TRANSDERMAL (TD) TESTOSTERONE (T)

A Critical Review of the Literature and Available Data

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KEY POINTS AND BEST PRACTICES

Treatment/Dosing

- **In most male patients, 50-100mg TD T gel produces clinical changes in alignment with typical T injections.**
  - Doses applied to the scrotum may have >20x higher absorption and doses <50mg are used.
- In female patients, 1-5mg TD T gel/cream is common, but doses as high as 20mg have been used without significant side effects.
- No published studies have assessed the clinical impact of TD T creams. Available data implies somewhat higher (~2x) doses may be needed to increase serum similarly to TD T gels.

Laboratory Monitoring

- **Serum testing for TD T monitoring appears to be a reasonable approach for clinical practice, especially when using alcohol-based gels.**
  - **No studies have been found where serum values lag behind the clinical impact and multiple studies have shown clinical improvement only when serum levels increase.**
- Urine testing provides a useful complement to serum testing for monitoring TD T.
  - Serum testing may be more reliable in patients with abnormal phase II metabolism (a harmless variant is seen in especially high percentages of Asians, resulting in falsely low urine levels).
  - The DUTCH Test offers additional information (progesterone, estrogen & androgen metabolites, free cortisol and cortisol metabolites, organic acids, melatonin, and 8-OHdG) to improve the overall interpretation.
- **Salivary and capillary blood spot testing should not be used to monitor TD T creams or gels.**
  - Values following therapy are routinely supraphysiological with doses not proven to be effective. The observed exaggerated responses seen are not known to be consistent with any clinical parameters from any published study.

NOTE: *This material is educational and not an endorsement for a particular HRT dose or route of administration.*

SUMMARY

CLINICAL ENDPOINTS STUDIED TO DATE

LH/FSH suppression, increased sexual characteristics and function, mood, bone mineral density (BMD), cognition, muscle mass, and hematocrit are a non-exhaustive list of clinical parameters that have been studied relative to testosterone (T) therapy.

DOSES ASSOCIATED WITH CLINICAL IMPACT

TESTOSTERONE GELS - Androgel, and AndroGel-like products, claim to deliver 9-14% of their product, which implies that the typical 50-150mg doses supply about the same testosterone as the testes make each day (Wang C, et al., 2004). A number of publications report transdermal testosterone doses of 10-30mg (some as high as 50mg) used in women without significant symptoms related to high testosterone. Therefore, it seems intuitive that male doses begin around 50mg. A 50mg dose suppresses LH and FSH modestly, in alignment with typical testosterone injections (Swerdloff RS, et al., 2000). Fifty to one-hundred milligram (50-100mg) doses were sufficient to increase muscle mass but only in the patients who saw an increased serum T (Sattler F, et al. 2011). Hematocrit exceeds expected levels when testosterone spends significant time in a supraphysiological state. A 50mg testosterone gel increases erythrocytosis only 17% as high as 100-200mg testosterone-cypionate/enanthate injections. Increasing the TD gel dose to 100mg increased erythrocytosis some but it remained less than both injections and pellets. (Ohlander SJ, et al., 2018). Sexual function, mood, lean body mass, and bone mineral density (BMD) were all shown to increase with 50-100mg comparable to other forms of testosterone therapy (Wang C, et al., 2004) when a normal male range was the target. The same doses also improved cognition in hypogonadal men (Cherrier MM, et al. 2003). Research using 10-30mg has shown to improve symptoms in women without significant side effects (Waldman T, et al., 2012; Chaikittisilpa S, et al., 2019; Nathorst-böös J, et al., 2005; Smith GI, et al., 2005; Kim CH, et al., 2005).

Conclusions:

- Transdermal gels, 50-100mg, produce clinical changes in alignment with injections or pellets.
- Excess testosterone signs (LH suppression, increased hematocrit) are significantly less with transdermal testosterone (100mg-200mg) compared to testosterone injections.

TESTOSTERONE CREAMS - There are limited studies involving testosterone creams because pharmaceutical companies have chosen to prefer alcoholic gel preparations. One product (Andromen Forte) has published data showing that doses twice as high as an alcoholic gel produced an equivalent serum response with similar clinical responses (LH suppression, increased hematocrit). The Andromen Forte study also showed improvements in mood, energy, and sexual function. It does not appear that these studies were placebo controlled. It may be significant that the doses were increased to as high as 150mg without significant negative effects. About 70% of the subjects decided to stay on the product while the remainder decided to return to other therapies that they felt were

more effective. No changes in therapy after the study appeared to be from excess testosterone. This product was also used in one study with female patients (10mg) showing modest clinical improvements and serum increases with no excess androgen effects.

Conclusions:

- Limited information is available, but available data implies that testosterone creams are slightly less effective than gels.
- Doses >100mg may be more common with testosterone creams to achieve clinical impact.

HOW DOES LAB TESTING CORRELATE WITH DOSES AND CLINICAL CHANGES?

SERUM - Serum testosterone concentrations increase with increasing transdermal doses and patient clinical impact. In men with suppressed endogenous testosterone, transdermal testosterone gel 50-100mg restored "normal" levels. These doses have also been used in many studies to increase hypogonadal men's T levels to within the reference ranges.

Brockenbrough AT, et al., 2006 highlighted serum's value through a negative study. Men were given 100mg of testosterone gel. Serum levels increased less than normal (77 vs. the usual 250-300ng/dL) and no improvements were seen in any clinical parameters (BMD, lean body mass, sexual function, mood). Studies with higher serum levels reported clinical success, many with the lower 50mg dose.

