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REVIEW

Topical Testosterone Gel for the Treatment of Male Hypogonadism

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Abstract

Objective: This review describes the current knowledge of biological external testosterone (T) application using dermal products for the treatment of late-onset male hypogonadism (LOH).

Methods: An English language search of medical literature using Pubmed was conducted between January of 1984 and March of 2012 using the search term 'testosterone gel'. Special emphasis was given to clinical controlled trials and large case studies.

Results: We describe the current knowledge on testosterone replacement therapy using gel applications. A reference search revealed 1567 publications; 44 were clinical studies in human patients with male hypogonadism, 80 were reviews, 27 were case reports, and 9 were retrospective studies. Data from the literature and from 20 clinical studies involving human patients were analyzed since they met the inclusion criteria of testosterone gel administration in hypogonadal males. For the purpose of this review, a total number of 2,378 human patients were studied. Overall, biological T administration resulted in improvement of sexual dysfunction and symptoms of metabolic syndrome and represented an effective and safe treatment option for hypogonadal men.

Conclusions: Administration of biological T gel appears to represent a valid alternative treatment option for male hypogonadism with a favorite efficacy and safety profile.

Keywords: testosterone gel, late-onset hypogonadism, testosterone deficiency, testosterone application

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Introduction

Testosterone (T) is the principal androgen in human male synthesized in the testis and adrenal cortex. Its major physiologic roles include the development of normal males as well as maintenance of many male characteristics, including muscle mass, strength, bone mass, libido, potency and spermatogenesis.[1] Epidemiology studies have found a decrease of serum T with normal aging.[1–4] A number of guidelines have since been published in an attempt to define the condition of low T and recommend appropriate treatment.[1,5,6] However, controversies remain as to the appropriate approach to the diagnosis and treatment of late-onset hypogonadism (LOH).[1]

LOH is characterized by T deficiency in aging men, accompanied by clinical symptoms that negatively affect quality of life and might lead to multiple organ system involvement associated with low T. The prevalence of LOH is approximately 1 in 100 adult men.[7,9] Diagnosis of LOH is based on symptomatic men with low serum T levels (total T levels $<$ 300 ng/dL and free T $<$ 5 ng/dL). The clinical presentation is often insidious and might be underrecognized because of nonspecific symptoms. Sexual dysfunction (SD) is the most frequent cause for medical consultation and the most specific symptoms associated with low T among middle-aged and older men. In 1734 subjects, the associations between low T and sexual function were studied.[7] Of interest, waist circumference displayed the greatest accuracy in predicting low total T levels.[7]

Structured inventories assessing symptoms and clinical signs are often used to better define clinical hypogonadism. Structured interviews such as the ANDROTEST, a 12-item tool initially validated for the screening of androgen deficiency in patients with SD have been demonstrated to have a greater accuracy when compared to self reported questionnaires in detecting low T levels.[7,10] Patients with a pathological test (ie, a score $>$ 8) showed a higher prevalence of hypogonadism with related signs such as reduced testis volume and depressive symptoms.[10]

Longitudinal data from the Massachusetts Male Aging Study (MMAS) indicated that the prevalence of symptomatic hypogonadism (ie, total T $<$ 300 ng/dL) in men between the ages of 40–69 years is between 6% and 12% (2, 11, 46). The Baltimore Longitudinal Study of Aging (BLSA) indicated that the prevalence of symptomatic hypogonadism (H) (ie, total T $<$ 325 ng/dL) increased from low levels for men less than 49 years of age to 12%, 19%, 28%, and 49% in men in their 50's, 60's, 70's, and 80's years of age, respectively.[11,12] A Cross-sectional study from the Boston Area Community Health (BACH) showed that the prevalence of symptomatic low total T levels $<$ 300 ng/dL and free T $<$ 5 ng/dL was 5.6% in men between the ages of 30 and 79 years.[11,18]

Hypogonadism is often treated with external testosterone (T) substitution. T can be administered in form of a gel, patch, pellet or injectable testosterone esters.

