Original Article

Low Testosterone Levels in Patients with Mild Hypertension Recovered after Antidepressant Therapy in a Male Climacterium Clinic

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Recently, middle-aged men who have begun frequently complaining of erectile dysfunction and nonspecific symptoms similar to those of postmenopausal women, visited a male climacterium clinic in Japan. Some patients, who were already taking antihypertensive medication, discontinued or reduced their dosages of antihypertensive medication after anti-depressant therapy. Forty-nine males over the age of 40 years were studied to evaluate the relationships between blood pressure, mental stress, and testosterone levels. The systemic blood pressure (sBP) of 24 patients was higher than the criteria for mild hypertension: 140/90 mmHg (HT group) at first visit. The sBP of the other 25 patients was normal (N group). The international index of erectile function (IIEF5) score (normal >21), self-rating depression scale (SDS) score (normal <40), and plasma testosterone levels were also evaluated before and after anti-depressant therapy without androgen replacement therapy.There were no significant differences between the groups in IIEF5 or SDS scores. The plasma testosterone levels in the HT group at first visit were significantly lower than those in the N group (230±77 *vs.* 343±92 ng/dL, $p<0.001$). After treatment, the IIEF5 scores were unchanged, whereas SDS scores were lower in both groups. Mean systemic blood pressure (mBP) in the HT group significantly decreased from 112±7 to 94±7 mmHg after treatment, concomitant with the disappearance of nonspecific complaints and the increase of testosterone levels. In the N group, however, neither mBP nor testosterone levels changed. Psychotherapy can ameliorate mild systemic hypertension in climacteric men with low testosterone levels. Mental stress might suppress the hypothalamic-pituitary-gonadal axis to decrease testosterone levels. (*Hypertens Res* 2008; 31: 243–248)

***Key Words*: plasma testosterone level, erectile dysfunction, depression, hypertension**

Introduction

In contrast to women, men do not experience a sudden cessation of gonadal function such as occurs in menopause. However, there is a progressive reduction in hypothalamic-pituitary-gonadal (HPG) axis activity in aging men: testosterone levels decline. Such progressive HPG-axis hypofunctioning is thought to be responsible for some signs and symptoms that are common in elderly men, such as fatigue, reduced muscle and bone mass, sexual dysfunction, and depression. Testosterone replacement in men with age-related mild hypogonadism is not apparently effective in reversing these symptoms (*1*). Seidman already reported that many of the studies conducted thus far on the specific association between psychiatric symptoms, such as depression, and plasma testosterone levels have been methodologically flawed. Although hypogonadism is not central to major depressive disorder, HPG hypofunction may have an etiological importance in mild depressive conditions, such as dysthymia (*2*).

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One of the authors (F.I.) received financial support from Astellas Pharma Inc. and GlaxoSmithKline.

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Received July 10, 2007; Accepted in revised form September 2, 2007.

Table 1. Medical Treatment

Dose	Normal (n=25)		HT (n=24)	
	n (%)	Mean dose (mg)	n (%)	Mean dose (mg)
Sulpiride (100–150 mg)	21 (84)	119	22 (92)	125
Fluvoxamine (25–100 mg)	16 (64)	69	21 (88)	60
Paroxetine (10–20 mg)	1 (4)	10	4 (17)	12.5
Milnacipran (15–60 mg)	3 (12)	35	0 (0)	—
Alprazolam (0.4–0.8 mg)	14 (56)	0.57	10 (42)	0.56

Shores *et al*. reported that age-associated hypogonadism (testosterone deficit) occurs in 30% of men after the age of 55, and the 2-year incidence of diagnosed depresive illness was 21.7% in hypogonadal men *vs*. 7.1% in other men (*3*). Hypogonadal men showed an increased incidence of depressive illness and a shorter time to a diagnosis of depression.

Recently, erectile dysfunction (ED) and nonspecific complaints, such as insomnia, headache, vertigo, shoulder stiffness, palpitation, chest pain, hyperventilation, cold sweat, diarrhea, constipation, and cold constitution, have become very common among middle-aged men, as they are among postmenopausal women. To address this phenomenon, we set up a male climacterium clinic in Japan. The chief complaint of about 30% of the patients was ED, and they asked about the possibility and safety of taking medications such as sildenafil citrate or valdenafil hydrochloride. The other 70% of patients had nonspecific complaints, depression, and anxiety.

