). For erectile function, the greatest response rate was in Group 3, with 73.6% of men noting improvement, compared with 46.2% for Group 1 and 45.3% for Group 2 ($P < 0.01$). For libido, the

**Table 3** Baseline age and blood test results in the study groups (total N = 211)

| Variable | Group 1 (0–200) N = 26 (12.3%) Mean ± SD | Group 2 (201–300) N = 64 (30.3%) Mean ± SD | Group 3 (301+) N = 121 (57.3%) Mean ± SD | *P* |
|---|---|---|---|---|
| Age (years) | 55.3 ± 9.79 | 55.1 ± 9.14 | 55.2 ± 10.05 | 0.995 |
| PSA (ng/dL) | 1.0 ± 0.98 | 1.2 ± 1.04 | 1.6 ± 1.52 | 0.081 |
| TT (ng/dL) | 147.7 ± 40.90 | 253.9 ± 26.76 | 444.4 ± 144.8 | 0.001 |
| FT (ng/dL) | 0.73 ± 0.349 | 1.08 ± 0.272 | 1.2 ± 0.429 | 0.001 |
| Estradiol (pg/mL) | 21.3 ± 12.9 | 28.3 ± 10.78 | 26.7 ± 7.85 | 0.149 |
| LH (mIU/L) | 3.8 ± 3.08 | 4.4 ± 3.86 | 5.15 ± 4.81 | 0.321 |
| PRL (ng/mL) | 12.0 ± 16.5 | 7.5 ± 3.36 | 9.5 ± 7.37 | 0.084 |
| Hct (%) | 42.0 ± 3.23 | 42.7 ± 5.43 | 43.2 ± 5.57 | 0.673 |

**Table 4** Baseline symptoms in four sexual domains

| Variable | Total N (%) | Group 1 (0–200) N (%) | Group 2 (201–300) N (%) | Group 3 (301+) N (%) | *P* |
|---|---|---|---|---|---|
| Erectile dysfunction | 211 (100) | 26 (100) | 64 (100) | 121 (100) | 0.884 |
| Normal | 13 (6.2) | 3 (11.5) | 4 (6.3) | 6 (5.0) | |
| Mild | 46 (21.8) | 5 (19.2) | 15 (23.4) | 26 (21.5) | |
| Moderate | 85 (40.3) | 9 (34.6) | 24 (37.5) | 52 (43.0) | |
| Severe | 67 (31.8) | 9 (34.6) | 21 (32.8) | 37 (30.6) | |
| Orgasm | 211 (100) | 26 (100) | 64 (100) | 121 (100) | 0.805 |
| Present | 104 (49.3) | 12 (46.2) | 33 (51.6) | 59 (48.8) | |
| Diminished | 104 (49.3) | 13 (50.0) | 30 (46.9) | 61 (50.4) | |
| Absent | 3 (1.4) | 1 (3.8) | 1 (1.6) | 1 (0.8) | |
| Morning erections | 211 (100) | 26 (100) | 64 (100) | 121 (100) | 0.760 |
| Normal | 100 (47.4) | 14 (53.8) | 29 (45.3) | 57 (47.1) | |
| Diminished | 111 (52.6) | 12 (46.2) | 35 (54.7) | 64 (52.9) | |
| Libido | 211 (100) | 26 (100) | 64 (100) | 121 (100) | 0.423 |
| Present | 58 (27.5) | 6 (23.1) | 18 (28.1) | 34 (28.1) | |
| Diminished | 114 (54.0) | 17 (65.4) | 30 (46.9) | 67 (55.4) | |
| Absent | 39 (18.5) | 3 (11.5) | 16 (25.0) | 20 (16.5) | |

**Table 5** Mean test results before and after testosterone replacement therapy

| Variable | Initial | Follow-up | *P* |
|---|---|---|---|
| PSA (ng/dL) | 1.41 | 1.66 | 0.001 |
| TT (ng/dL) | 350.05 | 553.88 | 0.002 |
| FT (ng/dL) | 1.14 | 1.70 | 0.001 |
| Estradiol (pg/mL) | 24.52 | 26.89 | 0.038 |
| LH (mIU/L) | 4.25 | 3.17 | 0.026 |
| Hct (%) | 43.16 | 45.13 | 0.001 |

best results were obtained in Group 2, with 96.9% reported improvement, compared with 61.5% for Group 1 and only 29.8% for Group 3 ($P < 0.01$). Improvement in orgasm was more commonly reported in Group 2 and Group 3 (75–76%) compared with for Group 1 (42.3%, $P < 0.01$). The greatest increase in morning erections was noted in Group 2.

