



# Compliance with Testosterone Replacement Therapy in Patients with Testosterone Deficiency Syndrome: A 10-Year Observational Study in Korea

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**Purpose:** To determine the compliance rate with testosterone replacement therapy (TRT) in patients with testosterone deficiency syndrome (TDS), we evaluated the treatment continuation rate and the reasons for discontinuation of initial treatment according to each formulations and patient characteristics.

**Materials and Methods:** Among men over 40 years of age who were diagnosed with TDS and then underwent TRT, their medical records were retrospectively analyzed for those who were followed up for more than 10 years.

**Results:** A total of 640 patients were included in the analysis. It was found that 75.9% of patients continued treatment for 1 year after starting. Patients treated with 1,000 mg of testosterone undecanoate injection had the highest treatment rate. Inconvenience of medication was the most common reason for discontinuing treatment, followed by cost, concern about side effects, lack of efficacy, and symptom recovery. The reasons for discontinuing treatment differed according to the type of formulations, and the longest continuous treatment period in all patients was  $15.4 \pm 7.6$  months on average. The treatment continuation rate tended to be high in patients with low serum total testosterone before starting treatment, in patients with severe erectile dysfunction, and in patients using phosphodiesterase-5 (PDE5) inhibitors.

**Conclusions:** Among the various formulations of TDS, testosterone undecanoate injection (1,000 mg) had the highest compliance rate. In addition, it was found that the reasons for discontinuation of treatment varied according to the characteristics of each formulation.

**Keywords:** Compliance; Hypogonadism; Personal satisfaction; Testosterone; Therapeutics

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## INTRODUCTION

Testosterone levels gradually decreases in men after middle age. If the testosterone level falls below a certain level, related symptoms appear. Testosterone deficiency syndrome (TDS) is defined as the presence

of typical symptoms along with low serum testosterone levels in men as they age. This clinical and biochemical syndrome associated with aging is referred to as late-onset hypogonadism [1,2].

According to the guidelines for TDS published in various academic societies, symptoms associated with

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sexual function are the most important for diagnosing TDS. However, the cutoff values of testosterone levels for laboratory diagnosis differ slightly according to each guideline. The International Society for the Study of the Aging Male and the International Society for Sexual Medicine use serum total testosterone level <350 ng/dL as the standard, while the Endocrine Society and American Urological Association follow the cutoff value of serum total testosterone level <350 ng/dL [3]. Currently available formulations include oral, buccal, transdermal, and intramuscular injections, and they vary in route of administration, dose, formulations, and safety profiles [4-7]. In patients with TDS, the treatment goal is to restore the decreased serum testosterone level to a physiological level [8]. When starting treatment, short-acting formulations, which can be easily stopped if side effects occur, are preferred [9], but in general, each formulation is selected through consultation between the patient and the physician [10].

Testosterone replacement therapy (TRT) causes positive changes in sexual functions represented by libido, erectile dysfunction (ED), and ejaculatory function. Although inconclusive, it improves physical function, mood, cognition, metabolic syndrome, diabetes, body composition, and bone density [11]. As life expectancy increases worldwide, the number of aging-related patients with TDS increases and, accordingly, the medical demand for TRT is expected to increase. There have been many studies on the long-term effects and safety concerns of TRT [12]. However, there are no studies on the compliance rate of TRT when establishing a treatment plan and performing long-term treatment.

In contrast, in the case of premature ejaculation (PE) or ED, satisfaction with pharmacotherapy such as dapoxetine and phosphodiesterase-5 (PDE5) inhibitors, discontinuation rate, and reason for discontinuing treatment have been studied. According to research results, treatment preference and the compliance with the treatment are not necessarily determined only by the efficacy and safety [13,14].

TRT does not basically lead to recovery from TDS but merely supplements insufficient testosterone. Therefore, in theory, treatment should be continued during the lifetime; however, it is difficult for physicians to recommend and manage long-term treatment in patients with TDS.