Ten of 100 patients in our clinic were already taking antihypertensive medication at the time of their first visit. After receiving psychiatric treatment, however, 6 of those 10 patients discontinued their antihypertensive medication, and the other 4 reduced their dosages.

This study focused on the specific association between systemic blood pressure (BP) and HPG axis activity in patients with psychiatric symptoms who visited a male climacterium clinic in Japan.

Methods

Subjects

We had 170 cases from April 2001 to November 2003 in a male climacterium clinic. The mean age of the patients was 52.5 years. There were two chief complaints: ED and menopausal symptoms, such as insomnia, headache, vertigo, palpitation, chest pain and hyperventilation. There were 48 cases that complained only of ED and requested sildenafil citrate. We excluded those patients from this study because their mental conditions were very good. There were 122 cases who complained of menopausal symptoms.

Of the remaining 122 patients, we selected 49 subjects above 40 years old for age matching. The criteria for enrolling patients in the study are: 1) Testosterone level was measured at first visit and 2) systemic BP was being tracked.

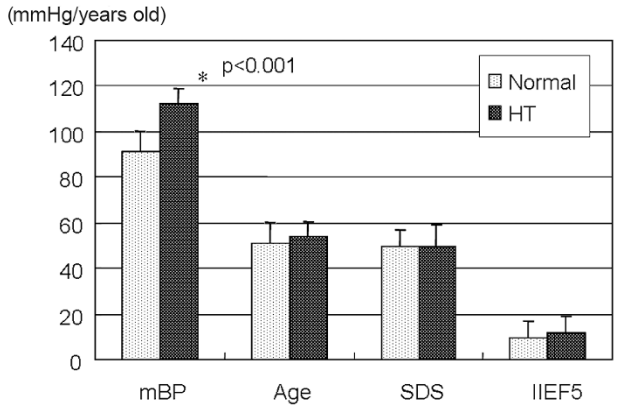

Fig. 1. *Background data at first visit. Not surprisingly, mean blood pressure of the HT group was significantly higher than that of the N group. However, there were no significant differences in age, SDS score, and IIEF5 between the groups.*

We employed the minimum BP at 5 min after bed rest. There were 25 cases with BP $<$140/90 mmHg at first visit, and those patients were defined as the N group. There were 24 cases with BP $\geq$140/90 mmHg at first visit, and those patients were defined as the HT group. In the HT group, there were 5 patients who were already taking antihypertensive medications; this did not change during this study.

According to Diagnostic and Statistical Manual of Mental-Disorder (DSM-IV), there were 15 patients in N and 13 in HT with a diagnosis of major depression.

Parameters

We measured systemic BP, self-rating depression scale (SDS) score (normal $<$40) (*4*), international index of erectile function (IIEF5) score (*5*), and plasma total or free testosterone levels during the first visit. Plasma total or free testosterone levels were measured by radioimmunoassay using commercially available kits (Dignostic Products, Los Angeles, USA).

About 3 months later, BP was measured again in all patients. The SDS and IIEF were also evaluated in 25 patients (N group: 12; HT group: 13), and plasma testosterone levels were measured in 32 patients (N group: 15; HT group: 17) about 3 months later.

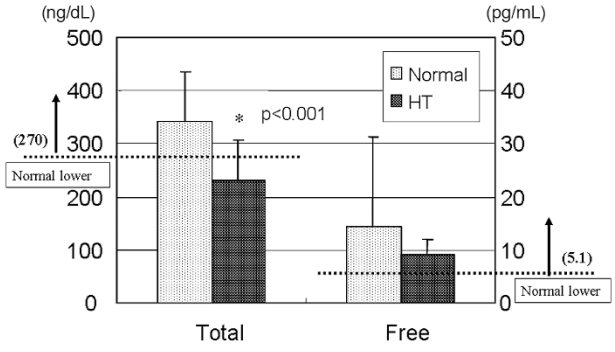

Fig. 2. *The plasma testosterone levels at first visit. In our institution, the normal lower level of total testosterone was 270 ng/dL and that of free testosterone was 5.1 pg/mL. Plasma total testosterone levels of the HT group were significantly lower than those of the N group. Also, plasma free testosterone levels of the HT group was lower than that of the N group, but the difference was not statistically significant.*

