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Hormone Profiles after Intramuscular Injection of Testosterone Enanthate in Patients with Hypogonadism

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Abstract. To examine hormone levels after androgen replacement therapy (ART) in Japanese male patients with hypogonadism, nine Japanese male patients with hypogonadism (serum total testosterone (tT) or free testosterone (fT) levels of ≤2.7 ng/mL or ≤10 pg/mL, respectively; average age, 59 years) were enrolled. They were treated with 125 mg of testosterone enanthate by single intramuscular injection. Blood samples were collected on the morning of the day of treatment, pre-ART, as well as on days 1 to 7 and day 14 after administration. Serum levels of tT, fT, estradiol (E2), follicle-stimulating hormone (FSH), luteinizing hormone (LH), and sex hormone-binding globulin (SHBG) were determined. On day 1 after administration, the mean serum levels of tT and fT were 7.62 ng/mL and 23.22 pg/mL, respectively. Serum levels of tT and fT on day 14 after administration were lower than their pre-ART values. One patient exhibited abnormally high serum tT and fT levels of 19.6 ng/mL and 44.4 pg/mL, respectively. Serum levels of LH and FSH began to decrease gradually on day 5 after administration. Serum levels of SHBG did not change throughout the observation period. Serum levels of E2 increased 1.7 times on day 1 after administration but returned to its pre-ART value by day 14 after administration. The dose of testosterone enanthate for male patients with hypogonadism requiring ART should be determined carefully because some patients exhibited high serum levels of androgen beyond the physiological range and gonadotropin was suppressed in all treated patients.

Key words: Hypogonadism, Androgen replacement therapy, Endocrine kinetics, Testosterone enanthate, PADAM
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HYPOGONADISM is a clinical condition in which low serum total testosterone (tT) levels are associated with specified clinical signs and symptoms, including decreased libido, reduced vitality, erectile dysfunction, reduced muscle mass, decreased bone density, anemia, and depression. These clinical manifestations reduce the quality of life of andropausal men, hence, androgen replacement therapy (ART) in patients with hypogonadism is an important measure to sustain their well-being.

In recent years, oral, injectable, transdermal, or other forms of drugs are available as the means to conduct ART [1]. In Japan, however, transdermal patches or gels of testosterone are still not available for ART, and to date intramuscular (IM)-ART is the only approved treatment for hypogonadism. Therefore, more data is needed on endocrine kinetics after IM-ART.

In the present study, we investigated hormone profiles after ART in patients with hypogonadism. We also examined hormone profiles after IM-ART, their relationship with the route of testosterone administration, and adverse events provoked by IM-ART.

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Patients and Methods

The cutoff values for serum testosterone levels in diagnosing hypogonadism differ among institutions and

research groups. For example, the International Society for the Study of the Aging Male (ISSAM) regards a serum tT level of <3.17 ng/mL as indicating hypogonadism [2]. In the present study, we regarded a serum tT level of ≤2.7 ng/mL or a serum free testosterone (fT) level of ≤10 pg/mL as indicating hypogonadism.

Nine Japanese male patients (average age, 59 years) with hypogonadism were selected out of those who visited our partial androgen deficiency of the aging male (PADAM) clinics. Informed consent was obtained from all the patients. Obvious prostate cancer was ruled out by determining the serum prostate-specific antigen (PSA) level of the patient or by performing transrectal ultrasonographic examination. Each patient received a single intramuscular dose (125 mg) of testosterone enanthate. Blood samples were collected from each patient at the following time points: morning (8 to 10 a.m.) of the day of treatment, pre-ART; days 1 to 7 after administration; and day 14 after administration. The protocol for the present site investigation was approved by the Ethics Committees at the hospitals where the present study was conducted.

Serum levels of hormones were determined with the following kits or by the following procedure: for tT, fT and estradiol (E2), a DPC kit (Diagnostic Products Corporation, US); for follicle-stimulating hormone (FSH) and luteinizing hormone (LH), a SPAC-S kit (SRL, Japan); and for sex hormone-binding globulin (SHBG), immunoradiometric assay. Serum levels of tT, fT, LH, FSH, SHBG, and E2 in Japanese healthy men, which were determined at Mitsubishi Kagaku Bio-Clinical Laboratories, Inc., Japan, ranged from 2.7 to 10.7 ng/mL, from 14 to 40 pg/mL, from 1.1 to 8.8 mIU/mL ± 2 SDs, from 1.8 to 13.6 mIU/mL ± 2 SDs, and from 9.87 to 55.8 pg/mL, respectively.