Chaikittisilpa S, et al., 2018 and Pelusi C, et al., 2014 offer compelling contrasts. Both of these studies gave TD T gel (50mg) to women. Pelusi only moved serum levels into an expected range for young women and had no reports of increased facial hair. The other study increased levels to normal male ranges when treating transsexual women-to-men transitions with expected accompanying symptoms (in this case symptoms that were desired). This study showed similar clinical outcomes and serum levels with injections. When comparing Chaikittisilpa S, et al. 2018 and Pelusi C, et al., 2014 serum T seems an accurate reflection of the clinical reality.

Korenman SG, et al., 1987 and Cunningham GR, et al., 1989 both showed higher than

expected serum levels using a scrotal delivery system. By dispensing only 5.2mg of testosterone from a patch containing 16.2mg, serum levels increased from 225 to 640ng/dL. Twice the dose was applied to the thigh (32.4mg) with the same system and serum levels increased only marginally. Testosterone is absorbed 20-30 times more efficiently with scrotal application, and this is reflected in serum testing.

Conclusions:

- Serum testing for TD T monitoring appears to be a reasonable approach for clinical practice, especially when using alcohol-based gels.
- No studies have been found where serum values lag behind the clinical impact.
  - If the exaggerated responses in salivary or capillary blood spot were accurate, we would expect to find studies with clinical improvement and little serum movement.
- Multiple studies have shown clinical improvements only when serum levels increase.

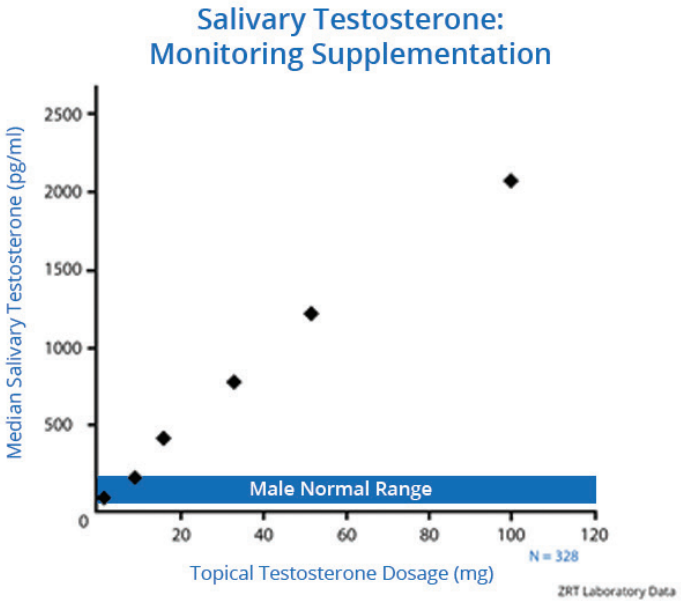
URINE - About 90% of testosterone is excreted in the urine (publication available but not included). Precision Analytical has provided data for gels and creams, and results increase linearly with increased doses. A general parallel is seen between TD T DUTCH urine data and TD T serum data. TD T in a cream base must be dosed twice as high as testosterone gels to achieve the same urine levels (as is the case with serum). Furthermore, the gels appear to suppress LH more so than creams. This is seen in the DUTCH test as epi-testosterone values (an indication of testicular androgen production) are about 50% higher with a 50mg TD T cream when compared to a gel formulation.

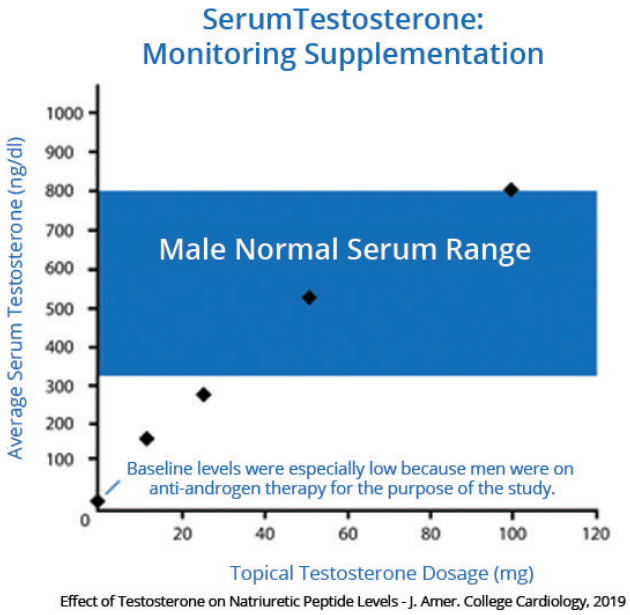
Conclusions:

- Serum testing may be more reliable in patients with abnormal phase II metabolism (a harmless variant is seen in especially high percentages of Asians, resulting in falsely low urine levels).
- The DUTCH Test offers additional information (progesterone, estrogen & androgen metabolites, free cortisol and cortisol metabolites, organic acids, melatonin, and 8-OHdG) to improve the overall interpretation.
- More research directly correlating increases in urine and serum results with clinical outcomes would increase confidence in using urine testing to monitor and adjust therapy.