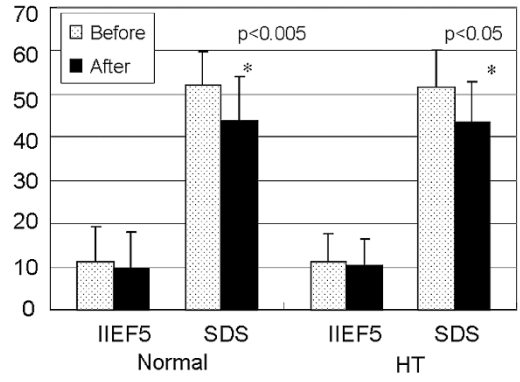

Fig. 3. *The changes in IIEF5 and SDS after treatment. IIEF5 did not change in either group. SDS score significantly decreased in both groups. The improvement in SDS score in both groups was almost the same.*

Medical Treatment

The counseling and autogenic training were very important treatments, so we always taught patients in autogenic training and allowed enough time to hear their clinical history and complaints. Basically, we prescribed 100 to 150 mg of sulpiride for almost all patients, and we added selective serotonin reuptake inhibitor (SSRI), such as fluvoxamine and paroxetine, or serotonin noradrenaline reuptake inhibitor (SNRI), such as milnacipran, depending on their complaints. We also prescribed alprazolam for patients with anxiety. There was no significant difference in medial treatments between the two groups by the χ^2 test, as shown in Table 1.

Statistical Analysis

Data represent means±SD. Interstage comparisons were performed using the paired Student's *t*-test. $p<0.05$ (two-sided) was considered statically significant for all comparisons.

Results

Background Data

Figure 1 shows the background data obtained at first visit. Not surprisingly, the mean BP (mBP) of the HT group was significantly higher than that of the N group (mBP: 91±9 *vs*. 112±7 mmHg; $p<0.001$). However, there were no significant differences in age, SDS score, and IIEF5 between the groups (age: N group, 51.3±8.2; HT group, 53.8±6.6; SDS: N group, 49.6±7.5; HT group: 49.8±9.2; IIEF5: N group, 9.4±7.1; HT group, 12.0±6.9).

Plasma Testosterone Levels at First Visit

Figure 2 shows the plasma testosterone levels at first visit. At our institution, the normal lower level of total testosterone was 270 ng/dL and that of free testosterone was 5.1 pg/mL, whose normal data was neither universal nor authorized. Plasma total testosterone levels of the HT group were significantly lower than those of the N group (230±77 *vs*. 343±92 ng/dL, $p<0.001$). Also, plasma free testosterone levels of HT were lower than those of N, but the difference was not statistically significant (9.2±2.7 *vs*. 14.4±17.0 pg/mL, $p=0.194$).

Changes in IIEF5 and SDS

Figure 3 shows the changes in IIEF5 and SDS after treatment. In both groups IIEF5 did not change (N: 11.1±8.2 to 9.5±8.5; HT: 11.2±6.2 to 10.1±6.3). However, SDS score significantly decreased in both groups (N: 52.1±7.6 to 43.8±10.3, $p<0.005$; HT: 51.4±8.6 to 43.5±9.3, $p<0.05$). The improvement in SDS score in both groups was almost the same. That is, the mental conditions of patients in both groups improved equally.

Changes in BP

Figure 4 shows the changes in BP in both groups after treatment. Systolic BP (sBP), diastolic BP (dBP), and mBP did not change after treatments in N (sBP: 121±13 to 118±11 mmHg; dBP: 76±8 to 74±7 mmHg; mBP: 91±9 to 89±8 mmHg). sBP, dBP, and mBP significantly decreased after treatment in HT (sBP: 154±10 to 127±9 mmHg; dBP: 91±8 to 77±6 mmHg; mBP: 112±7 to 94±7 mmHg; $p<0.001$).