If there are research findings related to treatment compliance according to various formulations even in

TRT, it will be helpful when planning patient treatment or counseling. Against this background, we analyzed the treatment continuation rate, reasons for discontinuation of initial treatment, *etc.* according to each formulation and patient characteristics for those who have been treated for a long period, using data accumulated in an actual practicing environment.

## MATERIALS AND METHODS

This was a retrospective observational study conducted over a 10-years period in a single clinical center.

Among men over 40 years of age who were diagnosed with TDS and then underwent TRT, their medical records were retrospectively analyzed for those who were followed up for more than 10 years.

Inclusion criteria were as follows: patients with serum total testosterone level of less than 300 mg/dL and associated with clinical symptoms or signs, and were diagnosed with TDS; patients who had normal pubertal development and, as a result, developed normal male secondary sex characteristics; patients who had TRT at least once; patients not subjected to TRT contraindications such as history of prostate cancer, breast cancer, severe lower urinary tract symptoms associated with benign prostate hyperplasia, hematocrit higher than 50%, and uncontrolled or poorly controlled congestive heart failure.

Exclusion criteria were as follows: patients with medical conditions that require TRT to continue throughout their lifespan, such as congenital anorchia, Klinefelter syndrome, 46,XX male syndrome, testicular radiation therapy or chemotherapy history, panhypopituitarism, Kallmann syndrome, pituitary tumor history, testicular cancer, and acquired anorchia; patients who have changed treatment formulations; and if the reason for discontinuing treatment is not disclosed.

The following data were retrieved: patients' baseline characteristics; erectile function; types of TRT formulations; treatment continuation rate at 1, 5, and 10 years after treatment; reasons for discontinuation; total treatment period.

### 1. Ethics statement

This study was conducted with Good Clinical Practice (GCP) and was consistent with the ethical principles of the Declaration of Helsinki (2013). All forms of the documents related to this study were approved

by the institutional review board (IRB; PNUH IRB No. H-2009-024-095). All patient data extracted were anonymized for the analysis. Informed consent was not necessary given the retrospective design and waived by IRB.

## 2. Statistical analyses

We compared the baseline characteristics of patients continuing and discontinuing treatment using the  $\kappa^2$  test to evaluate categorical variables. The duration of treatment according to the type of TRT formulations was analyzed using the analysis of variance. A p-value <0.05 was considered statistically significant. All statistical analyses were performed using IBM SPSS for Windows ver. 20.0 (IBM Corp., Armonk, NY, USA).

## RESULTS

A total of 640 patients were included in the analysis. The patients' distribution according to each treatment formulation were as follows: testosterone enanthate (Jenasteron 250 mg/1 mL every 3 weeks; Bayer Schering Pharma AG, Berlin, Germany) (n=100), testosterone undecanoate (Nebido 1,000 mg/4 mL every 12 to 16

weeks; Bayer Schering Pharma AG) (n=240), testosterone gel (Testo Gel 1% 5 g, HanmiPharma, Seoul, Korea; or tostrex Gel 2% 2.5 g, CJ CheilJedangPharma, Seoul, Korea) (n=156), and oral testosterone undecanoate (andrioltestocaps 80, 160, or 240 mg/day; MSD, Whitehouse Station, NJ, USA) (n=144).

### 1. Treatment status at 1 year after starting treatment

It was observed that 75.9% of patients continued treatment for 1 year after starting. The treatment continuation rate was highest in patients treated with 1,000 mg of testosterone undecanoate injection. About 65% of patients who discontinued treatment resumed treatment, and the mean interruption period from the first treatment to retreatment was 8.5±3.2 months (Table 1).

