Compounded Percutaneous Testosterone Gel: Use And Effects in Hypogonadal Men

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Background: **Current methods of testosterone replacement therapy are limited to fixed-dosage patches and depot injections. Neither of these methods provides ideal therapy because of the inflexibility of dosing and other nuisance problems associated with the patches and nonphysiologic hormone levels when depot injections are used. Testosterone gels offer the potential for convenience and ease of administration, as well as flexible dosing regimens, by means of a simple topical application.**

Methods: **Ten hypogonadal men were selected from the author's general practice, ranging in age from 44 to 77 years. Four of these men had newly diagnosed and 6 had preexisting hypogonadism. Patients were withdrawn from their previous hormone therapy (where applicable), and baseline laboratory studies were obtained for total testosterone, free testosterone, dihydrotestosterone, estradiol, luteinizing hormone, follicle-stimulating hormone, complete blood counts, lipid panels, and chemistry panels. The patients then started taking increasing dosages of the testosterone gel until physiologic levels of testosterone were realized or until the study period (6 weeks) was concluded. There was no blinding, and each patient served as his own control. Testosterone and free testosterone levels were monitored weekly, and estradiol and dihydrotestosterone less frequently. At the conclusion of the study, all the baseline laboratory tests were repeated. A questionnaire evaluating the psychosexual well-being of the patients was administered before and after the treatment period.**

Results: **The average total testosterone level rose from 136 ng/dL to 442.9 ng/dL ($P < .001$). Average free testosterone levels rose from 34.2 pg/mL to 120.3 pg/mL ($P < .001$). Average dihydrotestosterone levels rose from 20.5 to 199.2 ng/dL ($P = .006$). Average estradiol levels rose only slightly from 34.1 pg/mL to 40.0 pg/mL $P = .191$). Average total androgens (testosterone plus dihydrotestosterone) rose in all patients to therapeutic levels, from 149.3 ng/dL to 642.1 ng/dL ($P = .001$). The ratio of total androgen to estradiol rose from 5.1 to 17.1 ($P < .002$). Luteinizing hormone was suppressed in the 6 patients for whom meaningful data were available, and decreased on average from 5.66 to 1.10 mIU/mL ($P = .005$) Lipid effects were measured, and a 15% drop in all cholesterol fractions was noted ($P < .005$). Evaluation of the questionnaire showed considerable improvements in sexual function and overall well-being in all but 1 patient. No adverse effects or nuisance problems were detected during the duration of the study.**

Conclusion: **Topically applied testosterone gels are an effective and convenient means of hormone replacement in hypogonadal men. (J Am Board Fam Pract 2001;14:22–32.)**

Hormone replacement therapy for testosterone-deficient men can pose several challenges for the clinician. Specifically, the treating physician must deal with limited methods for delivery of testosterone, which can lead to inadequate levels of circulating sex steroid hormones. Furthermore, many patients are not satisfied with the existing methods of replacement, resulting in poor compliance. Proper replacement of androgens in hypogonadal men can avert the recognized sequelae of this condition, namely, sexual dysfunction, loss of virilization, excessive bone loss, depression, decreased cognition, and increased risk for cardiovascular disease.[1–19] At the current time the best available method for delivering testosterone is administration of bimonthly injections of depot testosterone or application of impregnated plastic patches.[3,10,14–16] Oral formulations of 17-alkylated androgens are not considered to be a safe or desirable means of replacement because of first-pass hepatic effects and the rare condition of peliosis hepatis.[14]

Although the depot injection method (using the enanthate or cypionate esters of testosterone) is

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inexpensive and serves as the reference standard of therapy, it can be both inconvenient and painful to receive. It also requires frequent visits to the physician's office or taught self-administration. There are disadvantages in that nonphysiologic levels of testosterone result from the peak and trough values inherent in the standard 2-week dosing interval of this depot preparation.[14,20] Estradiol levels can be much higher than desired because of increased aromatization of the testosterone molecule. Nankin[20] found that estradiol levels rose to 300% of baseline during the peak levels after intramuscular testosterone enanthate injections.

Plastic patches have the advantage of mimicking the physiologic production of testosterone but have several drawbacks. There are frequent problems with skin irritation and adhesion. The Androderm patch is reported in its package insert to cause pruritus in 37% of users, a blister-like rash in 12% of users, and simple erythema or vesicles in another 7% of users.[21] A British study with 50 hypogonadal men found that only 22% of their patients would continue with patches and that 84% experienced adverse reactions, almost all related to skin irritation.[22] Jordan[23] found that 12% of a study group of 60 men had true contact dermatitis from the patch, and that 32% had moderate to severe skin irritation. The newer Testoderm TTS (nonscrotal patch) package insert reports less pruritus (12%), and only 3% severe erythema, but adhesion problems were reported in 42% of men who used the patch for 14 days.[24] The Testoderm scrotal patches require shaving the scrotum and cannot be used on a patient with an underdeveloped scrotum. Lack of adhesion is also frequently reported.[24] The patches also offer limited opportunity for discretion and little dosing flexibility.