Changes in Plasma Testosterone Levels

Figure 5 shows the changes in plasma testosterone levels after

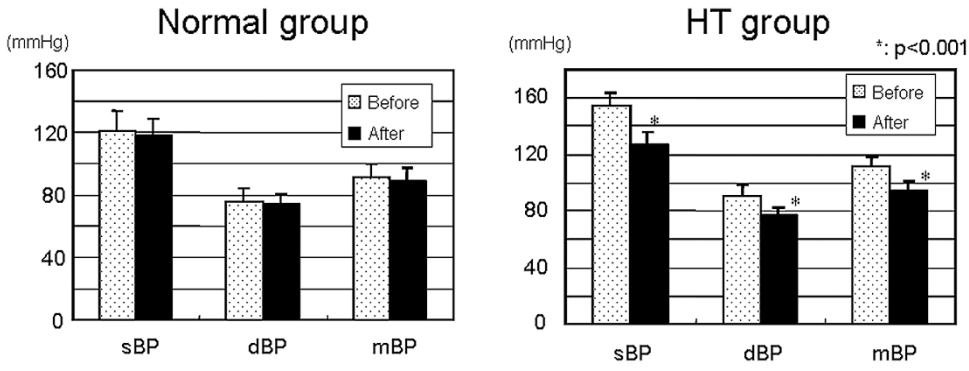

Fig. 4. *The changes in BP in both groups after treatment. Systolic (sBP), diastolic (dBP), and mean blood pressure (mBP) did not change after treatment in the N group, but significantly decreased after treatment in the HT group ($p < 0.001$).*

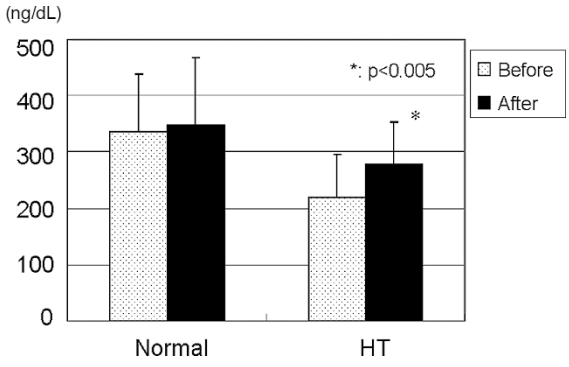

Fig. 5. *The change in plasma testosterone levels after treatment. Plasma total testosterone levels in the N group did not significantly change, but they significantly increased in the HT group ($p < 0.005$).*

treatment. Plasma total testosterone levels of the N group did not significantly change (335±103 to 349±118 ng/dL), whereas those of the HT group significantly increased (218±77 to 277±78 ng/dL, $p < 0.005$). In both groups, plasma free testosterone levels did not significantly change (N: 11.5±5.0 to 10.5±4.7 pg/mL; HT group: 9.4±2.9 to 10.1±2.3 pg/mL).

Discussion

In this study, almost all patients complained of self-referred men's andropause, which was the subject of a media campaign in Japan. T'Sjoen *et al*. reported that, after such a campaign in Belgium, 81 consecutive self-referred patients were evaluated, of whom only 7.1% were then diagnosed with "idiopathic" androgen deficiency in aged males (ADAM) (*6*). The majority of those patients presented with ED. In our study, many patients complained of depression, melancholy, and anxiety. According to DSM-IV, there were 28 patients with a diagnosis of major depression, and other patients were diagnosed with anxiety disorders or mood disorders out of 49 patients. So, the mean SDS score before treatment was about 50, because almost all patients, who would like to visit a male climacterium clinic in Japan, might suffer from mental problems. Also the mean score of IIEF5 before treatment was below 15, because almost all patients suffered from ED caused by mental stress. However, ED would not be a serious problem in those patients in Japan. So the mean score of IIEF5 after treatment did not change even if the mean SDS score after treatment improved significantly. This dissociation might be a unique feature within Japanese culture. Anyway, the mean SDS scores after treatment improved significantly in both groups after the anti-depressant therapy.

BP and Mental Stress

Many studies have reported a significant relationship between mental stress and hypertension (*7*). Markovitz *et al*. reported on the Framingham Study, which indicated that among middle-aged men, but not women, anxiety levels are predictive of later incidence of hypertension (*8*). Among patients with depression and anxiety, there were many patients with hypertension (*9*).

