

Novel testosterone gel improves serum testosterone concentrations and aging males' symptoms in patients with late-onset hypogonadism: an active control equivalence, randomized, double-blind, crossover study

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Abstract. Late-onset hypogonadism (LOH) is generally treated with testosterone replacement therapy. Intramuscular injection of testosterone enanthate is used for LOH in Japan but requires regular painful injections administered every 2–3 weeks at a clinic. Testosterone 2% (AndroForte 2® [AF2]) is available for treating LOH but is expensive because it is imported. We developed a new 2% testosterone gel (NTG) and hypothesized that in patients with LOH, NTG would improve serum testosterone concentrations and Aging Males' Symptoms (AMS) scores compared with AF2. We enrolled men with low levels of serum free testosterone (<11.8 pg/mL) and androgen deficiency symptoms (AMS score >27). The primary endpoint was equivalent change in serum testosterone concentrations with NTG compared to AF2. Secondary endpoints were equivalent change in AMS scores for each question with NTG compared to AF2. Each of AF2 or NTG was administered to the study subjects (23 men aged 42–71 years) for 4 weeks separated by a washout period of 2 weeks. The subjects were randomly divided into men who first received NTG and those who first received AF2. No subject experienced any adverse events throughout the study. Compared with the baseline values of serum testosterone, those following NTG and AF2 treatment were significantly higher and were also significantly higher in the subjects taking NTG *versus* AF2. NTG administration significantly improved the AMS score, whereas AF2 did not. This initial study has shown that this new NTG formulation may be effective in improving serum testosterone concentrations and also LOH-related symptoms.

Key words: Novel testosterone gel, Late-onset hypogonadism, Testosterone, Testosterone replacement therapy

AS A CLINICAL AND BIOCHEMICAL SYNDROME presenting in aging subjects who exhibit typical symptoms and a low serum testosterone concentration [1], late-onset hypogonadism (LOH) commonly affects the aging male, but its recognition and treatment are often difficult [2]. Symptoms and signs of LOH include physical changes (muscle strength, general well-being, sleep disturbance, hot flashes, and feeling tired), psychological changes (nervousness, anxiety, and depressive mood), and sexual changes (sexual desire, sexual activity, and erectile dysfunction) [3]. Testosterone replacement therapy (TRT) remains the standard treatment for LOH

[4, 5]. However, TRT is a concern due to its potential for increasing the risks of cardiovascular disease and myocardial infarction, obstructive sleep apnea, thromboembolic events, benign prostatic hyperplasia, and the development and recurrence of prostatic cancer. However, TRT may be less harmful than earlier thought, and its use in treating hypogonadal men is becoming more frequent [6]. The clinical guide book published in 2007 for LOH in Japan states that the diagnosis of LOH is made when the serum free testosterone concentration is <11.8 pg/mL [7].

Intramuscular injection of testosterone enanthate, 1% testosterone ointment (Glowmin®, Daito Pharmaceutical Co. Ltd., Tokyo, Japan), and human chorionic gonadotropin (HCG) are recommended for LOH in Japan for men with a serum free testosterone level <11.8 pg/mL [7]. However, testosterone enanthate must be regularly administered every 2–3 weeks at a clinic, may cause

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unphysiological elevation of the serum testosterone concentration, and can elicit pain. Testosterone undecanoate is a long-acting intramuscularly injected drug that maintains normal serum testosterone levels for 12 weeks following its injection [8], and patients with LOH tolerate it rather well [8]. However, its use is not permitted in Japan. Because self-injection of HCG is not allowed for LOH in Japan, it is not practical as it requires regular clinic visits 3 times per week. Compared with intramuscular injection, transdermal gel or cream containing testosterone is becoming preferable because it does not require injection, and liver dysfunction and unphysiological elevation of serum testosterone are avoided [9, 10]. A previous study in 50 patients with LOH after 12-week application of Glowmin 6 mg to scrotal skin showed elevation of serum free and total testosterone levels and improvement of the International Index of Erectile Function-5, Aging Males' Symptoms (AMS), and Short-Form-36 scores [10]. Glowmin is an over-the-counter drug that requires application twice per day for treatment of LOH.