Table 1 indicates patient characteristics. The chief complaints varied from patient to patient. Performance status, as evaluated using the SF36 v2™ (Japanese version), was poor overall, ranging from 10 to 60 points. The abbreviated version of the International Index of Erectile Function Questionnaire, which includes five questions regarding sexual function (IIEF5: the minimum and maximum total scores of 0 and 25 points, respectively), indicated ≤21 points in all the patients [3]. Overall, patients showed strong depression and anxiety as evaluated by the Hospital Anxiety and Depression (HAD) scale [4]. The ADAM (Androgen Deficiency in Aging Males) scores were positive in all the patients [5].

Table 1. Patient characteristics

Patient No.	Age (years)	Chief complaint (other complaints)	BMI	Performance status[a] (SF36)	IIEF5[b]	HAD scales[c]		ADAM score
						Depression	Anxiety	
1	52	Dizziness, hot flush, neck stiffness (numbness, chills)	23.7	60.0	15	8	14	Positive
2	59	Insomnia, lack of concentration (palpitation, decreased libido)	22.7	30.0	20	3	6	Positive
3	59	Neck stiffness, irritation (headache)	22.3	50.0	1	8	5	Positive
4	51	Lack of concentration, irritation (dizziness, insomnia)	22.9	30.0	12	10	7	Positive
5	58	Sudoresis, palpitation (lack of concentration)	23.6	45.0	13	10	8	Positive
6	67	Inertia, decreased libido	29.4	10.0	1	16	9	Positive
7	64	Amnesia, neck stiffness	17.0	55.0	14	4	6	Positive
8	55	Tinnitus, palpitation (lack of concentration, irritation)	23.4	35.0	13	19	17	Positive
9	66	Erectile dysfunction	26.0	50.0	7	3	6	Positive

[a] Scores of performance status (SF36) are raw data without age matching.
[b] Scores of IIEF5 in patients with erectile dysfunction are ≤21 points.
[c] Scores of the HAD scale in patients with anxiety and depression are 8 points.

Results

Serum levels of tT were 2.56 ± 0.69 ng/mL before ART, increased significantly after administration, peaked (7.62 ± 4.47 ng/mL) on day 1 after administration and remained within the normal range on days 2 to 5 after administration (Fig. 1A). Thereafter, serum levels of tT decreased gradually to drop below its pre-ART value by day 14 after administration (2.51 ± 0.78 ng/mL).

Profiles of serum fT levels (Fig. 1B) were similar to those described above for serum tT levels. Namely, serum levels of fT were 7.63 ± 1.14 pg/mL before ART, increased significantly to 23.22 ± 9.72 pg/mL on day 1 after administration, and remained in a range of 21.10 to 23.22 pg/mL above the upper limit of the normal range. Furthermore, we examined the profiles of serum fT levels on an individual basis. Serum levels of fT exceeded the upper limit of the normal range (19.0 pg/mL) in 6 of the 9 patients (Fig. 2). One patient exhibited an increase in serum fT levels which reached up to 44.4 pg/mL at 3 days after administration. This patient did not present any underlying disorder or en-