SALIVA - Dramatic increases in testosterone values following the application of both creams and gels are seen with saliva testing. No known clinical data parallels these exaggerated increases. Doses proven to be clinically effective in men increase salivary values 10-100 times above “normal” levels. Women using 1-2mg show levels higher than the salivary male reference range. In studies (Goldstat R, et al., 2003; Nathorst-Böös J, et al., 2005; Smith GI, et al., 2014; Kim CH, et al., 2014) where women received ≥ 10mg TD T, serum levels neither increased to the male reference

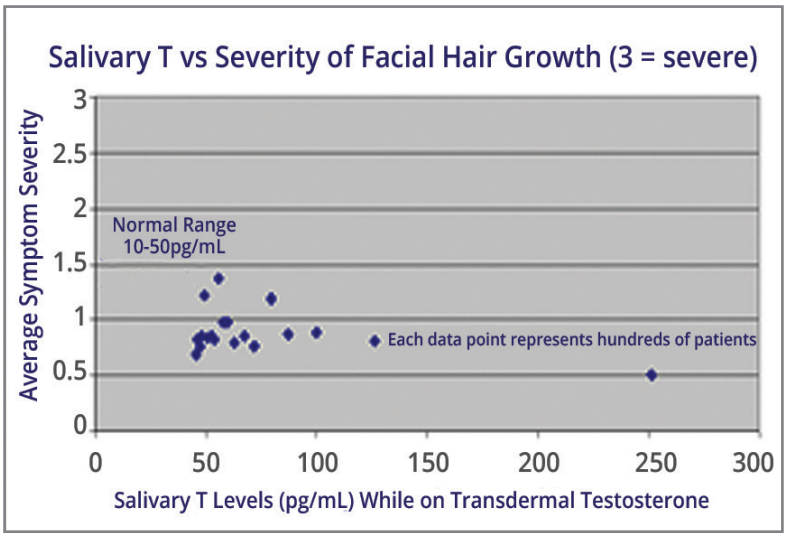
range nor did any subject have excess testosterone complaints. The following graphs show the dramatic difference between the responses in serum and saliva when using transdermal T (serum values are for men on anti-androgen therapy causing low baseline values).





Effect of Testosterone on Natriuretic Peptide Levels - J. Amer. College Cardiology, 2019

One salivary testing laboratory (RMA, Calgary) presented data showing a lack of testosterone-related symptoms with on-therapy levels. Hundreds of women on TD T therapy reported their symptoms and their salivary concentrations were measured. As salivary responses increased from the normal range to values 5x higher than the top of the range, symptoms did not change significantly. If salivary values told the true story of systemic testosterone exposure at the tissue level, one would expect women at these high levels to experience symptoms like excess facial hair growth. The highest point reported is more than two times higher than the high range limit for male patients.



Conclusions:

- Salivary testing should not be used to monitor transdermal testosterone cream or gels.
- The salivary gland seems to have some sort of preferential access to transdermal hormones.
  - This exaggerated response is not known to be consistent with any individual clinical parameters from any published study.
- There is NO evidence of laboratory validity or clinical utility using salivary testosterone testing when testosterone is applied as a transdermal cream or gel.
- If future studies prove that tissue other than the saliva gland is represented by the massive hormone uptake in salivary testing, these conclusions may be updated.

TRANSDERMAL TESTOSTERONE – A WALK THROUGH THE LITERATURE

EXECUTIVE SUMMARY

Part two of Precision Analytical's ongoing literature review's primary purpose is to evaluate serum and saliva testing's clinical utility for monitoring transdermal testosterone therapy. These studies were chosen because of their value in tying specific doses to changes in lab values and/or clinical parameters. Though urine testing has generally followed serum trends, urine testing is not the subject of this review. The following is a non-exhaustive review of the most compelling research published to date on this subject.

STUDIES REPORTING CLINICAL OUTCOMES WITH PARTICULAR DOSES OR SERUM RESULTS

1. Wang C, et al. Transdermal Testosterone Gel Improves Sexual Function, Mood, Muscle Strength, and Body Composition Parameters in Hypogonadal Men. J Clin Endocrinol Metab. 2000; 85: 2839-2853.

This study used 50-100mg doses, titrating to result in all men falling in the normal male range for testosterone. One study participant's dose was reduced to 25mg because of elevated levels on 50mg. The rest were fairly evenly spread between 50, 75 and 100mg of AndroGel. "The increase in lean mass and the decrease in fat mass were correlated with the changes in average serum T levels attained after transdermal T replacement."

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2. Wang C, et al. Long-term testosterone gel (AndroGel) treatment maintains beneficial effects on sexual function and mood, lean and fat mass, and bone mineral density in hypogonadal men. J Clin Endocrinol Metab. 2004; 89(5):2085-2089.

Conclusions are similar to their above 2000 study, but adds bone mineral density by extending the 6-month study to 42 months with 50-100mg dosing. "Sexual function and mood parameters improved rapidly and were maintained throughout T treatment." It was also noted that there were "beneficial effects similar to those with injectables" with similar serum T levels.

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3. Brockenbrough AT, et al. Transdermal Androgen Therapy to Augment EPO in the Treatment of Anemia of Chronic Renal Disease. Am J Kidney Dis. 2006; 47(2): 251-262.

In contrast to the two studies listed above, this research used 100mg of testosterone gel (Testim, in this case) and did not see significant serum increases. Wang C, et al., consistently found men on AndroGel therapy in the male reference range and saw clinical improvement. This study using Testim only increased T levels 77ng/dL on average (250-300ng/dL increase seen in AndroGel studies). None of the clinical parameters (including sexual function, mood, BMD and lean body mass) showed improvement.

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4. Sattler F, et al. Testosterone Threshold Levels and Lean Tissue Mass Targets Needed to Enhance Skeletal Muscle Strength and Function: The HORMA Trial. J Gerontol. 2011; 66(1): 122-129.

A terrific study in which men had their endogenous testosterone production suppressed and were then supplemented with transdermal T (50 or 100mg). The men were evaluated in two groups – those whose serum T was higher than at baseline and those for which serum T was not higher than before suppression and supplementation. Only those men whose T increased saw an increase in lean body mass.