It takes a long time to apply 2 cm of Glowmin in an amount equal to 3 mg of testosterone. The 2% testosterone medication AndroForte 2® (AF2) (Lawley Pharmaceuticals, Australia) is also available for treatment of LOH as a once-a-day application. AF2 was shown to improve symptoms of aging with a moderate rise in serum total testosterone [11]. We have used AF2 because there does not seem to be any better alternative, but AF2 is expensive in Japan because it must be privately imported. We have thus created a new 2% testosterone gel (NTG) for once-a-day application. We hypothesized that our NTG would improve serum testosterone concentrations and AMS scores in an equivalent manner to AF2 in patients with LOH and thus examined the efficacy of our NTG *versus* AF2 in improving symptoms related to LOH.

Materials and Methods

Men with a low concentration of serum free testosterone (<11.8 pg/mL) and androgen deficiency symptoms (AMS score >27) were enrolled in this active control equivalence, randomized, double-blind, crossover study. The men with LOH were administered 2% AF2 for 4 weeks or 2% NTG for an additional 4 weeks separated by a washout period of 2 weeks. We recruited outpatient Japanese males aged from ≥40 to <75 years who were treated at Juntendo University Urayasu Hospital, Chiba, Japan, and D Clinic Tokyo, Tokyo, Japan, and randomly divided them into group A, men administered NTG first, and group B, men administered AF2 first. We subsequently assessed serum hormonal values, AMS score,

and adverse events (Fig. 1). NTG 0.5-mL (10 mg testosterone) or AF2 0.5 mL (10 mg testosterone) was self-applied by each patient to his scrotum once daily in the morning. Simple randomization was performed using a computer-generated random number table at Juntendo University Urayasu Hospital. Angfa Co., Ltd. (Tokyo, Japan) prepared the NTG and AF2. The NTG 2% testosterone gel contained testosterone, base agent, solvent, thickener, moisturizing agent, buffering agent, antiseptic agent, and pure water (Table 1). The AF2 contained testosterone, dl-alpha-tocopheryl acetate, almond oil, cetomacrogol 1000, cetostearyl alcohol, carbomer 940 emulsion, trolamine, butylated hydroxytoluene, Phenonip containing hydroxybenzoates, citric acid, and purified water [12]. Patients excluded in this study were those with a testosterone-dependent tumor (*e.g.*, prostatic carcinoma, breast carcinoma), prostatic-specific antigen level ≥2.0 ng/mL, untreated sleep apnea syndrome,

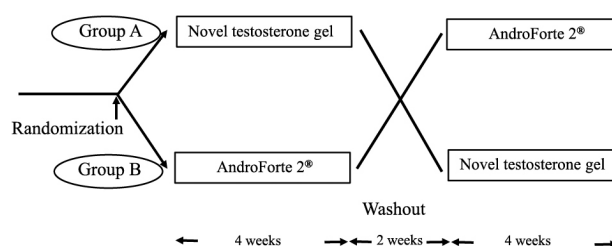


Fig. 1 Study protocol. The patients were randomly divided into two groups. Men with late-onset hypogonadism received 2% AndroForte 2® for 4 weeks or 2% novel testosterone gel for another 4 weeks separated by a 2-week washout period before crossover to the other treatment.

Table 1 Contents of the 2% novel testosterone gel

Ingredients	Purpose	Amount
Testosterone	Active agent	20 g
Polyethylene glycol 4000	Base agent	14 g
Polyethylene glycol 400	Base agent	105 g
Propylene glycol	Resolvent	410 g
Isopropyl alcohol	Resolvent	180 g
Isopropyl myristate	Resolvent	3.5 g
Hiviswako 104	Thickener	9 g
Metolose 90SH-100	Thickener	1.2 g
Glycyrrhizin	Moisturizing agent	3 g
Diisopropanolamine	Buffering agent	6.5 g
Benzyl alcohol	Antiseptic agent	30 g
Pure water		217.8 g
Total amount		1,000 g

hemoglobin level ≥ 18 g/dL indicative of erythrocythemia, or allergy to testosterone.