BP and Testosterone Levels

Jaffe *et al*. reported that testosterone and bioavailable testosterone levels were lower in hypertensive men and after stratification by age and body mass index, and that hypertensive men younger than 50 years with body mass index less than 30 kg/m^2 had significantly lower testosterone levels than the corresponding normotensive group (*10*). The most well-known cause of essential hypertension is mental stress. Also, mental stress is the most powerful cause of depression (*7*, *8*). Many papers reported that plasma testosterone levels were decreased in patients with major depression or mental stress. Christiansen *et al*. reported that there was a significant positive intersubjective relationship between the free testosterone from saliva samples and long-term plus concurrent somatic stress (*11*). Barrett-Connor *et al*. reported that the Beck

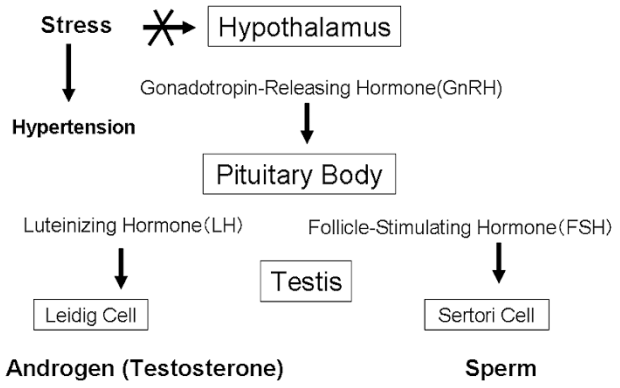

Fig. 6. *Secretion of testosterone: hypothalamic-pituitary-gonadal (HPG) axis. The hypothalamus is the most important portion to control many hormone levels and the autonomic nervous system, which also controls blood pressure. First, the hypothalamus secretes the gonadotropin-releasing hormone (GnRH), which stimulates the secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the pituitary gland. Luteinizing hormone (LH) also stimulates the secretion of testosterone from the testis. The hypothalamus is always exposed to mental or physical stress, and prolonged severe mental stress might suppress its function. As the result of mental stress, blood pressure might increase and plasma testosterone levels might decrease.*

Depression Inventory score was significantly and inversely associated with bioavailable testosterone, and that bioavailable testosterone levels were 17% lower for 25 men with categorically defined depression than the levels observed in all other men (*12*). Booth *et al*. reported that the relationship between testosterone and depression was inverse for men with below-average testosterone in a sample of 4,393 men, and that a parabolic model best fits the data (*13*). Schweiger *et al*. showed that, after adjustment for age only, daytime testosterone ($p<0.01$), nighttime testosterone ($p<0.05$), and 24-h mean testosterone secretion ($p<0.01$) were significantly lower in the depressed male inpatients (*14*).

Also, some papers suggested that psychological problems might induce hypogonadium and hypertension. Nilsson *et al*. reported that hypogonadal men showed a cluster of negative psychosocial variables and psychological as well as health-related problems along with higher pulse pressure than men with normal gonadal function (*15*). Theorell *et al*. also reported that total plasma testosterone (but not free testosterone) levels increased when strain diminished in sedentary work, but not in physically demanding work. Subjects with a family history of hypertension showed a greater decrease in testosterone levels than others when job strain increased (*16*).

Kaneda and Fujii reported that there was no significant difference in the mean levels of serum testosterone between patients diagnosed with depression and healthy subjects in the elderly (*17*). In the present study, we enrolled patients above 40 years old, but there were very few above 60. So hypogonadism and hypertension in middle-aged men might improve easily after the reduction of mental stress brought about by antidepressants.

Hypothesis of Low Testosterone Levels in Patients with Hypertension

Those previous reports indicate that mental stress could be a strong causal factor in hypertension and depression. The testosterone levels in patients with depression or hypertension are also lower than those in normal subjects. In our study, the testosterone levels in patients with hypertension are indeed lower than those in normotensive patients, even though the SDS scores in both groups are the same. Moreover, the testosterone levels in patients with hypertension increased concomitant with the improvement in SDS score after treatment. However, the testosterone levels in normotensive patients did not change after treatment. The scores of SDS and IIEF are very subjective, whereas BP is objective. So, BP could be a good index of the degree of mental stress when combined with SDS in patients with mental problems.

Figure 6 shows the mechanism of testosterone secretion and our hypothesis about this result. The figure shows the HPG axis. The hypothalamus is the most important portion to control many hormone levels and the autonomic nerve system, which also controls blood pressure. First, the hypothalamus secretes gonadotropin-releasing hormone (GnRH), which stimulates the secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the pituitary gland. Luteinizing hormone (LH) also stimulates the secretion of testosterone from the testis. The hypothalamus is always exposed to mental or physical stress. Prolonged severe mental stress might suppress the function of the hypothalamus. As a result of mental stress, BP might increase and plasma testosterone levels might decrease. This is our hypothesis. Exogenous testosterone, such as that in androgen replacement therapy, might induce further suppression of the HPG axis.