To investigate the effect of age on these results, each group was divided into two subgroups using the mean age of 55 years as a threshold. No statistically significant differences were noted for any comparisons.

Ten men developed erythrocytosis during treatment, requiring temporary discontinuation of treatment or dose reduction. Sixteen men had a rise in PSA of >1.0 ng/mL, and of these 13 underwent prostate biopsy. Cancer was found in a total of three men (1.4%), with one case occurring after 1 year, one after 2 years, and one after 3 years of treatment. Five men reported some degree of gynecomastia. No cases of edema were identified. Weight gain was not measured.

At time of last follow-up, the percentage of men continuing with TRT was 73.1%, 57.8%, and 58.7% for Groups 1, 2, and 3, respectively

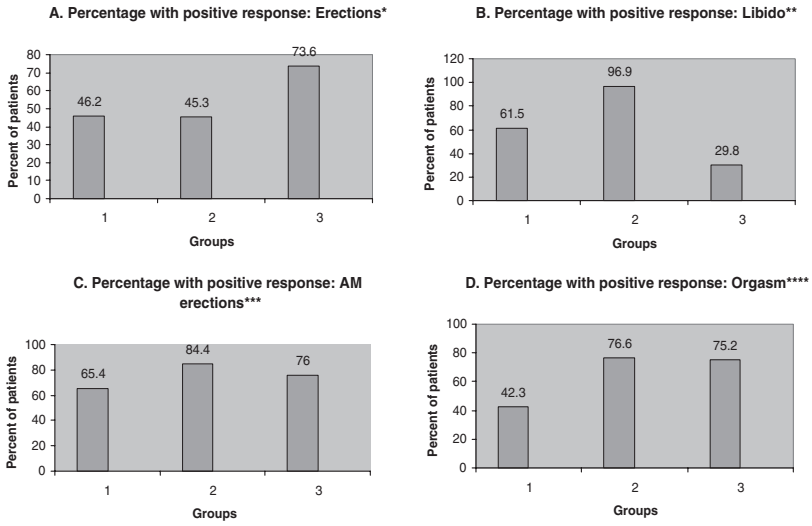


**Figure 1** Sexual response rates following testosterone replacement therapy. *All groups $P < 0.01$; Group 2 vs. Group 3 $P < 0.01$; Group 1 vs. Group 3 $P < 0.01$; all other comparisons nonsignificant (NS). **All groups $P < 0.01$; Group 1 vs. Group 2 $P < 0.01$; Group 1 vs. Group 3 $P < 0.01$; all other comparisons NS. ***All groups comparisons NS. ****All groups $P < 0.01$; Group 1 vs. Group 2, Group 2 vs. Group 3, and Group 1 vs. Group 3 all $P < 0.01$.

(*P* = nonsignificant). Reasons for discontinuation were not routinely captured in the medical records.

## Discussion

Multiple studies have demonstrated a benefit of TRT for sexual symptoms in hypogonadal men, including improvements in libido, sexual function, and erections [1–7]. Most of these studies have used strict biochemical criteria for inclusion, based on TT levels, and few investigations have examined differences in response rates among men with various degrees of testosterone deficiency. In this study, we investigated response rates following TRT among hypogonadal men with symptoms of sexual dysfunction, looking specifically at three groups: men with very low TT levels (<200 ng/dL), men with less severe reductions in TT (200–300 ng/dL), and men with low levels of FT but with TT levels in what is commonly considered the normal range (TT > 300 ng/dL).