The above-mentioned problems become more relevant when one considers that the number of men with diagnosed and undiagnosed hypogonadism in the average primary care practice can be substantial. Although no reported studies have estimated or measured the incidence of this population in a primary care setting, many other studies have looked at various subpopulations. For example, Tenover[16] found that 20% of healthy men aged 60 to 80 years were hypogonadal, and others found that up to 30% of men in long-term care facilities have low testosterone levels.[11] Low testosterone levels have been found in up to 16% of men who complain of erectile dysfunction[25] and in 62% of men who are current or former heavy drinkers of alcohol.[11] Thirty percent of men with osteoporotic fractures have been found to have hypogonadism[4,19] Diabetes is also strongly associated with low testosterone levels[26] and, in fact, many chronic illnesses in men will cause a permanent or temporary drop in the testosterone levels.[3,4,12,14,15]

Topically applied gels containing various concentrations of hormone have been available through compounding pharmacists for some time. These products are handmade ointments that are prepared by specially-trained pharmacists for specific patient applications as directed by a physician's prescription. The Professional Compounding Centers of America (9901 S Wilcrest, Houston, TX 77099, 1–800-331–2498) suggested several formulations. The idea of using these gels was intriguing, but I could not find documentation of their effectiveness in the English literature. The information from the compounding pharmacists was incomplete, and there is a need to define the proper way to use these products and to prove that they are viable alternatives for replacement therapy.

Methods

This study was conducted at a private medical office using patients drawn from a panel of family practice patients. Approval from the Institutional Review Board Committee of the Motion Picture and Television Fund Hospital (Woodland Hills, California) was granted, and all the patients gave full informed consent.

This pilot study was nonblinded and without placebo control. Each patient served as his own control, using a pre-post intervention design. Funding for this project consisted of an $800 grant from the Motion Picture and Television Fund Medical Group, as well as legal support for developing a consent form. I performed all the research and report preparation, as well as statistical evaluation.

Patients

Several dozen men were screened from a general family practice based on histories of decreased libido or erectile dysfunction, with or without concomitant mood disorder, cognitive dysfunction, or loss of virilization. From this larger pool, I selected 10 men to participate in the study based on their ability and willingness to participate and an absence

Table 1. Patient Characteristics.

Patient Number	Previous Treatment	Age (years)	Body Mass Index	Initial Testosterone Level (ng/dL)	Hypogonadism Type	Comorbid Conditions
1	Yes	47	21	3	Pituitary failure	Short stature, hypercholesterolemia
2	Yes	41	30	23	Cryptorchidism	None
3	No	61	20	29	Acquired idiopathic hypogonadotropic hypogonadism	Sideroblastic anemia, coronary artery disease
4	No	42	24	63	Acquired idiopathic hypogonadotropic hypogonadism	Pulmonary fibrosis, hepatitis C
5	Yes	62	24	197	Acquired idiopathic hypogonadotropic hypogonadism	Former ethanol abuser
6	No	49	29	160	Acquired idiopathic hypogonadotropic hypogonadism	Mild diabetes
7	Yes	65	32	188	Acquired idiopathic hypogonadotropic hypogonadism	None
8	No	41	22	268	Sertoli cell failure	None
9	Yes	77	26	239	Acquired idiopathic hypogonadotropic hypogonadism	None
10	Yes	62	35	203	Acquired idiopathic hypogonadotropic hypogonadism	Hypertension, vascular disease

of contraindications. The criterion for hypogonadism was a testosterone level of less than 300 ng/dL on repeat morning serum testing.[10] The characteristics of these men are summarized in Table 1. The group consisted of 4 men with newly diagnosed hypogonadism and 6 men with previously treated hypogonadism. The men ranged in age from 41 to 77 years. Both primary and secondary causes of hypogonadism were included. Comorbid medical conditions were common and are listed in Table 1. Men with potentially pregnant partners or men desiring imminent fertility were excluded from the study, as were men with any signs or symptoms of breast or prostate cancer.

Study Design

The 6 men who had previously received treatment for hypogonadism had used either depot testosterone injections or the Androderm patch. Only 1 patient (patient 2) had been truly compliant with his therapy and had used his last patch 2 weeks before the initiation of the gel treatment. This patient became highly symptomatic without treatment and refused to be off hormone therapy for the requested 4 weeks. Despite this limitation, he was at castrate levels at the beginning of the study period. He had not, however, regained his hypergonadotropic state, and so his data were excluded from the analysis based on luteinizing hormone suppression. A second patient (patient 5) received his last depot testosterone injection only 3 weeks before the beginning of the gel initiation. All the other men had not had testosterone therapy for a period of 5 weeks to 1 year.