T in a hydroalcohilic gel was first introduced to the United States in 2000 as an effective and convenient open system for transdermal delivery and is gaining popularity in the treatment of male hypogonadism.[11]

Diagnosis of Hypogonadism

Hypogonadism in males refers to a decrease in either of the two major functions of the testes: sperm production or testosterone production. These abnormalities can result from diseases of the testes (primary hypogonadism) or the diseases of the pituitary or hypothalamus (secondary hypogonadism).[11,12]

Hypogonadism is a clinical syndrome consisting of signs and symptoms in the presence of low serum T. Professional societies such as the Endocrine Society.[6,11] the American Association of Clinical Endocrinologists (AACE),[11,45] the International Society of Andrology (ISA), the European Academy of Andrology (EAA), the European Association of Urology (EAU), and the American Society of Andrology (ASA)[5,11] have recommendations and published guidelines for the diagnoses and treatment of symptomatic male hypogonadism.

The Endocrine Society guidelines (2006) state that the diagnosis of hypogonadism (androgen deficiency) should be made only in men with persistent signs and symptoms and low serum T levels.[6,11] The diagnostic evaluation of hypogonadism consists of three steps. The first step is evaluation of general health including lifestyle and the use of recreational drugs and also exclusion of systemic illnesses and medications that may interfere with function of the testes. The second step is the measurements of total T levels, preferably in the morning hours. The third diagnostic step is to determine whether androgen deficiency is due to

either a primary disorder or a secondary disorders ie, a result of any treatable disease condition.

The application of these guidelines is challenging in clinical practice because of the following reasons: signs and symptoms of hypogonadism in men are non-specific and vary with age of onset,[6,11] the measurements of T by commercial immunoassays vary since most of the circulating T is bound to sex hormone binding globulin and albumin, and only 0.5% to 2% of circulating testosterone (T) is free. The Endocrine Society's expert panel concluded that calculation of free T concentration from reliably measured total T and sex hormone binding globulin (SHBG) using the law of mass action equations provides the best approach for the estimation of free T concentration levels.[11]

LOH (secondary hypogonadism) is a medical condition characterized by T deficiency in aging men, accompanied by clinical symptoms. Cross-sectional studies such as the MMAS showed a decline of 0.8% per year of total T and a 2% per year decrease of bioavailable testosterone. This study confirmed that low T levels are associated with erectile dysfunction (ED) as well as loss of libido.[1,2,17] Longitudinal follow-up showed a decline of 1.6% per year of total T and a 2% to 3% per year for bioavailable T.[1,2,12] The Boston Area Community Health Survey showed that ED was more prevalent in the overall population than decreased libido; the proportion of patients with decreased libido had lower total and free T levels.[18] Although the relationship between sexual function (SF) and low T seems intuitive, the difficulty in delineating the clinical boundaries of the age-associated decrease in T is confounded by the fact that several non-sexual age-related symptoms and diseases are also associated with low T, to a varying degree. Testosterone deficiency has been associated with decreased muscle mass,[1,19] decreased bone mineral density[1,20,21] and an increased risk of cardiovascular disease, type 2 diabetes, dyslipidemia, atherosclerosis, and the metabolic syndrome (MS).[1,14,22] Increases of inflammatory cytokines and changes toward unfavorable lipid profiles are associated with the incidence of atherosclerosis and cardiovascular disease and increased mortality.[1,22]

Hypogonadism that develops in adults with formerly normal T levels is usually due to secondary causes. Secondary hypogonadism usually is associated with a subsequent decrease in sperm and T production.

Testosterone Therapy for Hypogonadism

The following items are reviewed: (1) T and its effect on hypogonadism; (2) different types of topical T application; (3) side effects of T replacement therapy; (4) T effects on sexual dysfunction; (5) T effects on the cardiovascular system, and (6) T effects in women.