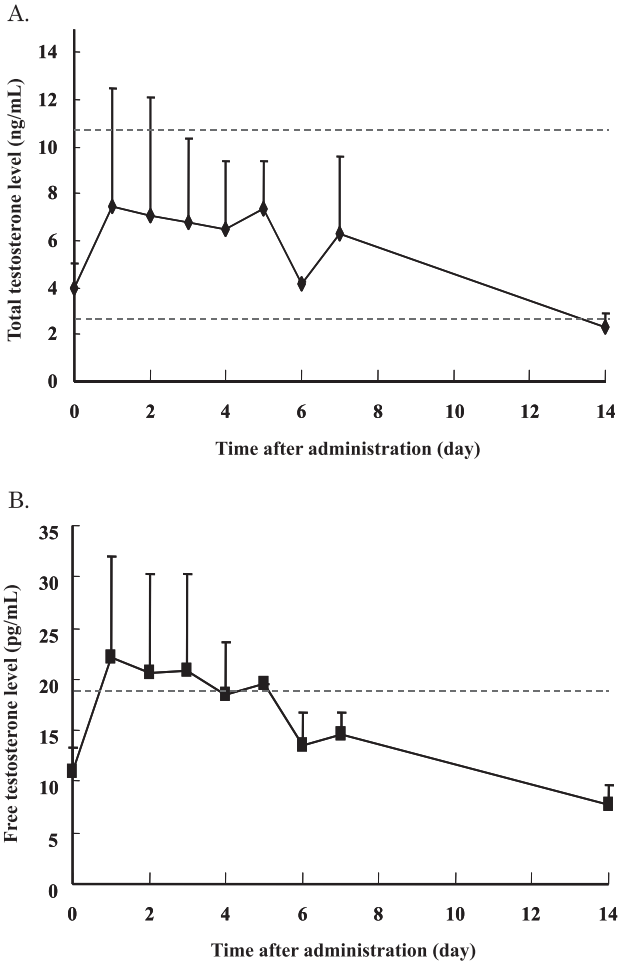

Fig. 1. (A) Serum levels of total testosterone before (day 0) and after administration in nine Japanese male patients with hypogonadism. Values are shown as the mean ± SD. The dotted lines represent the upper and lower limits of serum total testosterone levels. (B) Serum levels of free testosterone before (day 0) and after administration in nine Japanese male patients with hypogonadism. Values are shown as the mean ± SD. The dotted line represents the upper limit of serum free testosterone levels.

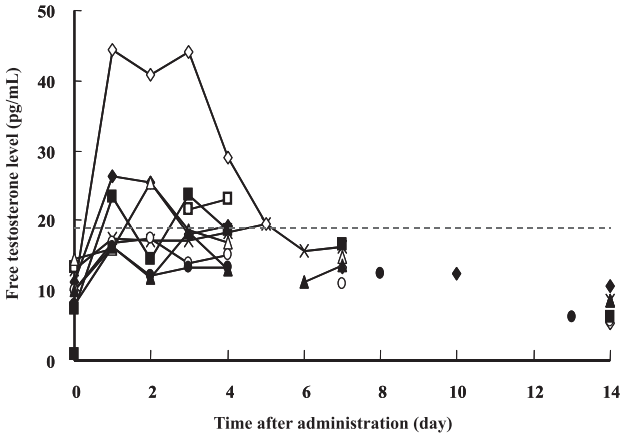

Fig. 2. Individual profiles of serum free testosterone levels before (day 0) and after administration in nine Japanese male patients with hypogonadism. The dotted line represents the upper limit of serum free testosterone levels.

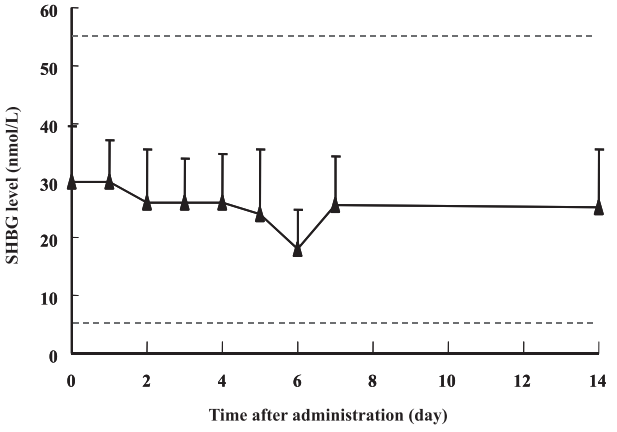

Fig. 3. Serum levels of SHBG before (day 0) and after administration in nine Japanese male patients with hypogonadism. Values are shown as the mean ± SD. The dotted lines represent the upper and lower limits of serum SHBG levels.