At the initial intake visit for the study, I conducted baseline physical examinations, with special attention to the prostate, testicular, and breast examination. I developed a questionnaire that asked the patient to rate aspects of his sexual health, mood, cognition, aggression, and symptoms of prostatism. This questionnaire was given to the patient during the initial intake examination.

Baseline laboratory evaluation consisted of morning (8 AM to 10 AM) measurements of free and total testosterone, dihydrotestosterone, estradiol, luteinizing hormone, follicle-stimulating hormone, prolactin, prostate-specific antigen, a lipid panel, a hemogram (complete blood cell count), and a comprehensive metabolic panel. Other laboratory values were measured if indicated by the patient's medical condition.

The patients were then given testosterone gel in a dosing syringe and instructed on administration, the site of application (either the upper inner arm or chest near the axilla or the inner thigh and scrotum), and the amount of gel (1–3 mL). The concentration of the gel varied from 0.5% to 10% testosterone. The men were also told that their female

Table 2. Testosterone Gel Effects on Major Sex Steroid Hormones.

Patient No, Gel Amount, Strength, and Site of Application	Total Testosterone (normal 300–1,200 ng/dL)		Free Testosterone (normal 34–194 pg/mL)		Dihydrotestosterone (normal 30–100 ng/dL)		Estradiol (normal 25–50 pg/mL)	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1. 2 mL, 1.5%, 30 mg, scrotum	3	463	15	118	13	160	10	19
2. 3 mL, 3.0%, 90 mg, scrotum	23	644	5	198	8	298	16	37
3. 2 mL, 3.0%, 60 mg, scrotum	19	301	2	39	2	440	10	27
4. 1 mL, 10%, 100 mg, scrotum	63	245	28	120	10	114	137	103
5. 1 mL, 1.5%, 15 mg, axilla	197	338	30	68	48	85	28	36
6. 2 mL, 3.0%, 60 mg, axilla	160	285	48	95	–	98	38	33
7. 2 mL, 3.0%, 60 mg, axilla	188	320	31	97	31	49	37	36
8. 2 mL, 6.0%, 120 mg, scrotum	268	922	60	250	33	395	23	32
9. 2 mL, 3.0%, 60 mg, scrotum	239	411	74	133	–	228	10	53
10. 2 mL, 6.0%, 120 mg, scrotum	203	320	49	85	19	125	32	24
Average	136.3	442.9	34.2	120.3	20.5	199.2	34.1	40.0
P value	<.001		<.001		.006		.191	

partners should avoid direct contact with application site, and not to bathe until at least 8 hours after application. Compliance was assured by reviewing the doses with the patient, examining the used dosing syringes, and assessing the need for refills. All the testosterone gel was personally dispensed directly to the patient at the office visit.

The patients were seen at weekly intervals, and either the concentration or the amount of the gel was increased or kept the same based on the results of the past week's testosterone levels. Initially the patients started with very low concentrations and amounts of the gel because there existed no published data on which to base starting doses. It was necessary to titrate the dose this way to reach the desired therapeutic levels of testosterone. At each visit I examined the patients; obtained their temperature, blood pressure, heart rate, and respiration rate; and assessed their general well-being. They were queried about side effects as well as sexual function. Each patient had his levels of total and free testosterone measured at weekly intervals. After 4 to 6 weeks, when therapeutic levels had been reached, the patients were withdrawn from the study, and a posttreatment questionnaire (similar to the pretreatment questionnaire) was administered. The baseline laboratory tests were repeated, and results were tabulated. Even though the study period was formally ended after 4 to 6 weeks, some of the patient data beyond that time are presented in the graphs.

The statistical evaluation of the data was performed by averaging the pretreatment and posttreatment levels of the various hormones, lipids, and responses to the questionnaire. These data were then subjected to the Student paired *t* test (single tail) to calculate the *P* values for statistical significance. A Microsoft Excel (Microsoft Corp, Redmond, Wash) program was used for all calculations.

Testosterone Assay Method

All the steroid hormone levels were determined by SmithKline Beecham Clinical Laboratories using a competitive chemiluminescent immunoassay. The reported accuracy for their testosterone measurements is 11.5% coefficient of variation (CV) for levels between 30 and 100 ng/dL, and 6.2% CV for levels between 200 and 500 ng/dL.