We evaluated symptoms and signs with the AMS score, Sexual Health Inventory for Men (SHIM), and Erection Hardness Score (EHS), which are all validated tools for assessing aging males' symptoms [13] and erectile function [14, 15] and have been validated in Japanese [7, 16]. Blood examinations including weekly serum hormonal data (total testosterone, free testosterone, luteinizing hormone [LH]), complete blood count, biochemistry tests, and prostate-specific antigen were also assessed. Total and free testosterone concentrations and LH were measured by radioimmunoassay. We collected the questionnaires, which were all self-reported, from the participants in the clinic. The study period was from May 27, 2018 to March 31, 2020.

Main and secondary outcome measures

The main outcome measure was the equivalent change in the serum testosterone concentration by NTG compared with that by AF2 at the end of treatment. The secondary outcome measures were the equivalent change in the score for each question of the AMS by NTG compared with that by AF2, and the evaluation of adverse events.

Ethics and informed consent statements

The study protocol, which was registered in the University Hospital Medical Information-Clinical Trials Registration (UMIN number: UMIN000034704), complied with Good Clinical Practices and the Declaration of Helsinki (1996), as well as with the regulations of the Juntendo University Urayasu Hospital Institutional Review Board, which approved the protocol (approval number: U30-016). The study participants provided informed consent prior to beginning any of the study-related procedures or medications.

Statistical analysis

Data are presented as the mean \pm standard error. Statistical significance was determined by a paired *t*-test

for the questionnaires and the generalized linear mixed model for hormonal data and was indicated by a *p*-value of <0.05 . Statistical analysis was performed with IBM SPSS Statistics for Windows, Japanese version 28 (IBM Japan, Tokyo, Japan).

Results

The present study enrolled 23 patients (age, 42–71 [54.3 ± 1.6] years old) who completed the study with no adverse events experienced (group A, $n = 11$; group B, $n = 12$). No patients were withdrawn or withdrew from this study. At the 4-week measurement points, serum concentrations of total testosterone and free testosterone were significantly higher than those at baseline for NTG and AF2 (Table 2). Further, both concentrations at this time point were significantly higher for NTG than for AF2 (Figs. 2, 3). Serum concentrations of LH at the 4-week measurement were significantly lower than those at baseline for NTG and AF2 (Table 2). However, there was no significant change in LH concentrations at this time point between NTG and AF2 (Fig. 4).

The total score and the physical, mental, and sexual subscores of the AMS improved significantly with NTG but not with AF2 (Table 3). The SHIM total score and EHS were not significantly improved with either NTG or AF2 (Table 3).

Compared with the baseline scores, the mean scores in the domains of AMS-2, -6, -7, -8, -9, -13, -14, -15, and -17 increased significantly with NTG but not with AF2 (Table 4). The domains of SHIM showed no significant increase compared with the baseline scores with either NTG or AF2 (Table 4).

Discussion

We examined the efficacy of our NTG to improve serum testosterone concentrations and symptoms related to LOH. Serum concentrations of total and free testosterone were significantly higher and those of serum LH were significantly lower with NTG and AF2 compared

Table 2 Assessment of serum free testosterone, total testosterone, and LH concentrations at baseline and 4 weeks after using novel testosterone gel and AndroForte 2®

	Novel testosterone gel		AndroForte 2®	
	Baseline	4 weeks	Baseline	4 weeks
Free testosterone	9.86 \pm 0.54	26.93 \pm 3.41*	10.44 \pm 0.67	18.43 \pm 1.44*
Total testosterone	4.59 \pm 0.28	9.86 \pm 1.04*	4.71 \pm 0.24	7.30 \pm 0.54*
LH	6.41 \pm 0.40	3.89 \pm 0.59*	6.79 \pm 0.75	4.38 \pm 0.61 [#]

[#] $p < 0.05$ compared with baseline; * $p < 0.001$ compared with baseline.

LH, luteinizing hormone.