At present, there is no substantial evidence-based treatment for late onset hypogonadsm (LOH) other than replacement of the deficient hormones.[1,5,6] T replacement therapy for hypogonadal men has proved to be effective at improving sexual function (SF) including sexual desire, erection, sexual performance and sexual attitudes[25–28] among patients with hypogonadal ED. A meta-analysis indicated a 57% clinical response rate to T therapy in patients with ED, a 64% response rate in those with primary hypogonadism, and a 44% response rate in those with secondary hypogonadism. However, these studies lacked placebo-control groups and men with hypogonadism of other etiologies were included.[29] In a clinical trial of T monotherapy with a transdermal gel formulation, maximal improvements in SF occurred by day 30 and continued for 6 months.[25,30] The beneficial effects of SF were maintained with long term treatments with T gel.[25,31] Improved scores of the international index of erectile function (IIEF) scores were reported at 4 weeks with a lesser response at 12 weeks.[25,32] Most SF evaluations in trials using T monotherapy were performed using the patient sexual diaries or questionnaires, reflecting overall sexual function.

The desirable effects of T administration include the development or maintenance of secondary sexual characteristics and increases in libido, muscle strength, fat-free mass, and bone density. Undesirable effects related directly to T include acne, prostate disorders (such as benign prostatic hyperplasia), sleep apnea and erythrocytosis.[24]

Testosterone Application (Gels/Patches)

Testosterone replacement therapy (TRT) in a form of hydroalcoholic gel or patch can improve the signs, symptoms and well being of hypogonadal men by restoring serum T concentrations to physiologic levels.[44]

TRT improves sexual function, decreases body fat, increases lean body mass and decreases cardiovascular events in hypogonadal men.[11,31,33] These beneficial effects are often accompanied by slight lowering of high density lipoprotein (HDL) cholesterol, increase in hematocrit/hemoglobin, and increase in the size of the prostate gland, mostly within the normal range.[14,31,33] Five testosterone gels are approved by the US Food and Drug Administration (FDA). These are AndroGel™ (Solvay Pharmaceuticals, Inc., Marietta, GA), Testim™ (Auxilium Pharmaceuticals, Inc., Norristown, PA), Fortesta™ (Endo Pharmaceuticals Inc., Chadds Ford, PA), Axiron™ (Lilly USA, LLC Indianapolis, IN) and Bio-T-Gel™ (BioSante Pharmaceutical, Inc., Lincolnshire, IL).

A multicenter, open-label non-comparative trial of men with androgen deficiency evaluated the pharmacokinetics profile and safety of a testosterone 2% gel (Fortesta™ Gel), administered once daily to the front and inner thighs at starting doses of 40 mg/day. The metered-dose delivery system allowed adjustments in 10 mg increments between 10 to 70 mg/day. T 2% gel was generally well-tolerated, with the most common adverse events being mild and moderate skin reactions. There were no serious adverse related to testosterone 2% gel. Once daily T gel restored levels of T in more than 75% of patients with low risk of supraphysiologic T levels.[44] Delivery of adequate amount of T mimics the daily production rate using the skin as the route of administration. 9%–14% of T applied to the skin is bioavaliable.[31] Pharmacokinetics analysis of transdermal T gel versus T patch demonstrated that the average serum of T levels over the 180-day treatment period were highest in the 100 mg daily transdermal T gel group. These levels were 1.4 and 1.9-fold higher than those achieved by the 50 mg daily trandermal T gel and T patch groups respectively. Daily application of the gel, daily resulted in steady state serum T pharmacokinetics with proportional increases in serum estradiol and suppression of both LH and FSH. Serum 5 alpha-dihydrotestosterone concentration was elevated but the 5 alpha-dihydrotestosterone-to-testosterone ratio increased slightly after T application. Daily T application appears to provide more flexibility in dosing, dose proportionality in T pharmacokinetics and less discontinuation rate than the permaetio-enhance.[31,34]