Testosterone Gel Compounding

All the testosterone gel was supplied by the Compounding Pharmacy of Beverly Hills by the same pharmacists (9629 West Olympic Blvd., Beverly Hills, CA 90212). The gel consisted of micronized testosterone in a vehicle of Pluronic F-127 (Organogel) and mixed with lecithin. This product left a nonstaining oily residue on the skin. The product is stable at room temperature, and refrigeration is not recommended, as it will cause the gel to liquefy.

Table 3. Hormone Gel Effects on Total Androgens, Total Androgen-Estradiol Ratio, and Luteinizing Hormone.

Patient Number	Total Androgen (ng/dL)		Total Androgen-Estradiol Ratio ([ng/dL]/[pg/mL])		Luteinizing Hormone (mIU/mL)	
	Pre	Post	Pre	Post	Pre	Post
1	16	623	1.6	32.78	–	–
2	31	942	1.93	25.46	–	–
3	21	741	2.1	27.44	–	–
4	73	539	0.53	5.23	1.3	0.1
5	245	423	8.75	11.75	–	–
6	–	383	–	11.6	2.7	0.82
7	219	369	5.92	10.25	3.3	0.2
8	301	1317	13.09	41.15	7.33	0.3
9	–	639	–	12.06	7.4	1.0
10	222	445	6.94	18.54	11.8	4.2
Average	149.3	642.1	5.1	17.1	5.6	1.1
P value	.001		<.002		.005	

Results

Table 2 summarizes the results of the changes in testosterone, free testosterone, dihydrotestosterone, and estradiol levels for each patient. The desired therapeutic end-point for testosterone levels (>300 ng/dL) was attained in 9 of the 10 patients by the end of the fourth week. The average pretreatment level of testosterone was 136 ng/dL, which increased nearly threefold to 442.9 ng/dL at the conclusion of the study ($P < .001$). The levels of free testosterone rose in parallel with the rise in testosterone values, and the average pretreatment level went from 34.2 pg/mL to 120.3 pg/mL ($P < .001$). (The normal range of free testosterone is defined by the reference laboratory as 34–194 pg/mL). Dihydrotestosterone levels increased to physiologic (30–100 ng/dL) or supraphysiologic (>100 ng/dL) levels in every patient. The supraphysiologic levels of dihydrotestosterone occurred in all patients who applied all or part of the gel to the scrotal and thigh area (patients 1,2,3,4,8,9, and 10). The testosterone gel induced changes from an average of 20.5 ng/dL to 199.2 ng/dL ($P = .006$).

The reference laboratory defined normal estradiol levels for men as 50 pg/mL or less; however, most normal men will have estradiol levels between 25 pg/mL and 50 pg/mL. Before the administration of the testosterone gel, estradiol levels were low or normal in all but 1 patient (patient 4) who had the abnormally high level of 137 pg/mL at the start. This patient had a slight decrease of his estradiol level to 103 pg/mL after 4 weeks of hormone therapy. Patients with abnormally low levels of estradiol (secondary to severe hypogonadism) showed an increase to normal male levels. In the remaining patients, whose estradiol levels started in the normal range, there was no significant change. The average pretreatment level was 34.1 pg/mL and increased to 40.0 pg/mL at the conclusion of the study. ($P = .19$)

Table 3 displays the results for changes in total androgen levels, the total androgen-estradiol ratio, and luteinizing hormone levels. All patients reached therapeutic levels of total androgens (defined as testosterone plus dihydrotestosterone > 330 ng/dL). The pretreatment average was 149.3 ng/dL and increased more than fourfold to 642.10 ng/dL ($P = .001$). A striking change in the total androgen-estradiol ratio was observed in all men; the average ratio of 5.10 ([ng/dL]/[pg/mL]) increased by a factor of greater than 3 to 17.08 ($P < .002$). Normal ratios of total androgen-estradiol are defined as being between 10 to 22.[27] In this analysis the ratios are slightly higher because of the inclusion of the dihydrotestosterone levels, which comprise a considerable portion of the androgen pool in these men.

Luteinizing hormone suppression was evident in the 6 patients for whom meaningful data were collected. Patient 1 was excluded because of panhypopituitarism, and patient 2 had not stopped taking his previous therapy long enough to regain his hypergonadotropic status at baseline. Patient 3 failed to have a follow-up luteinizing hormone level

Table 4. Lipid Effects Attributable to Use of Transdermal Testosterone Gel.