The primary findings were benefits in the domains of erectile function, libido, orgasm, and morning erection for all three groups studied; however, there were differences in the pattern of response rates for different sexual domains based on initial TT values. For example, the highest positive response rate for erections was noted in men with TT > 300 ng/dL, whereas the most frequent improvement in libido occurred in men with TT 200–300 ng/dL. It was somewhat surprising that men with the lowest TT levels failed to demonstrate the greatest improvement in any domain. These results fail to adequately support the idea that different TT thresholds exist for sexual domains, although a larger and more rigorous study might be better able to explore this possibility.

Of considerable interest is that the group with TT levels greater than 300 ng/dL reported a high rate of improvement in several sexual domains. This group has generally been excluded from clinical trials as they appear biochemically normal when hypogonadism is defined by TT alone. This report provides data on this understudied population.

In a meta-analysis of 17 eligible placebo-controlled TRT trials, Isidori et al. [7] concluded that TRT improved nocturnal erections, sexual thoughts and motivation, erectile function. A greater response was seen in trials that included men with lower TT entry criteria. This observation was not supported by our results, but it should be noted that entry into the current study was based on low levels of FT even if TT was above 300 ng/dL, and these low levels of FT may have selected out a somewhat different population from those in the meta-analysis.

These results in men with normal TT may seem counterintuitive at face value, but it is well recognized that men with low levels of bioavailable testosterone may present with falsely normal TT levels due to high levels of SHBG. Levels of SHBG rise in older men [11], many of whom develop symptoms of hypogonadism. FT is believed to be a more accurate re"ection of bioavailable testosterone than TT [2], and all men in this study with TT > 300 ng/dL had low levels of FT. Although concerns exist regarding the value of clinically available FT assays such as the one used in this study, Vermeulen et al. has shown that this particular assay correlates strongly with the more rigorous equilibrium dialysis, with an *r* value of 0.94, although with lower reported values [10].

Although 94% of men in this study presented initially with symptoms that included erectile dysfunction, it bears noting how many of these men also reported additional sexual symptoms associated with hypogonadism. Nearly half described difficulty achieving orgasm or a sense of diminished orgasmic intensity, nearly three-quarters reported diminished libido, and morning erections were rare or absent in one-half. Hypogonadism thus appears to have multiple sexual manifestations in the majority of affected men. It is important to note that the study group represents a special population of men presenting to a urology practice with sexual dysfunction, and that these results may not be applicable to a broader population.

The sexual domain with the highest overall response to TRT was improvement in orgasm, in 71.6%. Erections improved in 61.6%, a value consistent with previous reports. For example, Greenstein et al. showed that 31 of 49 (63%) hypogonadal men noted improved erections with the use of TRT alone [12]. Wang et al. in an extension study of 163 men receiving testosterone gel up to 42 months noted significant improvement in sexual desire, activity, and satisfaction with erection that was maintained from the initial results at 6 months [6]. Entry criterion for all these men was a single TT determination of <300 ng/dL. Snyder et al. [13] also reported significant improvement in sexual function with TRT in a group of men selected for TT < 250 ng/dL, even though sexual function per se was not an entry criterion, and it is unknown how many of these men had no erectile dysfunction at baseline.

It is noteworthy that 65% of men in the study presented with one or more comorbidities. This

high figure is consistent with studies demonstrating an association between hypogonadism and other significant medical conditions, such as diabetes and the metabolic syndrome [14,15]. This frequency of vascular risk factors may also have contributed to the negative erectile dysfunction response to TRT in many men.

As a retrospective review of subjective clinical responses to treatment, this study has several important limitations. These include the lack of a control group, and the absence of objective measures. In addition, blood tests were obtained during regular clinic hours of 08:00–17:00, and a single blood test result was considered adequate for a diagnosis of hypogonadism. Therefore, these results should be considered as pilot data for further, more rigorous investigation. Nevertheless, these findings re" ect what is encountered in routine medical practice, and may thus be of practical interest to the clinician.

## Conclusions

Men with sexual symptoms of hypogonadism respond well to TRT across a wide range of initial TT values, including men with low-normal TT levels. These men may have low bioavailable levels of testosterone, which may be confirmed or suggested by additional testing.

**Corresponding Author:** Abraham Morgentaler, MD, One Brookline Place, Suite #624, Brookline, MA 02445, USA. Tel: +1-617-277-5000; Fax: +1-617-277-5444; E-mail: amorgent@caregroup.harvard.edu

*Con ict of Interest:* None declared.