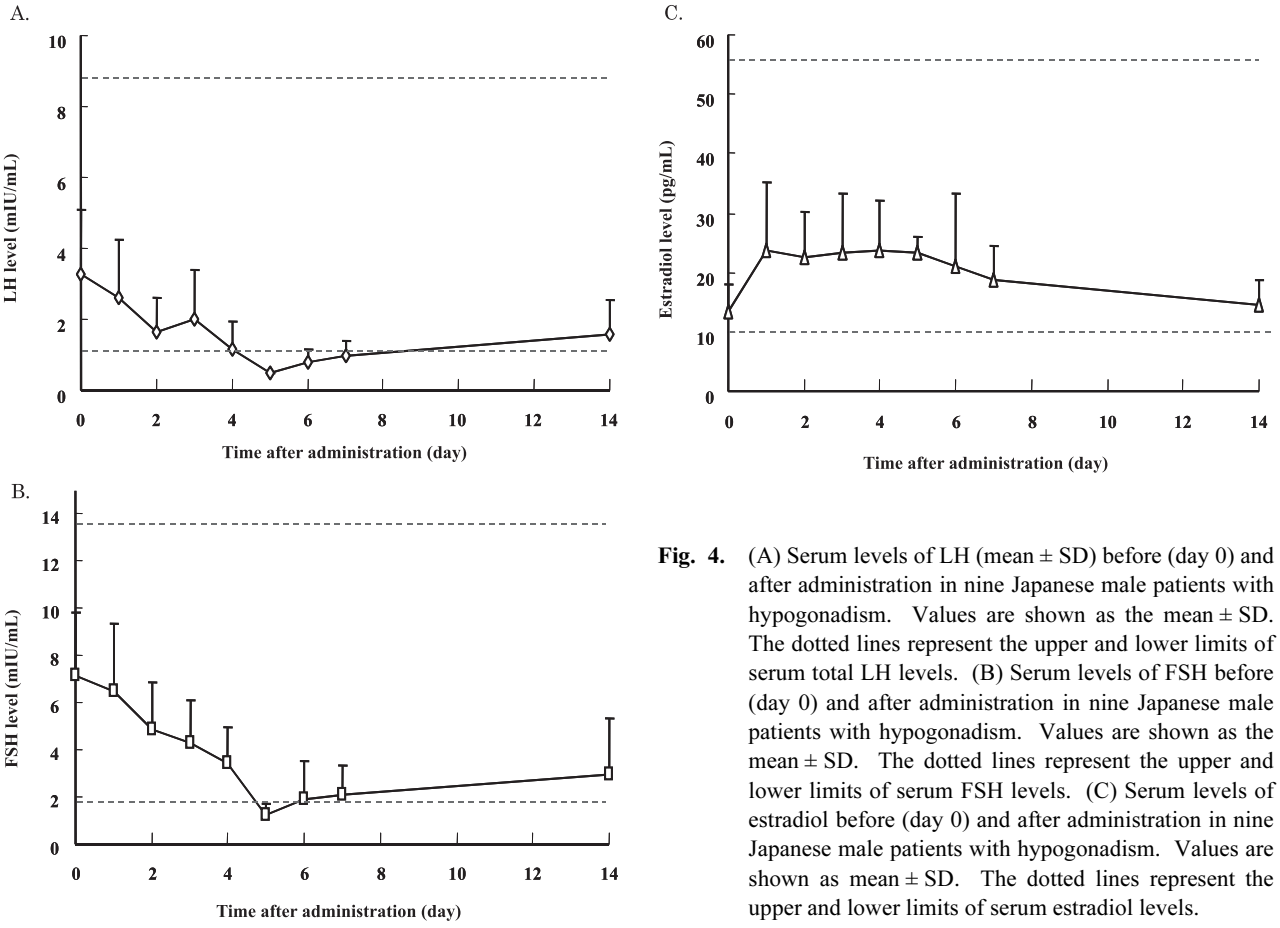

Fig. 4. (A) Serum levels of LH (mean ± SD) before (day 0) and after administration in nine Japanese male patients with hypogonadism. Values are shown as the mean ± SD. The dotted lines represent the upper and lower limits of serum total LH levels. (B) Serum levels of FSH before (day 0) and after administration in nine Japanese male patients with hypogonadism. Values are shown as the mean ± SD. The dotted lines represent the upper and lower limits of serum FSH levels. (C) Serum levels of estradiol before (day 0) and after administration in nine Japanese male patients with hypogonadism. Values are shown as mean ± SD. The dotted lines represent the upper and lower limits of serum estradiol levels.

docrinopathy other than hypogonadism. A comparison of this patient with others revealed no significant difference in serum fT, tT, LH, or FSH levels before IM-ART.

No significant change was found in serum SHBG levels after administration in any of the patients (Fig. 3).

Serum levels of FSH and LH decreased significantly after administration. The lowest serum levels of FSH and LH were observed on day 5 after administration. In the case that serum levels of tT decreased even once, serum levels of LH and FSH failed to recover by day 14 after administration (Figs. 4A and B).

Serum levels of E2 increased slightly subsequent to the day of treatment, remained high for several days, and then decreased gradually (Fig. 4C).

Discussion

The present study revealed hormone profiles after IM-ART in nine Japanese male patients with hypogonadism. To our knowledge this is the first study on IM-ART to be conducted in Japan. Serum levels of tT and fT peaked on day 1 after the intramuscular injection of 125 mg of testosterone enanthate. It is noteworthy that serum levels of fT exceeded the upper limit of the normal range in 6 (67%) of the 9 patients, and that these high levels of serum fT are characteristic of IM-ART [6].