### 2. Reasons for discontinuation of initial treatment

Inconvenience of medication was the most common reason for discontinuing treatment, followed by cost, concern about side effects, lack of efficacy, and symptom recovery. The distribution of reasons for dis-

**Table 1.** Treatment status at 1 year after starting treatment

Treatment	No. of patients	First treatment period (mo) <sup>a</sup>	Retreatment rate after first interruption <sup>b</sup>	Interruption period from first treatment to retreatment (mo)	Treatment continuation rate at 1 year <sup>b</sup>
Testosterone enanthate injection 250 mg	100	8.2±4.5	51 (51.0)	9.1±4.1	58 (58.0)
Testosterone undecanoate injection 1,000 mg	240	20.5±7.2	180 (75.0)	8.5±4.8	218 (90.8)
Testosterone gel	156	11.3±5.8	90 (57.7)	8.4±4.4	111 (71.2)
Oral testosterone undecanoate	144	14.2±6.2	95 (66.0)	7.3±3.3	99 (68.8)
Total	640	15.5±7.3	416 (65.0)	8.5±3.2	486 (75.9)

Values are presented as number only, mean±standard deviation, or number (%).

<sup>a</sup>p<0.05 between groups differences by  $\kappa^2$  test. <sup>b</sup>p<0.05 between groups differences by ANOVA.

**Table 2.** Reasons for discontinuation of initial treatment

Reason	Testosterone enanthate injection 250 mg	Testosterone undecanoate injection 1,000 mg	Testosterone gel	Oral testosterone undecanoate	Total
Inconvenience of medication	10 (23.8)	0 (0)	23 (51.1)	13 (28.9)	46 (29.9)
Cost	1 (2.4)	15 (68.2)	10 (22.2)	10 (22.2)	36 (23.4)
Concern about side effects	22 (52.4)	4 (18.2)	5 (11.1)	5 (11.1)	36 (23.4)
Lack of efficacy	4 (9.5)	1 (4.5)	5 (11.1)	15 (33.3)	25 (16.2)
Symptom recovery	5 (11.9)	2 (9.1)	2 (4.4)	2 (4.4)	11 (7.1)
Total	42 (100)	22 (100)	45 (100)	45 (100)	154 (100)

Values are presented as number (%).

continuing treatment differed according to the type of formulation. In patients receiving testosterone enanthate injection (250 mg), concern about side effects was the most common reason for discontinuation. On the contrary, it was cost in patients using testosterone undecanoate injection (1,000 mg), inconvenience of medication in patients using testosterone gel, and lack of efficacy in patients using oral testosterone undecanoate (Table 2).

### 3. Treatment continuation rate over 10 years

The longest continuous treatment period in all patients was 15.4±7.6 months on average. In the case of

treatment with testosterone undecanoate injection (1,000 mg), the total treatment period was longer than that of the other treatments, and the treatment continuation rate tended to be higher (Table 3).

### 4. Patient baseline characteristics and treatment continuation rate

The treatment continuation rate tended to be high in patients with low serum total testosterone before starting treatment, in patients with severe ED, and in those using PDE5 inhibitors. In these patients, the total treatment period was long, over the past 10 years (Table 4).

**Table 3.** Treatment continuation rate over 10 years

Treatment	No. of patients	Treatment continuation rate at 1 year <sup>a</sup>	Treatment continuation rate at 5 year <sup>a</sup>	Treatment continuation rate at 10 year <sup>a</sup>	Total treatment period for 10 years per patient (mo) <sup>b</sup>	Longest continuous treatment period per patient (mo) <sup>b</sup>
Testosterone enanthate injection 250 mg	100	58 (58.0)	41 (41.0)	13 (13.0)	29.5±11.9	15.1±9.1
Testosterone undecanoate injection 1,000 mg	240	218 (90.8)	110 (45.8)	40 (16.7)	42.3±20.7	22.5±10.6
Testosterone gel	156	111 (71.2)	20 (12.8)	4 (2.6)	18.7±10.5	9.5±4.8
Oral testosterone undecanoate	144	99 (68.8)	40 (27.8)	15 (10.4)	26.2±11.3	10.2±5.2
Total	640	486 (75.9)	211 (33.0)	72 (11.3)	30.9±15.7	15.4±7.6

Values are presented as number only, number (%), or mean±standard deviation.

<sup>a</sup>p<0.05 between groups differences by  $\chi^2$  test. <sup>b</sup>p<0.05 between groups differences by ANOVA.