### References

1 Morales A, Buvat J, Gooren LJ, Guay AT, Kaufman JM, Tan HM, Torres LO. Endocrine aspects of sexual dysfunction in men. J Sex Med 2004;1:69–81.
2 Morgentaler A. Testosterone replacement therapy: Benefits, risks, and controversies. Curr Sex Health Rep 2004;1:67–71.
3 Gruenewald D, Matsumoto A. Testosterone supplementation therapy for older men: Potential benefits and risks. J Am Geriatr Soc 2003;51:101–15.
4 Steidle C, Schwartz S, Jacoby K, Sebree T, Smith T, Bachand R, North American AA2500 T Gel Study Group. AA2500 testosterone gel normalizes androgen levels in aging males with improvements in body composition and sexual function. J Clin Endocrinol Metab 2003;88:2673–81.
5 Foresta C, Caretta N, Rossato M, Garolla A, Ferlin A. Role of androgens in erectile function. J Urol 2004;171:2358–62.
6 Wang C, Cunningham G, Dobs A, Iranmanesh A, Matsumoto AM, Snyder PJ, Weber T, Berman N, Hull L, Swerdloff RS. Long-term testosterone gel (AndroGel) treatment maintains beneficial effects on sexual function and mood, lean and fat mass, and bone mineral density in hypogonadal men. J Clin Endocrinol Metab 2004;89:2085–98.
7 Isidori AM, Giannetta E, Gianfrilli D, Greco EA, Bonifacio V, Aversa A, Isidori A, Fabbri A, Lenzi A. Effects of testosterone on sexual function in men: Results of a meta-analysis. Clin Endocrinol 2005; 63:381–94.
8 Page ST, Amory JK, Bowman FD, Anawalt BD, Matsumoto AM, Bremner WJ, Tenover JL. Exogenous testosterone (T) alone or with finasteride increases physical performance, grip strength, and lean body mass in older men with low serum T. J Clin Endocrinol Metab 2005; 90:1502–10.
9 Amory JK, Watts NB, Easley KA, Sutton PR, Anawalt BD, Matsumoto AM, Bremner WJ, Tenover JL. Exogenous testosterone or testosterone with finasteride increases bone mineral density in older men with low serum testosterone. J Clin Endocrinol Metab 2004;89:503–10.
10 Vermeulen A, Verdonck L, Kaufman J. A critical evaluation of simple methods for the estimation of free testosterone in serum. J Clin Endocrinol Metab 1999;84:3666–72.
11 Morley JE, Kaiser FE, Perry HM 3rd, Patrick P, Morley PM, Stauber PM, Vellas B, Baumgartner RN, Garry PJ. Longitudinal changes in testosterone, luteinizing hormone, and follicle-stimulating hormone in healthy older men. Metabolism 1997;46:410–3.
12 Greenstein A, Mabjeesh N, Sofer M, Kavier I, Matzkin H, Chen J. Does sildenafil combined with testosterone gel improve ED in hypogonadal men in whom testosterone supplement therapy alone failed? J Urol 2005;173:530–2.
13 Snyder PJ, Peachey H, Berlin JA, Hannoush P, Haddad G, Dlewati A, Santanna J, Loh L, Lenrow DA, Holmes JH, Kapoor SC, Atkinson LE, Strom BL. Effects of testosterone replacement in hypogonadal men. J Clin Endocrinol Metab 2000;85:2670–7.
14 Laaksonen DE, Niskanen L, Punnonen K, Nyyssonen K, Tuomainen TP, Valkonen VP, Salonen JT. The metabolic syndrome and smoking in relation to hypogonadism in middle-aged men: A prospective cohort study. J Clin Endocrinol Metab 2005;90:712–9.
15 Laaksonen DE, Niskanen L, Punnonen K, Nyyssonen K, Tuomainen TP, Valkonen VP, Salonen R, Salonen JT. Testosterone and sex hormone-binding globulin predict the metabolic syndrome and diabetes in middle-aged men. Diabetes Care 2004; 27:1036–41.