Patient Number	Total Cholesterol (mg/dL)		Low-Density Lipoprotein Cholesterol (mg/dL)		High-Density Lipoprotein Cholesterol (mg/dL)		Total Cholesterol—High-Density Lipoprotein Cholesterol Ratio	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1	308	218	222	153	49	38	4.53	4.02
2	227	169	141	115	54	35	2.61	3.28
3	78	68	31	21	35	33	0.88	0.63
4	160	145	92	77	47	37	1.96	2.08
5	242	223	182	165	41	35	4.43	4.71
6	227	221	145	130	30	34	4.83	3.83
7	233	205	155	137	59	50	2.63	2.74
8	196	171	112	110	63	52	1.78	2.11
9	187	156	100	79	36	30	2.78	2.63
10	160	134	73	69	35	35	2.08	1.97
Average	201.8	171	125.3	105.6	44.9	37.9	2.851	2.80
Change (%)	−15		−15.7		−15.5		−1.7	
P value	<.002		<.005		.004		.369	

measured. Patient 5 had his first luteinizing hormone measured a week into his replacement therapy, and the results already reflected suppression from the hormones. The average level for the remaining 6 patients was 5.66 mIU/mL, which decreased to 1.10 mIU/mL by the conclusion of the study. ($P = .011$)

Table 4 summarizes the effects that occurred on serum lipids during the course of treatment. In 4 to 6 weeks, all 10 patients had a statistically significant decrease (15% on average) in their total cholesterol levels ($P < .002$). The low-density lipoprotein level decreased an average of 15.5% ($P < .005$). The high-density lipoprotein levels also decreased in each patient by an average of 15.5% ($P = .004$). The ratio of total cholesterol to high-density lipoprotein decreased insignificantly from 2.85 to 2.80 ($P = .369$).

The survey questionnaire results, summarized in Table 5, showed important improvements in several areas attributable to testosterone replacement. Most importantly, the answers to questions 2 and 3 indicated significant increases in the ability to have sexual relations and increases in spontaneous erections ($P = .005$ and .02, respectively). The responses to questions 8, 9, 10, 11, and 13 indicate improvements in memory and clarity of thought, lessening of depression, increased ability to enjoy pleasurable activities, and lessening of apathy. Statistical significance was reached in all but the clarity of thinking ($P = .06$). The responses to questions 4, 5, and 6 indicate a slight increase in oily skin, no increase in nocturia, and an improvement in urinary stream ($P = .012$, .254, and .026, respectively). The answers to questions 12 indicated a decreased level of aggression ($P = .025$). Finally, the responses to questions 14 and 15 indicated an overwhelming satisfaction with the treatment and a strong desire to continue to use a topical gel or cream in the future.

The data from questions 14 and 15 were further examined to determine whether there were any significant differences between the satisfaction levels of the group of men who had previously been on testosterone therapy compared with those who had never been on any treatment. The numerical average to questions 14 and 15 for men who had never had testosterone treatment was 1.75 and 1.25, respectively. For men who had previously been on treatment, the responses were 2.2 and 1.0. For both of these questions, there was no statistical difference between the two groups.

Testosterone levels for patients with little or no endogenous production of testosterone (patients 1, 2, 3, and 4) showed an almost continuous rise to maximum levels and reached steady state levels in 1 to 4 weeks. Figure 1 is a graph of levels in response to testosterone gel in patient 2, a man with severe hypogonadism on an increasing dose of testosterone gel. For men who were still producing some

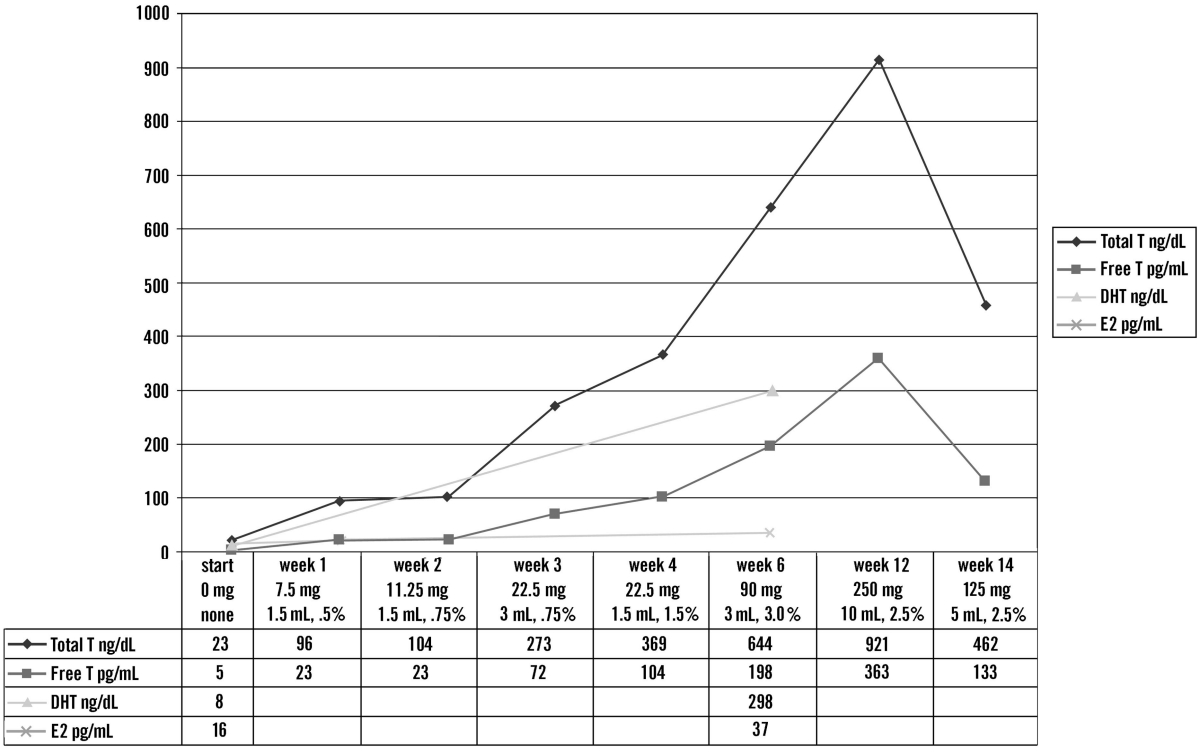
Table 5. Pretreatment and Posttreatment Questionnaire Results.