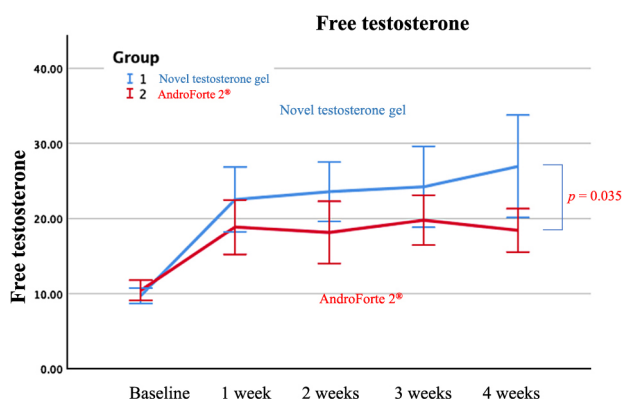


Fig. 2 Weekly serum free testosterone concentrations are presented as the generalized linear mixed model and the mean \pm standard error. Serum free testosterone concentrations at 4 weeks were significantly higher than those at baseline with novel testosterone gel and AndroForte 2®. Furthermore, concentrations at 4 weeks were significantly higher in the patients taking novel testosterone gel *versus* those taking AndroForte 2®.

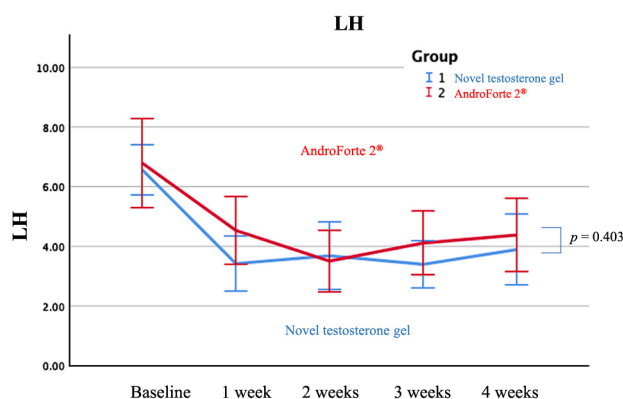


Fig. 4 Weekly serum luteinizing hormone (LH) concentrations are presented as the generalized linear mixed model and the mean \pm standard error. Serum LH concentrations at 4 weeks were significantly lower than those at baseline with novel testosterone gel and AndroForte 2®. However, LH concentrations at 4 weeks did not change significantly between the patients taking novel testosterone gel *versus* those taking AndroForte 2®.

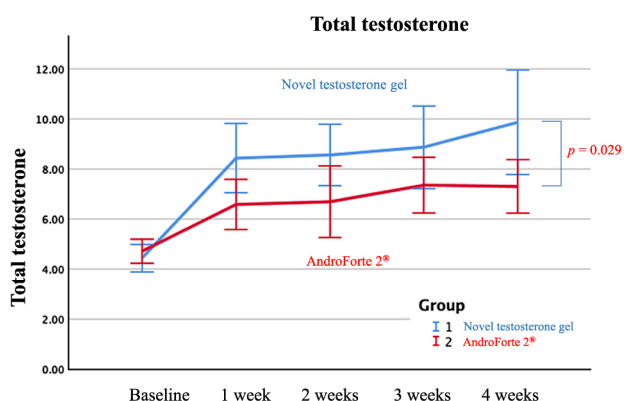


Fig. 3 Weekly serum total testosterone concentrations are presented as the generalized linear mixed model and the mean \pm standard error. Serum total testosterone concentrations at 4 weeks were significantly higher than those at baseline with novel testosterone gel and AndroForte 2®. In addition, concentrations at 4 weeks were significantly higher in the patients taking novel testosterone gel *versus* those taking AndroForte 2®.

with baseline values. Furthermore, both testosterone concentrations were significantly higher with NTG than with AF2. The AMS total score also improved significantly with NTG, whereas no significant improvement was noted with AF2. This is the initial study showing that our newly developed NTG may be effective not only in improving serum testosterone concentrations but also symptoms related to LOH compared with AF2.