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5. Wang C, et al. Pharmacokinetics of Transdermal Testosterone Gel in Hypogonadal Men: Application of Gel at One Site Versus Four Sites: A General Clinical Research Center Study. J Endocrinol Metabol. 2000; 85(3): 964-969.

This study seems to be the source others use in claiming an AndroGel absorption rate of 9-14%. The author states, "assuming all endogenous T was suppressed." This assumption seems faulty given that the 100mgs given in this study has been shown to only partially suppress testosterone. If this assumption is NOT true, the 9-14% absorption for 100mg dosing would be a high estimate. Absorption can be improved by applying to the scrotal skin which has a thin outer layer and unique vascularity.

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6. Korenman SG, et al. Androgen Therapy of Hypogonadal Men with Transscrotal Testosterone Systems. Am J Med. 1987; 83(3): 471-478.

A testosterone patch for scrotal application was developed and utilized. The amount of testosterone left in the patch after 24 hours was determined. A 16.2 mg dose resulted in 5.2mg lost to absorption; serum levels increased from 225 to 640ng/dL, an increase comparable to that seen with testosterone injections. When the dose was doubled to 32.4mg and the patch was applied to the thigh, only 2.3mg (7%) was absorbed and serum levels increased very slightly. This study showed that when the absorption of a transdermal product is improved, it is seen in serum results. This review and these statements are in no way an endorsement of any particular method of testosterone delivery (such as scrotal).

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7. Cunningham GR, et al. Testosterone Replacement with Transdermal Therapeutic Systems. JAMA. 1989; 261(17): 2525-2530.

Korenman's work (above) was continued with 5, 10, and 15mg doses of a scrotal testosterone patch. Serum levels around 500ng/dL were established after 8 weeks of therapy.

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8. Iyer R, et al. Pharmacokinetics of Testosterone Cream Applied to Scrotal Skin. Andrology. 2017; 5(4): 725-741.

This study more definitively defined the scrotum's absorption differences. A direct comparison (same formulation and same LC-MS/MS serum assay) between 12.5mg applied to the scrotum and 100mg applied to the abdomen showed that maximum serum levels differed by just 2% (4.6 vs 4.7ng/mL). The men in this study had their endogenous T production completely suppressed, so levels of 460ng/dL (normal male levels) were achieved with these applications, with 8-times more T used when applied to the abdomen. This study also shows that creams (most data is for alcoholic gels) can increase serum levels, but it seems to be poorly absorbed from most skin locations.

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9. Rolf C, et al. Interpersonal Testosterone Transfer After Topical Application of a Newly Developed Testosterone Gel Preparation. Clin Endocrinol (Oxf). 2002; 56(5): 637-641.

Rolf showed that 8 hours after testosterone gel application (about the time serum and saliva levels peak), 60% of the testosterone could be recovered from the skin (with alcohol and a swab), which implies that the delivered dose is likely considerably smaller than the actual size administered.

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10. Ohlander SJ, et al. Erythrocytosis Following Testosterone Therapy. Sex Med Rev. 2018; 61(1): 77-85.

If 50-100mg of transdermal testosterone is a reasonable dose, testosterone-induced erythrocytosis should not be excessive. T gels were compared to typical injections and pellet insertions. Nearly 70% of patients receiving 100-200mg intramuscular injections showed a rate of erythrocytosis >50%. For 750-1050mg pellet insertions 35% were >50%. Testosterone gels only resulted in 13% of patients with erythrocytosis >50%. Serum levels in the three treatment arms of the study were not significantly different.

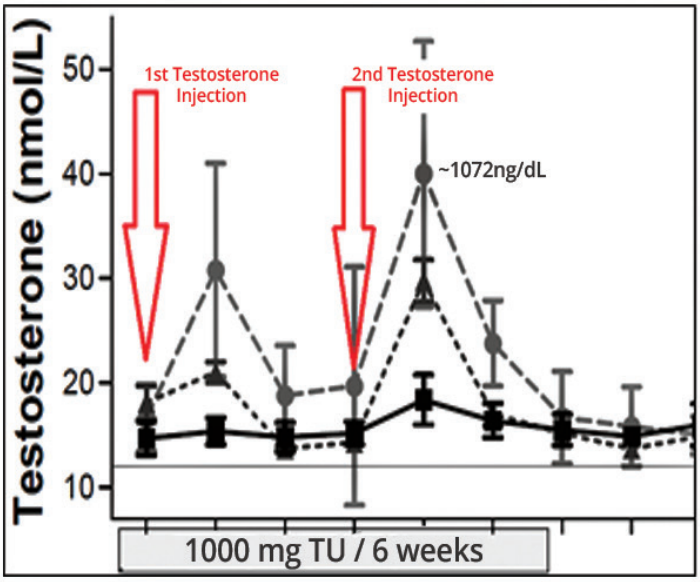
STUDIES SHOWING LESS LH SUPPRESSION WITH TRANSDERMAL THERAPY COMPARED TO INJECTIONS

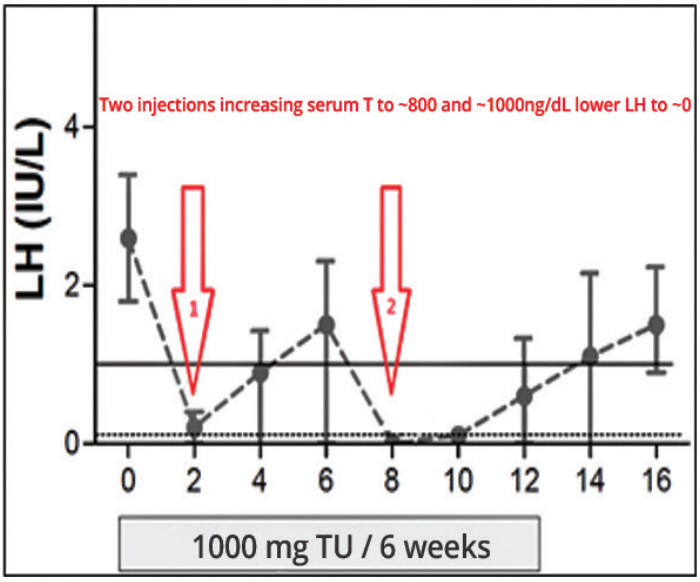
11. Swerloff RS, et al. Long-Term Pharmacokinetics of Transdermal Testosterone Gel in Hypogonadal Men. J. Endocrinol Metab. 2000; 85(12): 4500-4510.