Limitations of the Present Study

In this study, we could not evaluate other hormones, such as the GnRH or LH. So, we could not explain our hypothesis clearly. However, anti-depressant therapy and counseling were very effective therapies for reducing systemic BP in middle-aged patients with hypertension who visited a male climacterium clinic. Testosterone level might be a good indicator of the degree of mental stress in middle-aged men.

Some lipid-lowering drugs were reported to affect plasma testosterone levels, so we did not change those medications during this study.

Clinical Implications

From our data, the mild hypertension in the patients with mood disorder could be controlled by using anti-depressants, such as fluvoxamine or paroxetine, without androgen replacement therapy. The monitoring of BP and plasma testosterone levels could be useful during treatment for depression or anxiety in middle-aged men.

Conclusion

Psychotherapy ameliorated systemic BP in patients with male menopause whose testosterone levels were relatively low. Mental stress caused by depression or anxiety might decrease testosterone levels during male menopause

References

1. Seidman SN: The aging male: androgens, erectile dysfunction, and depression. *J Clin Psychiatry* 2003; **64**: 31–37.
2. Seidman SN: Testosterone deficiency and mood in aging men: pathogenic and therapeutic interactions. *World J Biol Psychiatry* 2003; **4**: 14–20.
3. Shores MM, Sloan KL, Matsumoto AM, Moceri VM, Felker B, Kivlahan DR: Increased incidence of diagnosed depressive illness in hypogonadal older men. *Arch Gen Psychiatry* 2004; **61**: 162–167.
4. Zung WW: A self-rating depression scale. *Arch Gen Psychiatry* 1965; **12**: 63–70.
5. Rosen RC, Riley A, Wagner G, Osterloh IH, Kirkpatrick J, Mishra A: The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. *Urology* 1997; **49**: 822–830.
6. T'Sjoen G, Feyen E, De Kuyper P, Comhaire F, Kaufman JM: Self-referred patients in an aging male clinic: much more than androgen deficiency alone. *Aging Male* 2003; **6**: 157–165.
7. Yan LL, Liu K, Matthews KA, Daviglus ML, Ferguson TF, Kiefe CI: Psychosocial factors and risk of hypertension: the Coronary Artery Risk Development in Young Adults (CARDIA) study. *JAMA* 2003; **290**: 2138–2148.
8. Markovitz JH, Matthews KA, Kannel WB: Pychological predictors of hypertension in the Framingham Study. Is there tension in hypertension. *JAMA* 1993; **270**: 2439–2443.
9. Rabkin JG, Charles E, Kass F: Hypertension and DSM-III depression in psychiatric outpatients. *Am J Psychiatry* 1983; **140**: 1072–1074.
10. Jaffe A, Chen Y, Kisch ES, Fischel B, Alon M, Stern N: Erectile dysfunction in hypertensive subjects. Assessment of potential determinants. *Hypertension* 1996; **28**: 859–862.
11. Christiansen K, Knussmann R, Couwenbergs C: Sex hormones and stress in the human male. *Horm Behav* 1985; **19**: 426–440.
12. Barrett-Connor E, Von Muhlen DG, Kritz-Silverstein D: Bioavailable testosterone and depressed mood in older men: the Rancho Bernardo Study. *J Clin Endocrinol Metab* 1999; **84**: 573–577.
13. Booth A, Johnson DR, Granger DA: Testosterone and men's depression: the role of social behavior. *J Health Soc Behav* 1999; **40**: 130–140.
14. Schweiger U, Deuschle M, Weber B, *et al*: Testosterone, gonadotropin, and cortisol secretion in male patients with major depression. *Psychosom Med* 1999; **61**: 292–296.
15. Nilsson PM, Moller L, Solstad K: Adverse effects of psychosocial stress on gonadal function and insulin levels in middle-aged males. *J Intern Med* 1995; **237**: 479–486.
16. Theorell T, Karasek RA, Eneroth P: Job strain variations in relation to plasma testosterone fluctuations in working men—a longitudinal study. *J Intern Med* 1990; **227**: 31–36.
17. Kaneda Y, Fujii A: No relationship between testosterone levels and depressive symptoms in aging men. *Eur Psychiatry* 2002; **17**: 411–413.