The present study revealed that all AMS subscores (physical, mental, and sexual subscores) improved significantly after NTG. The following domains of the AMS also improved significantly after NTG: Joint pain

and muscular ache (AMS-2), Irritability (AMS-6), Nervousness (AMS-7), Anxiety (AMS-8), Physical exhaustion/lacking vitality (AMS-9), Feeling burn out/having hit rock-bottom (AMS-13), Decrease in beard growth (AMS-14), Decrease in ability/frequency to perform sexually (AMS-15), and decrease in sexual desire/libido (AMS-17). NTG showed extensive effects on physical, mental, and sexual symptoms of aging males, similar to those reported in previous studies [17]. Contrary to our expectation, no significant change occurred in the SHIM score, EHS, and AMS-16 domain (morning erection) after NTG. The EAU guideline does not state that TRT may improve erectile function [5], but the AUA guideline states that TRT administered in hypogonadal men may improve erectile function [4]. A meta-analysis revealed that TRT significantly improved erectile function of men with mild ED but not with moderate to severe ED [8]. The mean baseline values of the EHS and SHIM total score in the present study were 2.65 and 13.0, respectively, indicating moderate ED. Thus, the present study revealed that NTG might provide a possible limited effect on erection after its use and might be more effective in improving libido and sexual ability among the symptoms of aging males.

A previous study of a similar testosterone gel (2.5% testosterone) revealed that serum total and free testosterone were significantly elevated after 2, 4, 8, and 12 hours compared with circadian variation in 6 healthy volunteers [18]. At 24 hours after application, serum concentrations of total and free testosterone were revealed to be the same as the previous levels [18]. We decreased the testosterone concentration from 2.5% to

Table 3 Assessment of the AMS, AMS subscores, SHIM, and EHS at baseline and 4 weeks after using novel testosterone gel and AndroForte 2[®]

	Novel testosterone gel		AndroForte 2 [®]	
	Baseline	4 weeks	Baseline	4 weeks
AMS total	35.95 ± 2.67	28.59 ± 1.60 [#]	32.23 ± 2.03	31.91 ± 2.41
AMS-PS	12.68 ± 1.03	10.45 ± 0.60 [#]	11.77 ± 0.70	11.68 ± 0.83
AMS-MS	10.82 ± 1.01	8.05 ± 0.59 [#]	9.13 ± 0.70	9.35 ± 0.86
AMS-SS	12.45 ± 0.75	10.09 ± 0.73 [#]	11.22 ± 0.83	10.74 ± 0.88
SHIM total	13.17 ± 0.98	13.83 ± 1.17	14.09 ± 1.01	14.45 ± 1.05
EHS	2.72 ± 0.16	2.91 ± 0.16	2.77 ± 0.16	2.86 ± 0.15

[#] $p < 0.05$ compared with baseline.

AMS, Aging Males' Symptoms; SHIM, Sexual Health Inventory for Men; EHS, Erection Hardness Score; PS, physical subscore; MS, mental subscore; SS, sexual subscore.

Table 4 Assessment of the domains of the AMS and SHIM at baseline and 4 weeks after using novel testosterone gel and AndroForte 2[®]