On the other hand, transdermal-ART gels (Andro-Gel™, Testim™, and Androderm™) are reported to increase serum fT levels to reach the normal range within one hour after administration and maintain them within that range thereafter. Testosterone gels (Andro-Gel™ and Testim™), which are applied to the patient's body surface every day, maintain serum levels of tT and fT within the normal range [7, 8] and also maintain serum FSH and LH at a constant level.

However, the only ART which is currently approved in Japan is intramuscular testosterone enanthate. This modality fails to maintain serum levels of tT and fT within the normal range. Therefore, LH and FSH are mark-

edly suppressed by negative feedback regulation after the intramuscular injection of testosterone enanthate.

The autosecretion of testosterone was anticipated to be further suppressed by this negative feedback regulation. In fact, the present study confirmed serum levels of tT which were lower than their pre-ART values levels on day 14 after administration. Therefore, the further decrease in serum tT levels on day 14 after administration is considered to relapse symptoms of hypogonadism and to reduce the patient's quality of life. Snyder and Lawrence. conducted IM-ART to examine hormone profiles in patients with hypogonadism according to the following regimens: 1) 100 mg every week; 2) 200 mg biweekly; 3) 300 mg every three weeks; and 4) 400 mg every four weeks. Regimens 1) and 2) markedly suppressed FSH and LH, while regimen 4) did not [6]. The abovementioned suppression of FSH and LH is presumed to occur if testosterone enanthate were injected multiple times according to the IM-ART regimen in the present study.

Furthermore, since IM-ART with low-dose testosterone enanthate in the present study provoked abnormally high serum levels of fT, it elicited concern about the possible development of adverse reactions of the drug, *i.e.*, polycythemia, an increase in serum PSA level, urinary retention, gynecomastia, and sleep apnea [9–11]. Also, prostate cancer is an important risk factor of ART for men in their prime.

The status of high serum testosterone levels provokes polycythemia, a disease associated with serum levels of physiologically active testosterone and which is observed more frequently in patients receiving testosterone by intramuscular injection than in patients receiving testosterone by means of gels and patches [12]. ART is beneficial in patients with anemia because the modality increases hematocrit but possibly increases the risk of provoking thrombotic disorders, *e.g.*, myocardial, cerebral, and pulmonary infarctions, as well as embolism in patients without anemia.

The progression of benign prostatic hypertrophy is well known to be androgen-dependent. No evident causality is considered to be present between prostate volume and urinary symptoms. However, caution should be exercised in administering androgen to the patient who complains of urinary symptoms which are clearly attributable to increased prostate volume [12].

Although the relationship between ART and the progression of prostate cancer has drawn much attention, there are few reports to date which discuss the relationship. Nevertheless, the patient should be protected from extremely elevated levels of serum tT. No study has reported an obvious increase in the incidence of prostate cancer during ART for men in their prime. Prostate cancer should be explored carefully prior to testosterone administration, if necessary by determining serum PSA levels and by conducting digital rectal examination, transrectal ultrasonographic examination, needle biopsy of prostate, and other tests [12–14].

On the other hand, low serum fT levels are constantly associated with highly malignant prostate cancer, and testosterone is well known to stimulate cancer cells [12–14]. Furthermore, there is a report which describes that a decrease in serum tT level provokes the downregulation of estrogen receptors, and that the decrease is associated with the progression from normal epithelial cells to cancer cells in the prostate [15]. Therefore, ART for patients with hypogonadism is considered not only to improve the patient's well-being, but also to contribute to the mitigation of malignant changes that occur when prostate cancer progresses in prostate tissue. The present study revealed that a single intramuscular injection of 125 mg of testosterone enanthate leads to peak serum levels of tT and fT on day 1 after administration. However, we found that serum fT levels actually exceeded the normal range in 67% of patients, and that the autosecretion of testosterone was decreased in all the patients.

Testosterone has been reported to be related with the development of polycythemia, thrombosis, and BPH. The present regimen for IM-ART, which showed abnormally high and low serum levels of tT, infers a decrease in patient's quality of life and a risk of provoking adverse reactions. Hence, we are concerned that the regimen might induce adverse events in the future, especially prostate cancer.

The results of the present study do not lead us to consider IM-ART as the best therapeutic modality. However, testosterone enanthate for intramuscular injection is the only drug which is currently available in Japan for the treatment of hypogonadism. On the other hand, the drug is not sufficient as a therapeutic modality to improve the patient's quality of life. In the future, we can expect the development of a drug regimen which is capable of adjusting to daily physiological endocrine environment generated by ART.

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