Authors increased serum levels from 220ng/dL to 514ng/dL with 50mg and 736ng/dL with 100mg of AndroGel. LH values were suppressed about 60% from baseline values with 50mg and about 80% when using 100mg T. See below for LH suppression responses to testosterone injections.

12. Kornmann B, et al. Body Fat Content and Testosterone Pharmacokinetics Determine Gonadotropin Suppression After Intramuscular Injections of Testosterone Preparations in Normal Men. J Androl. 2009; 30(5): 602-605.

This study tracks LH suppression in men receiving Testosterone Undecanoate (TU) injections every six weeks. LH levels two weeks after the first two injections, in men whose serum T rose to ~1,000ng/dL, were around zero (total suppression).





13. Shulte-Beerbuhl M, Nieschlag E. Comparison of Testosterone, Dihydrotestosterone, Luteinizing Hormone, and Follicle-Stimulating Hormone in Serum After Injection of Testosterone Enanthate or Testosterone Cypionate. Fertil Steril. 1980; 33(2): 201-203.

This study shows LH suppression in alignment with 50-100mg of testosterone gel, potentially implying the appropriateness of these dosing strategies.

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14. Camino-Torres R, et al. Testosterone-Induced Inhibition of the LH and FSH Responses to GnRH Occurs Slowly. J Clin Endocrinol Metabol. 1976; 44(6): 1142-1153.

Researching testosterone injections, this study was able to show that LH will be fully suppressed after 1-2 months of high testosterone exposure. They concluded that "in order to inhibit markedly the LH and FSH responses to synthetic GcRH, the serum testosterone concentration must be raised to 150% above mean normal level for 28 days in normal men and for 28 to 56 days or longer in men with primary hypogonadism." This is significant because salivary values in men using 50mg of testosterone cream or gel are typically >150% above normal levels continuously with daily use. ZRT Laboratory reports a 20th to 80th percentile range of 500-4000pg/mL (normal male range 44-148pg/mL) for AndroGel 50mg when samples were collected a full 24 hours after application (much higher 8-12 hours after application).

STUDIES SHOWING A LACK OF EXCESS TESTOSTERONE SYMPTOMS IN WOMEN USING 10-50MG TD TESTOSTERONE

15. Nathorst-Böös J, et al. Percutaneous Administration of Testosterone Gel in Postmenopausal Women – A Pharmacological Study. Gyn Endocrinol. 2005; 20(5): 243-248.

Women given 10-30mg of transdermal testosterone (Testogel) increased serum levels from 1.1nmol/L (29.5ng/dL) to 3.2nmol/L (normal for a premenopausal woman) with 10mg and as high as 7.5nmol/L with 30mg. Even with the highest dose, the treatment was well tolerated by all participants.

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16. Smith GI, et al. Systemic Delivery of Estradiol, but not Testosterone or Progesterone, Alters VLDL-Triglyceride Kinetics in Postmenopausal Women. J Clin Endocrinol Metab. 2014; 99(7): E1306-E1310.

17. Kim CH, et al. Ovarian Features After 2 Weeks, 3 Weeks and 4 Weeks Transdermal Testosterone Gel Treatment and Their Associated Effect on IVF Outcomes in Poor Responders. Dev Reprod. 2014; 18(3): 145-152.

The two studies above are examples of treatment protocols for women, both using 12.5mg of AndroGel without reporting any symptoms of excess testosterone (locally or systemically).

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18. Goldstat R, et al. Transdermal Testosterone Therapy Improves Well-Being, Mood, and Sexual Function in Premenopausal Women. Menopause. 2003; 10(5): 390-398.

This paper reported 10mg of T cream with increased serum levels (1nmol/L to 2.6nmol/L) and improved sexual health. None of the women reported acne, voice changes, or skin reactions.