**Table 4.** Patient baseline characteristics and treatment continuation rate

Variable	No. of patients	Treatment continuation rate at 1 year	Treatment continuation rate at 5 year	Treatment continuation rate at 10 year	Total treatment period for 10 years per patient (mo)
Testosterone (ng/dL)					
<200	275	233 (84.7) <sup>a</sup>	100 (36.4) <sup>a</sup>	50 (18.2) <sup>a</sup>	35.4±19.6 <sup>b</sup>
200–300	365	253 (69.3)	111 (30.4)	22 (6.0)	27.5±20.1
IIEF-5a					
≤7	200	189 (94.5) <sup>a</sup>	90 (45.0) <sup>a</sup>	39 (19.5) <sup>a</sup>	42.4±27.8 <sup>b</sup>
8–11	247	200 (81.0)	88 (35.6)	30 (12.1)	37.2±29.6
12–16	103	60 (58.3)	20 (19.4)	3 (2.9)	22.2±16.3
≥17	90	37 (41.1)	13 (14.4)	0 (0)	22.9±15.4
Age (y)					
>60	450	326 (72.4)	148 (32.9)	49 (10.9)	31.7±19.2
<60	190	160 (84.2)	63 (33.2)	23 (12.1)	29.0±18.5
PDE5 inhibitor status					
User	501	410 (81.8) <sup>a</sup>	198 (39.5) <sup>a</sup>	65 (13.0) <sup>a</sup>	35.8±20.1 <sup>b</sup>
Non-user	139	76 (54.7)	13 (9.4)	7 (5.0)	13.2±8.8
Total	640	486 (75.9)	211 (33.0)	72 (11.3)	30.9±15.7

Values are presented as number only, number (%), or mean±standard deviation.

IIEF-5: International Index of Erectile Function-5, PDE: phosphodiesterase.

<sup>a</sup>p<0.05 between groups differences by  $\chi^2$  test. <sup>b</sup>p<0.05 between groups differences by ANOVA.

## DISCUSSION

Testosterone, which decreases as aging progresses in men after middle age, is closely related to the major functions of various parts of the body. Testosterone and sexual function are the most closely related, but it is well known that body composition, cognitive function, mood change, and physical function are also related to testosterone [1-3,11,15]. The main mechanism that lowers testosterone levels is the reduction of testosterone production due to the decrease in the function of Leydig cells in aging testes [16]. Currently, TRT, the only treatment for TDS, is not a fundamental treatment that induces the production of testosterone in aged testes but only compensates for the deficit. Therefore, in TDS patients, TRT is theoretically required for life-long treatment. However, it is difficult to lead long-term treatment by making patients aware of this situation in an actual treatment environment. Nevertheless, given the many positive effects of TDS, patients should be given adequate counseling to ensure that treatment is provided for a sufficient period. With this background, this study attempted to obtain information that may be helpful in establishing a treatment strategy for patients planning TRT. As this is the first study on adherence to TRT, no previous data from other researchers could be found for comparisons. Although it is not the same disease, compared with the study on the discontinuation rate of dapoxetine in patients with PE, it was found that the treatment continuation rate for TRT was significantly higher [13]. Although dapoxetine used to treat PE was the only oral pharmacologic agent approved for the treatment of PE, the treatment continuation rate at 1 year was only 12.7%. Contrarily, in this study, the treatment rate of TRT reached approximately 76% in the first year of treatment, which was much higher than that of the PE treatment. In patients with ED, although PDE5 inhibitors are the most effective and widely used ED therapeutics, dropout rates are reported to be between 11% and 57% [14]. While PE, ED, and TDS are all important male health problems that affect quality of life, TDS has a far greater overall impact on general health, including sexual function, than the other two disorders. Therefore, it can be inferred that patients' satisfaction with TRT treatment will be relatively high. In the first year of treatment, several formulations showed the highest treatment continuation rates in patients using

testosterone undecanoate injection (1,000 mg), followed by those using testosterone gel, oral testosterone undecanoate, and testosterone enanthate injection (250 mg). Overall, "inconvenience of medication" was the most common reason for stopping treatment, but the reasons were quite different for each formulation.