Question	Pretreatment	Posttreatment	*P* Value
1. I feel that my interest in sex has been above average	3.7	2.9	.091
2. I am able to obtain an erection strong enough for sex at least 3 times per week	3.9	1.9	.005
3. I have noticed spontaneous erections either on awakening or during the day at least 3 times per week	3.4	2.3	.024
4. My facial skin has been more oily than normal	4.5	3.8	.012
5. I am having to arise from sleep more than once to urinate	2.8	3.0	.254
6. My urinary stream has decreased noticeably	3.4	4.2	.026
7. My energy level throughout the day is as high as it should be	4.0	2.6	.001
8. I feel that my memory is good	3.3	2.1	.011
9. I feel that my thinking is clear	2.5	1.8	.066
10. I frequently feel sad or depressed	3.7	4.3	.041
11. I am enjoying the activities that I normally enjoy	2.3	1.6	.022
12. I feel that I am overly aggressive or angry	3.2	4.4	.012
13. I feel listless and apathetic frequently	2.7	4.0	.025
14. The hormone therapy that I have used in this study has worked well for me	–	1.8	–
15. If available, I would prefer to use a hormone cream for my future treatment	–	1.1	–

Score: 1 = strongly agree, 2 = mostly agree, 3 = not sure if I agree, 4 = mostly disagree, 5 = strongly disagree.

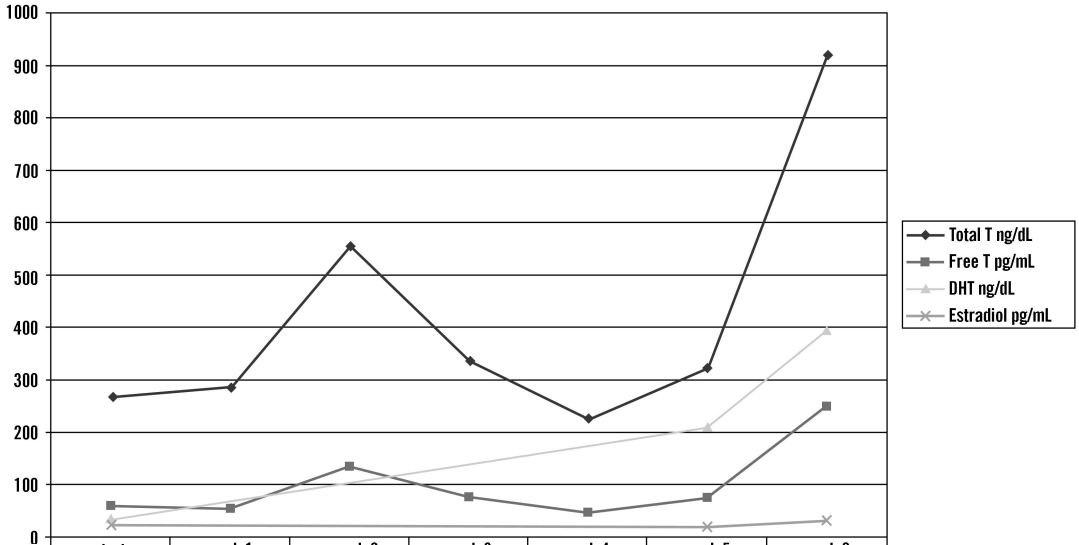
testosterone, (patients 5 through 10), there was a notable dip between weeks 2 and 4, presumably because of a shutoff of internal production. In some cases this shutoff will occur in the face of increasing dosages. The graphs for patients 2 and 8 (Figure 2) illustrate these differences.