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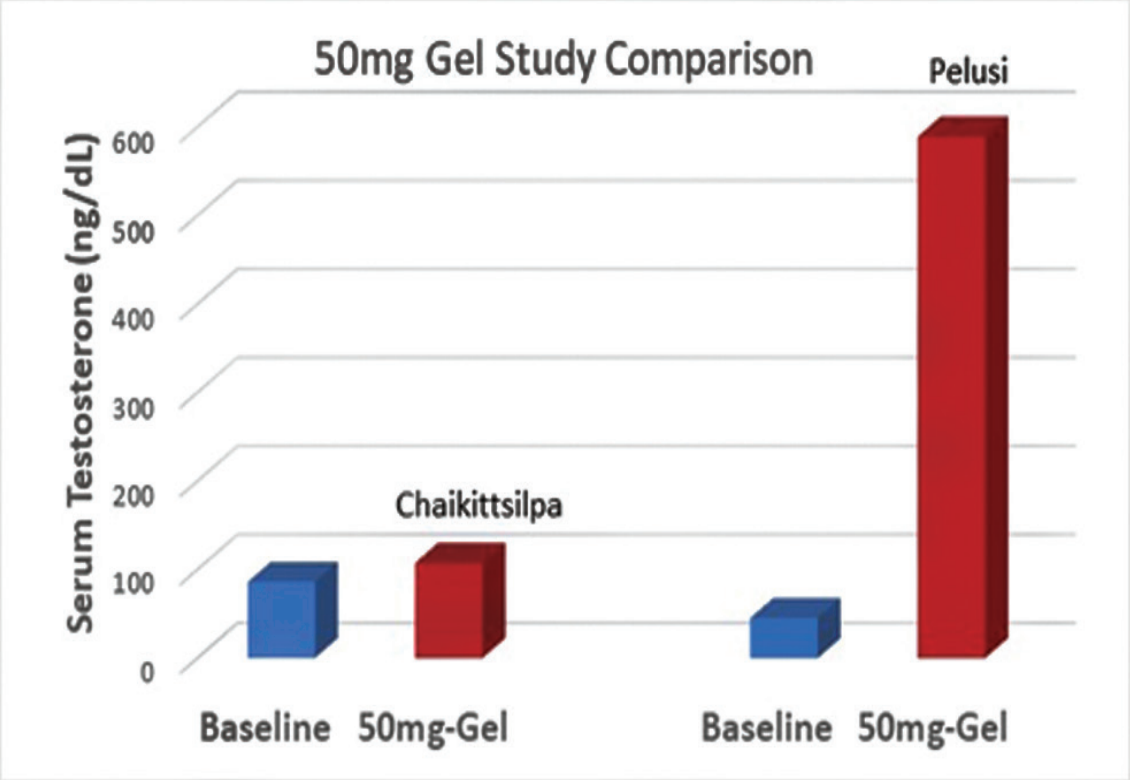
19. Chaikittsilpa S, et al. Efficacy of Oral Estrogen Plus Testosterone Gel to Improve Sexual Function in Postmenopausal Women. Climacteric 2019. DOI: 10.1080/13697137.2019.1577378.

20. Pelusi C, et al. Effects of Three Different Testosterone Formulations in Female-to-Male Transsexual Persons. J Sex Med. 2014; 12: 3002-3011.

The two studies above show serum testing's utility for monitoring the biological effect of treatment. Both studies used 50mg of transdermal testosterone. In the first study, serum levels increased marginally (0.32 to 0.4nmol/L) as the 50mg was administered weekly. The women reported improved sexual function and no adverse effects (some acne was reported). Conversely, the second study reported massive serum T increases (45 to 589ng/dL) which was similar to 100mg testosterone enanthate (typical male dose) injection. Female-to-male transitions obviously desire male secondary sex characteristics, and the gel and injections performed similarly.



STUDIES USING TESTOSTERONE CREAMS

Pharmaceutical products heavily favor alcoholic gels. There are no FDA approved testosterone cream products, though they are used routinely in compounded products. Five studies using testosterone creams were located, and all five studies (four in men, one in women) used the same Australian product (Andromen-Forte). Conclusions about this particular cream may not translate to other creams.

21. Kelleher S, et al. Long-Term Pharmacokinetics and Clinical Efficacy of Andromen Forte 5% Cream for Androgen Replacement Therapy in Hypogonadal Men – Industry publication by Lawley Pharmaceuticals. 2004.

22. Kelleher S, et al. Pharmacokinetics of Andromen Forte 5% Cream: A Dose Finding Study – Industry publication by Lawley Pharmaceuticals.

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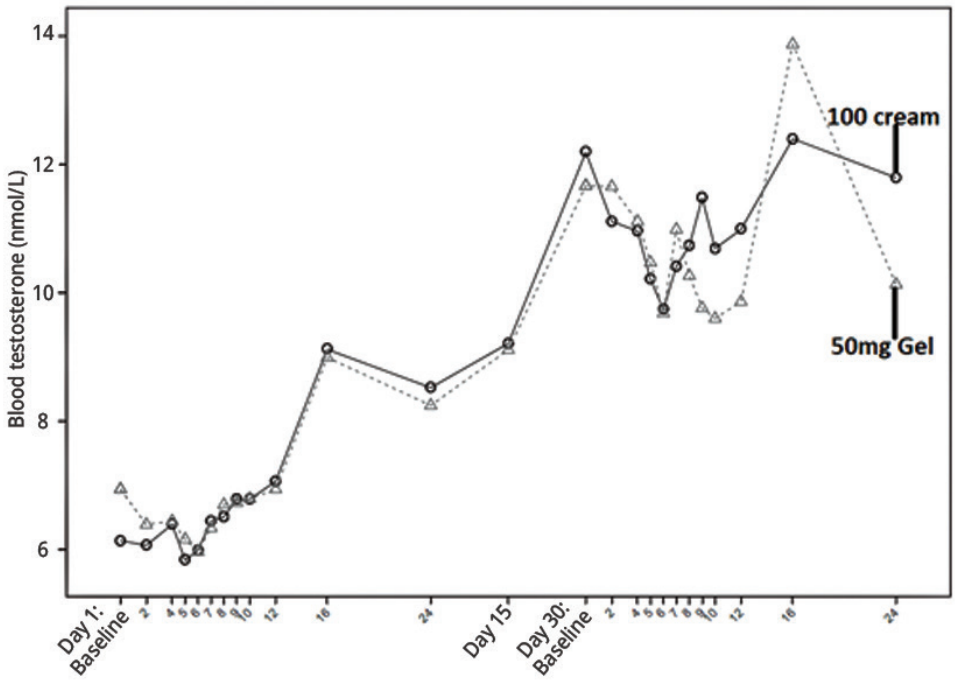
23. Wittert GA, et al. An Open-Label, Phase 2, Single Centre, Randomized, Crossover Design Bioequivalence Study of AndroForte 5% Testosterone Cream and Testogel 1% Testosterone Gel in Hypogonadal Men: Study LP101. Andrology. 2016; 4(1): 41-45. [Data seen in graph below comparing 100mg cream with 50mg gel (equivalent serum T)].