In the case of testosterone enanthate injection (250 mg), which can cause a rapid increase in serum testosterone after injection, "concern about side effects" was the biggest reason for discontinuation. On the other hand, "Cost" was the most significant factor in patients who used testosterone undecanoate injection (1,000 mg), "inconvenience of medication" in those using testosterone gel, and "lack of efficacy" in those using oral testosterone undecanoate were the most common reasons for discontinuation. As such, the reasons for discontinuation of treatment showed various distributions according to the characteristics of each formulation.

In Korea, where the study was conducted, testosterone undecanoate injection (1,000 mg) is not covered by the national health insurance, so the cost to be paid directly by the patient is high. Oral testosterone undecanoate is fully absorbed and effective when taken with a diet containing sufficient lipids. However, since the diet of Koreans mainly consists of vegetables and grains, the amount of lipids is insufficient, which is presumed to be the cause of the decline in the efficacy of the drug. In addition, it is thought that the reason for stopping the gel treatment was the strangeness of using medicines applied on the body in Korean culture and lifestyle.

In this study, testosterone undecanoate injection (1,000 mg) showed the highest treatment continuation rate at 1, 5, and 10 years of treatment compared with other formulations. And, in those who used this treatment, the total duration of treatment and the continuous duration of treatment were the longest in 10 years. These results can be interpreted as follows: the highest patient satisfaction was observed with testosterone undecanoate injection (1,000 mg). This may be associated with the fact that it is currently the longest acting agent and maintains blood concentration most stably at the target concentration for treatment [17].

However, in this study, the correlation between the serum testosterone level after treatment and the treatment continuation rate could not be confirmed because the data on the change in serum testosterone after treatment were not sufficient for analysis.

In the comparison according to the patient baseline characteristics, patients with low serum total testosterone level, severe ED, or PDE5 inhibitors, showed high adherence to treatment. This finding is thought to be due to the high motivation for treatment, since sexual dysfunction is the most directly related and important symptom of TDS. However, no difference was found with regard to the age of the patients.

To the best of our knowledge, this is the first study with the longest follow-up period (10 years) to analyze the compliance of TRT in TDS. However, several limitations should be noted.

First, patients who changed their treatment formulation during the follow-up period were excluded from the analysis. Some TDS guidelines recommend starting with a short-acting product at the beginning of treatment, so some patients may have made such changes of treatment at the doctor's recommendation. However, this study aimed to investigate the duration and discontinuation of treatment at the patient's own choice, so patients who changed the treatment midway were inevitably excluded.

Second, since this study was conducted in a single country and in a single research institution, there will be a bias. There will be differences between Koreans' preference for taking drugs and that of other regions and countries. In addition, there is an influence on the price of each formulation in the Korean national health insurance system. In Korea, oral testosterone undecanoate is supported by insurance, while patients have to pay out of pocket for the others.

Third, since the serum testosterone level after treatment could not be analyzed, the recovery effect of the treatment and compliance was unknown.

Fourth, treatment efficacy and incidence of side effects were not analyzed for each formulation, which was not the main purpose of this study. However, information on the treatment efficacy and side effects could be indirectly identified through the analysis of the reason for discontinuing treatment.

## CONCLUSIONS

Through a 10-year retrospective observational study, we found that, among the various formulations of TDS, testosterone undecanoate injection (1,000 mg) had the highest treatment compliance. In addition, the reasons for discontinuation of treatment varied according to

the characteristics of each formulation. When counseling patients with TDS who need long-term treatment and establishing a treatment plan, the use of information on treatment compliance and reasons for discontinuation found in this study should be helpful in the actual treatment environment.

## Conflict of Interest

The authors have nothing to disclose.

## Author Contribution

Conceptualization: HJP. Data curation: BK, MN. Formal analysis: BK, MN, HJP. Funding acquisition: HJP. Investigation: BK, MN, HJP. Methodology: HJP. Project administration: BK, HJP. Resources: BK, HJP. Software: BK, HJP. Supervision: NM, HJP. Validation Visualization: BK, MN, HJP. Writing – original draft: BK, HJP. Writing – review & editing: MN, HJP.

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