	Novel testosterone gel		AndroForte 2 [®]	
	Baseline	4 weeks	Baseline	4 weeks
AMS-1	1.82 ± 0.20	1.41 ± 0.16	1.48 ± 0.14	1.52 ± 0.20
AMS-2	1.86 ± 0.20	1.50 ± 0.17 [#]	1.59 ± 0.16	1.50 ± 0.16
AMS-3	1.23 ± 0.09	1.18 ± 0.11	1.30 ± 0.12	1.30 ± 0.16
AMS-4	2.00 ± 0.23	1.72 ± 0.18	2.17 ± 0.21	2.00 ± 0.24
AMS-5	2.32 ± 0.24	1.95 ± 0.18	2.17 ± 0.17	2.09 ± 0.15
AMS-6	2.45 ± 0.24	1.91 ± 0.16 [#]	1.96 ± 0.17	2.04 ± 0.19
AMS-7	2.32 ± 0.25	1.72 ± 0.19 [#]	1.87 ± 0.18	2.04 ± 0.21
AMS-8	2.05 ± 0.23	1.50 ± 0.13 [#]	1.91 ± 0.20	1.91 ± 0.20
AMS-9	2.00 ± 0.20	1.50 ± 0.13 [#]	1.70 ± 0.15	1.83 ± 0.18
AMS-10	1.45 ± 0.17	1.18 ± 0.11	1.22 ± 0.11	1.35 ± 0.10
AMS-11	1.91 ± 0.23	1.50 ± 0.13	1.57 ± 0.14	1.61 ± 0.17
AMS-12	1.45 ± 0.18	1.31 ± 0.12	1.30 ± 0.12	1.43 ± 0.14
AMS-13	2.09 ± 0.24	1.41 ± 0.14 [#]	1.83 ± 0.20	1.74 ± 0.20
AMS-14	1.82 ± 0.18	1.41 ± 0.14 [#]	1.78 ± 0.18	1.91 ± 0.21
AMS-15	3.31 ± 0.18	2.59 ± 0.22 [#]	2.82 ± 0.22	2.52 ± 0.22
AMS-16	3.09 ± 0.25	2.50 ± 0.25	2.70 ± 0.25	2.39 ± 0.27
AMS-17	2.77 ± 0.20	2.27 ± 0.26 [#]	2.61 ± 0.26	2.48 ± 0.27
SHIM-1	1.91 ± 0.12	2.22 ± 0.15	2.23 ± 0.17	2.23 ± 0.17
SHIM-2	2.91 ± 0.23	3.09 ± 0.23	2.81 ± 0.23	3.09 ± 0.23
SHIM-3	2.91 ± 0.24	2.91 ± 0.27	3.05 ± 0.23	3.05 ± 0.24
SHIM-4	2.70 ± 0.26	2.83 ± 0.29	3.14 ± 0.23	3.05 ± 0.24
SHIM-5	2.74 ± 0.23	2.78 ± 0.29	2.86 ± 0.27	3.05 ± 0.25

[#] $p < 0.05$ compared with baseline.

AMS, Aging Males' Symptoms; SHIM, Sexual Health Inventory for Men.

2% in NTG, the same as that of AF2, and consider the dosage applied in this study to be safe and effective.

The present study showed that the AMS score improved significantly with NTG but not with AF2. One previous study showed significant improvement of the AMS score with significant elevation of the serum testosterone concentration after a 12-week testosterone treatment [10]. Another previous study showed an inverse relation between improvement of aging male symptoms and the baseline testosterone level [19]. The present study showed no significant change in baseline testosterone levels between group A and group B. We speculated that the more significant improvement of serum testosterone concentration observed with NTG was likely related to improvement of the AMS score.

In Japan, national health insurance covers 70% of a patient's medical fees for testosterone enanthate, and the copayment is reasonable. However, health insurance does not cover AF2, a privately imported drug, and the payment is expensive, which increases the patient's charges. NTG will not be covered by health insurance, but it will be inexpensive compared to the cost of AF2.

Although this is a prospective crossover study, it has some limitations. First, this study was planned so that the testosterone concentration and daily dose would be

equal between NTG and AF2. A previous study in hypogonadal men showed that 5% testosterone cream and 1% testosterone gel were bioequivalent [9]. It is possible that absorption of AF2 through skin is different from that of NTG, despite the same 2% concentrations of testosterone. We speculated that the difference in contents between AF2 and NTG might affect skin absorption of testosterone. The two solvents of propylene glycol and isopropyl myristate are included in NTG but not in AF2 (Table 1). Second, the study duration was short, at only 10 weeks, and the sample size was small. Thus, we could not evaluate the long-term efficacy of NTG. We are planning a longer-duration study that will include additional institutions.

In conclusion, this initial study of our NTG showed that it may be effective in improving both serum testosterone concentrations and physical, mental, and sexual symptoms in patients with LOH. The present findings clearly indicate the potential for our NTG to be a possible option in the treatment of patients with LOH.

Disclosure

None of the authors have any potential conflicts of interest associated with this research.

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