SEE #18: Goldstat R, et al. Transdermal
Testosterone Therapy Improves well-being, Mood, and Sexual Function in Premenopausal Women. Menopause. 2003; 10(5): 390-398. [Referenced earlier]



The Andromen Forte studies show that men titrated into a male normal range for serum T reported improved mood, energy, and sexual health; but the study did not seem to be placebo controlled. Wittert showed similar serum increases using 100mg of Andromen Forte and 50mg of a T gel. Studies performed by the manufacturer reported more significant T increases in serum using this dose of the T cream. Testosterone creams may increase serum levels and, when they do, clinical improvements seem to parallel serum increases. There is far more data to support the use of testosterone gels compared to creams, but the data available implies tracking both with serum (and presumably urine) values can lead to successful treatment.

SEE #8: Iyer R, et al. Pharmacokinetics of Testosterone Cream Applied to Scrotal Skin. Andrology, 2017; 5(4): 725-741. [Referenced earlier]

As was shown with other delivery systems, testosterone creams were absorbed (as estimated by observed increases in serum levels) much more readily when applied to the scrotum. The Iyers study reported 8 times higher absorption with scrotal application compared to abdominal application. Scrotal application is the only reported transdermal application in which less than 25mg successfully raised serum levels.

ARE THERE STUDIES SHOWING CLINICAL PARAMETERS INCREASING IN PARALLEL WITH SALIVA OR CAPILLARY BLOOD SPOT VALUES?

We were not able to locate any studies that implied that serum levels underestimate the clinical impact when on TD T therapy. One study, Basaria S, e al., 2010 reported negative outcomes with typical TD T doses but none of the critiques of the study (or the study itself) implied that serum testing or overdosing was problematic.

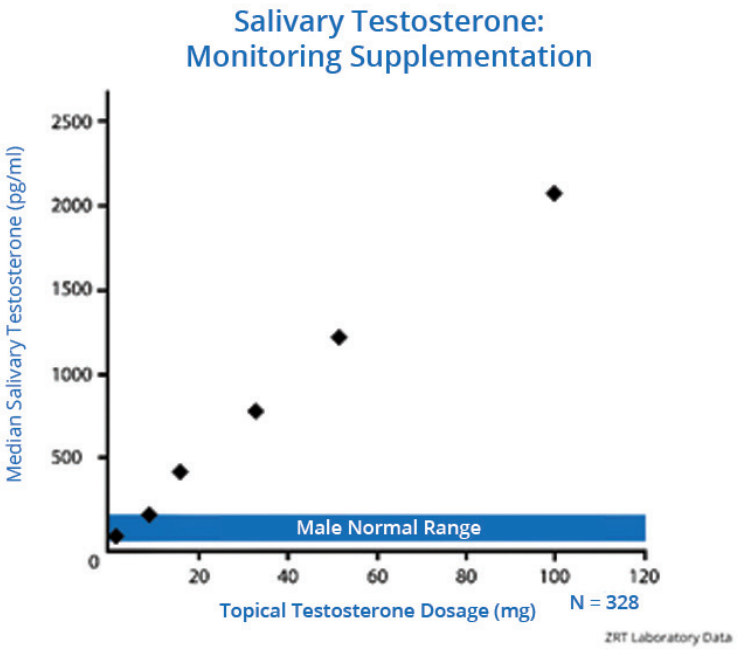
It has been reported that salivary testosterone values increase as much as 75 times above normal male levels. An abstract entitled "Can Salivary Testosterone be used in the Monitoring of Men using Transdermal Testosterone Replacement Therapy?" was published in Endocrine Abstracts (2017) by Tomas Ahern. In this abstract, salivary T values were reported to increase 75x with 30-60mg of T with typically modest increases in serum T.

ZRT Laboratory has reported salivary values 12 and 24 hours after therapy for both men and women. The normal ranges (with no therapy) given are 44-148pg/mL for men and 16-55pg/mL for women. As can be seen below, the range for women on 2mg of transdermal T exceeds the normal male range. The male range on 50mg T (cream) is 700-30,000pg/mL at 12 hours and 400-6,000pg/mL 24 hours after treatment. One in five men present with salivary testosterone values more than 200 times the high end of the normal range 12 hours after just 50mg of T. Various doses do show a linear, dose-dependent relationship. Given the vast amount of clinical data reported in the pages above, clinical utility seems unlikely. To date, no published study has correlated any clinical outcome with the increased concentrations found in saliva.

Data provided by ZRT Laboratory (recent educational presentation) shows that 50mg of transdermal T produces salivary levels >1,000pg/mL (normal male levels 44-148pg/mL). These values are believed to be collected 24 hours after therapy. The remainder of the day, values would be

OBSERVED SALIVARY TESTOSTERONE RANGES FOR BIOIDENTICAL TESTOSTERONE PRODUCTS

Route of Administration	Time Since Dosage (hours)	Dosage (mg)	Observed Range 20th %	50th %	80th %
Topical (Female)	12	1	35	75	180
Topical (Female)	12	2	40	120	350
Topical (Female)	24	1	25	44	100
Topical (Female)	24	2	30	56	135
Topical (Male)	12	50	700	3000	30000
Topical (Male)	24	50	400	1175	6000
Topical (Male)	24	50 (Androgel)	500	1600	4000
Topical (Male)	24	100	700	2000	8500



much higher, falsely implying that these modest doses of T are massive doses. We would expect this type of increase to behave similarly to the types of doses seen in men taking anabolic steroids in excessive doses (complete LH suppression, atrophied testes, hyperandrogenic behavior, etc.). Some saliva labs offer a solution of waiting longer after supplementation to collect samples, but this doesn't eliminate the fact that dramatic increases seen directly following supplementation do not correlate to any clinical change.