The testosterone gel was completely free of any skin irritation. There was no erythema, rash, or



	start 0 mg none	week 1 7.5 mg 1.5 mL, .5%	week 2 11.25 mg 1.5 mL, .75%	week 3 22.5 mg 3 mL, .75%	week 4 22.5 mg 1.5 mL, 1.5%	week 6 90 mg 3 mL, 3.0%	week 12 250 mg 10 mL, 2.5%	week 14 125 mg 5 mL, 2.5%
Total T ng/dL	23	96	104	273	369	644	921	462
Free T pg/mL	5	23	23	72	104	198	363	133
DHT ng/dL	8					298		
E2 pg/mL	16					37		

Figure 1. Total testosterone (T), free testosterone, dihydrotestosterone (DHT), and estradiol (E2) levels in patient 2 (no endogenous testosterone production) during the course of the study.



	start 0 mg none	week 1 5 mg 1 mL, 0.5%	week 2 5 mg 1 mL, 0.5%	week 3 15 mg 2 mL, .75%	week 4 30 mg 2 mL, 1.5%	week 5 30 mg 2 mL, 1.5%	week 6 120 mg 2 mL, 6.0%
Total T ng/dL	268	287	555	336	226	322	922
Free T pg/mL	60	55	135	77	47	75	250
DHT ng/dL	33					210	395
Estradiol pg/mL	23					20	32

Figure 2. Total testosterone (T), free testosterone, dihydrotestosterone (DHT), and estradiol levels in patient 8 (moderate endogenous testosterone production) during the course of the study.

blistering. No participants complained of clothing staining or any other nuisance effects

Discussion

The adult human male testicles produce 7 to 10 mg of testosterone per 24 hours to maintain normal levels of virilization.[15] The goal of replacement therapy is to maintain a testosterone level between 300 to 1200 ng/dL[10] (preferably in the middle of that range), while simultaneously restoring normal sexual function, maintenance of secondary sexual characteristics, bone density, and overall well-being. This goal was attained in this study by using a convenient and simple application of a topical testosterone gel.

By providing testosterone in as physiologic a manner as possible, the milieu of sex steroid hormones will come into optimal balance. Nearly all estradiol in men is derived from peripheral aromatization of the testosterone molecule. When serum testosterone levels rise to supraphysiologic levels (as observed during the peak of a depot injection of testosterone cypionate or enanthate), the equilibrium of that conversion is pushed toward increased estradiol, with a concurrent decrease in the total androgen-estradiol ratio, and gynecomastia often results.[20] An ideal method of testosterone administration would provide an almost constant serum testosterone level with a small, early morning "pulse." Topically applied testosterone gels are absorbed rather slowly and presumably form a reservoir in the stratum corneum of the skin.[28,29] This reservoir of testosterone is then leached into the capillary circulation. In a limited kinetic study using testosterone gel performed on a normal male volunteer (unpublished), I found that testosterone levels peaked in about 6 to 8 hours, which would correspond well with an early morning peak if the patients applied the gel at bedtime.

The dihydrotestosterone levels in the study patients varied greatly from patient to patient. It was obvious, however, from looking at the data that the site of application was the primary determinant of the dihydrotestosterone levels. The 5-α-reductase enzymes are highly concentrated in the skin of the scrotum,[3,14] and those patients who applied the gel to that area had the highest levels. It is possible, therefore, to control the level of dihydrotestosterone by choosing the site of application. An elevated dihydrotestosterone level has been a source of some

concern, because of its perceived effects on prostate growth.[30] Even so, researchers reviewing the effects of the Testoderm scrotal patch and other nonscrotal patches have found few problems with prostatism.[24,31–35] Other researchers have actually shown a 15% decrease in prostate size on patients using a pure dihydrotestosterone gel.[33] Of great interest is the ability to reduce such side effects as gynecomastia by having a nonaromatizable androgen (dihydrotestosterone) as a major component of the androgen pool. Further research into using dihydrotestosterone as replacement therapy is in progress[28,36]

In this study, amounts as small as 15 mg and as much as 120 mg of topically applied testosterone gel were required to reach physiologic levels of testosterone, dihydrotestosterone, and estradiol, which implies an absorption efficiency of anywhere from 50% to as low as 6%. This finding is consistent with other researchers using gels,[28,33] where great interpatient and intrapatient variability has been observed. Patches, such as the Alza Testoderm TTS, which, in fact, actually contains 328 mg of testosterone, also suffer from low absorption efficiency.[24] The scrotal patch contains only 10 mg of testosterone.[24] Androderm 5 mg patches contain 24.3 mg of testosterone.[24] Thus, there exists little qualitative difference in the efficiency between gels and patches. Alza researchers originally developed their first patch, Testoderm, to be applied to the shaved scrotum. They found that, compared with other skin sites, the scrotal skin is about five times more efficient at absorbing percutaneously applied steroids.[17,24]

This study shows that the topical testosterone gels will suppress luteinizing hormone in most of the patients, probably after 2 weeks or more of use. This effect, in turn, results in down-regulation of the endogenous testosterone production. The levels of men who were only moderately hypogonadal (patients 5, 6, 7, 8, 9 and 10) showed a significant dip at about the third to fourth week of therapy, even in the face of increasing concentrations of the gel. This phenomenon was partially attributed to the shutting off of endogenous testosterone production and partly due to intrapatient variability in absorption. This observation is important, because clinicians must understand that once therapy is initiated in mild to moderate cases of hypogonadism, the patient will become dependent on the exogenous source for all his androgens. Hence, one cannot "give a little testosterone"; eventually full replacement doses will be required to maintain physiologic levels of androgens. Thus, the decision to start androgen replacement therapy in borderline cases must be well thought out.

The effects observed in this study on serum lipids are surprisingly uniform; however, the effects in medical reports on this subject are not.[11–13,37,38,] Despite this lack of uniformity, researchers are increasingly recognizing that testosterone is not detrimental in regard to cardiovascular effects in men. Not only is there a lowering of all the lipid fractions with replacement therapy, but there is also lowering of apolipoprotein A1 and lowering of the hepatic triglyceride lipase activity.[5,11–13,37,38] Future research in this area will help clarify the role of normal testosterone levels in cardiovascular health.

Clinicians need alternatives to the current methods available for hormone replacement therapy in men. Compliance among hypogonadal men often suffers because of the perceived inconveniences of therapy. The lack of compliance in these men leads not only to loss of sexual function but also to premature bone loss[2,4,6,10] and possibly increased coronary artery disease.[5,11,12,] Furthermore, testosterone therapy has been found to aid in the treatment of depression,[39] cognition,[8,9] wasting syndrome associated with acquired immunodeficiency syndrome[3,40] and wasting associated with chronic obstructive pulmonary disease.[41]

Despite being limited by a small sample size and a relatively short observation period, this study shows the feasibility of using topically applied gels for testosterone replacement therapy. Although the absence of blinding or placebo control has little bearing on the legitimacy of the objective measurement of the hormonal outcomes, it does compromise the significance of the subjective observations of the treatment. Thus the responses to the questionnaire (which had no previous validation of reliability testing) must be viewed with caution. Even so, the overwhelmingly positive results and comments of the patients speak highly for this mode of replacement therapy.

I have treated many men since the beginning of this study and have found that the most useful starting dose for most men is a 6% gel, 2.5 mL, applied to the nonhairy area of the axilla. After 3 to 4 weeks, testosterone, dihydrotestosterone, and es-

tradiol can be measured. If the testosterone levels are low, or if the estradiol levels are too high, then a switch to the scrotal area will usually increase both the testosterone and dihydrotestosterone levels while lowering the estradiol levels. After each change in dose, a 3- to 4-week period is required for steady state levels to be reached, even though actual levels of the hormones will increase within days.

The issue of safety was not addressed in this study. Although it might be presumed that this form of therapy would have no serious differences in safety profile compared with the transdermal patches, there are, in fact, some important concerns. Inadvertent transmission of the gels could occur if the patient did not exercise caution in application and usage. There is now one reported case of precocious puberty in a 2-year-old boy whose father was using the gel on his arms and back.[42] This child had serious virilization symptoms, and some of them did not abate after the problem was corrected (penile size was not reversible). By using the gel in the axillary area, at bedtime, transmission can be avoided. If applied to the scrotal area, sexual contact would be contraindicated until after bathing. This product should not be used in cases where a female partner might be pregnant, because effects on a female fetus might be severe and irreversible.

Until retail production of a testosterone gel is commercially available, physicians might be able to use preparations made by compounding pharmacists. It is essential that the prescribing physician keep in mind the great inter- and intra-patient variability in the absorption of topical gels. Some men might not satisfactorily absorb testosterone through the skin at all, necessitating that parenteral methods be used instead. It is the responsibility of the treating physician to ascertain the effectiveness of these preparations by appropriate measurement of the serum levels in each patient. Finally, it is essential that the family physician spend time with his hypogonadal patient explaining not only the benefits and limitations of treatment but also safety issues. Some hypogonadal men will not respond to testosterone therapy with improved sexual function.[43,44] It is critically important that the patient understand that his treatment regimen is designed to offer him many benefits that do not simply begin and end with sexual performance.

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