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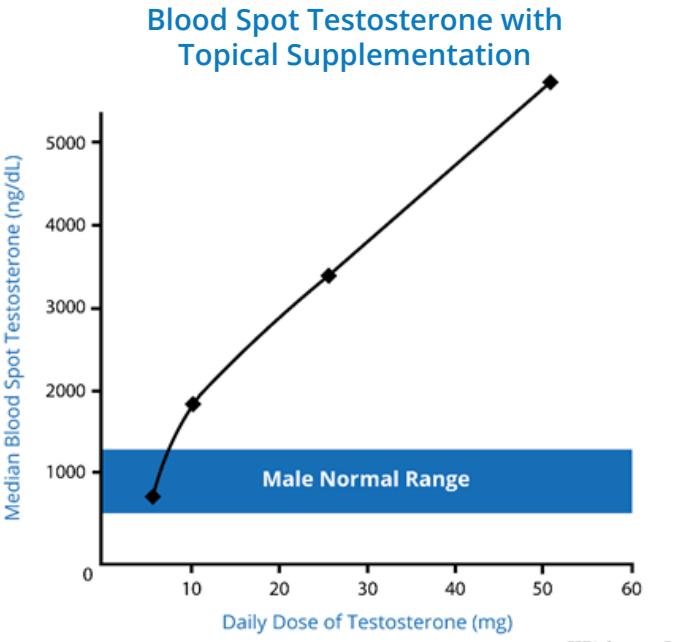
24. Flyckt RL, et al. Comparison of Salivary Versus Serum Testosterone Levels in Postmenopausal Women Receiving Transdermal Testosterone Supplementation Versus Placebo. Menopause. 2009; 16(4): 680-688.

This study looked at salivary testosterone levels compared to serum (total and free) testosterone concentrations. Correlation between salivary T and any serum measurement was poor.

It has also been reported (by ZRT Laboratory) that capillary blood from a fingerstick also shows very high levels of testosterone when transdermal T is administered (similar to salivary values). Results are reported to correlate with serum concentrations with no exogenous testosterone application.

Serum levels in the thorough study by Swerdloff RS, et al. (#11, referenced earlier) increased from 220ng/dL (hypogonadal) to 526ng/dL with transdermal T 50mg and to 736ng/dL with 100mg. Precision Analytical's urine results show analogous results in the middle of the male range with 50mg (63ng/mg) and were 20% higher with 100mg dosing.

Capillary blood spot values for men without therapy should be similar to serum values (likely 200-300ng/dL). With TD T 50mg, the average male has a blood spot value of >5,000ng/dL. Even a 10mg dose (that in females has regularly been shown to not be excessive) increased blood spot levels to nearly 2,000ng/dL. The latter exemplifies the exaggerated blood spot values seen with transdermal testosterone supplementation.



GIVEN THE LACK OF SUPPORTING DATA, WHAT DEFENSE IS OFFERED FOR SALIVARY TESTING?

As it specifically relates to transdermal testosterone salivary monitoring, there is no scientific evidence available to support this testing modality. Instead, labs offering this modality point to a list of references that center around the fact that when applying transdermal progesterone, salivary progesterone levels increase whereas serum levels do not.

The lack of clinical utility for salivary monitoring of transdermal progesterone is addressed in an additional publication. However, testosterone and progesterone do not behave in a sufficiently similar manner to make assertions about testosterone based on progesterone data. 64mg of transdermal progesterone DOES NOT increase serum progesterone levels, whereas similar doses of transdermal testosterone consistently increase serum T levels.

In serum, progesterone's highly lipophilic nature creates unique behavior, and parallels between the two hormones (progesterone and testosterone) should not be made without independent verification of testosterone's behavior. This finding has been confirmed with Precision Analytical's urine testing. Transdermal progesterone does not increase urine metabolites in a dose-dependent manner. On the other hand, testosterone (and estrogen) urine values do increase in a dose-dependent manner. Each hormone (and each route of administration) must be independently validated for a particular test. In addition to no clinical utility studies, there are no laboratory validity studies (published or unpublished) confirming salivary testing as a reliable option.

CONCLUSION:

The current scientific evidence does not support the use of capillary blood spot or salivary testing for monitoring transdermal testosterone therapy. Each of the ~ 25 listed references point towards the relevance of transdermal testosterone serum monitoring. None of the references support the concept of using salivary testing (or capillary blood spot) either using a healthy male range or an exaggerated supplementation range. Salivary T has been shown to correlate with free T levels measured in serum when there is no therapy.

In men, at least 10 different clinical parameters improved when testosterone levels increased to the normal male serum range. Conversely, multiple studies have shown a lack of clinical improvement when the TD T therapy did not significantly increase serum T.

TD T urine values usually correlate with the increase in serum levels. More research needs to be done to further connect urine testosterone (and metabolites) to specific clinical endpoints. Unfortunately, most clinical research has yet to include urine measurements.

Finally, a great deal of confusion remains, and additional research is needed to further clarify the clinical reality following transdermal testosterone application.

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