Two randomized, controlled studies demonstrated that T 1% gel (Testim™) significantly improved sexual function, desire, motivation, performance mood and body composition after 90 days of therapy compared to baseline.[9] The magnitude of sexual improvement is similar to that achieved with T patches with lesser application site reactions. Another study demonstrated improvements in sexual function and mood within two weeks of treatment. Clinical benefits with T gel were maintained for ≤12 months without significant side effects.[9]

Results from the Testim Registry in the United States (TRiUS) demonstrated that TRT in 271 hypogonadal men over 12 months resulted in increased total T (500.6 ± 248.2 ng/dL) and free T (240.1 ± 296.0 pmol/L) The Brief Male Sexual Function Inventory (BMSFI) was increased at 12 months (27.4 ± 10.3 to 33.8 ± 9.8, $P < 0.001$ versus baseline, ie, male sexual function such as erectile function, ejaculatory function, sexual drive and libido, were all increased as measured by BMSFI.[35]

In a randomized, double-blind, placebo-controlled, multicenter study of men (234 active; 40 placebo) between the ages of 18 and 80 with androgen deficiency receiving 1.62% AndroGel™ (1.25 g, 2.5 g, 3.75 g, 5.0 g) on shoulders and upper arms or abdomen resulted in increased T by 81.6% to 82.5% compared to placebo (range 28.6% to 37.0%).[36] 1.62% AndroGel™ applied to the abdomen or upper arm and shoulder of hypogonadal men, increased serum testosterone concentration to an eugonadal range of 300–1000 ng/dL. However, if applied to the abdomen the bioavailability of T concentration was only 30%–40%.[37] An animal study showed that the addition of Isopropyl alcohol potentially increases the bioavalability of T.[83]

Data from a multinational, open-label study with T 2% gel (Axiron™) applied in the axilla of 155 hypogonadal men demonstrated only mild skin reactions in some patients. Skin irritation (n = 12) as well as mild and transient erythema (n = 10) were the most common skin reactions reported. Other less common reaction were edema (n = 3), acne (n = 2) and folliculities (n = 1).[38]

Bio—T-Gel™ is a 1% gel manufactured by BioSante Pharmaceuticals, Inc., Lincolnshire, IL. After a multicenter, randomized, parallel-group, active-controlled 180 day trial in 227 men with hypogonadism this gel

has just been approved by the FDA in 2012 for the treatment of male hypogonadism and/or androgen deficiency. During the Day 1–90 period of treatment, 73 patients were randomized to transdermal T gel 5 g daily, 78 patients to T gel 10 g daily, and 76 patients to a non scrotal T transdermal system. This study was double—blinded for the T gel doses but open-labeled for active controls. Patients who were originally randomized to T and who had single-sample serum T levels above or below the normal reference range on day 60 were titrated to 7.5 g T daily on day 91. During the day 91–180 extended period of treatment, 51 patients continued transdermal T gel 5 g daily, 52 patients continued T gel 10 g daily, 41 patients continued a non-scrotal T transdermal system (5 mg daily), and 40 patients received T gel 7.5 g/day. Mean peak, trough, and average serum T concentrations within the normal range of 298–1043 ng/dL were achieved on the first day of treatment with doses of 5 g and 10 g. Subjects continuing on transdermal T gel 5 g and 10 g were maintained for the 180-day duration of this study. Concentrations of T were maintained as long as the patients continued to properly apply the gels.

The recommended doses of Bio-T-gel (T 1%) is 50 mg of T applied topically once daily (morning) to dry, intact skin on the shoulders and upper arms. The dose can be adjusted to a maximum of 100 mg of T if the desired clinical response is not achieved or serum levels are below the normal range.

The recommended starting dose of T 1% gel has been 5 g/day and this provides a nominal delivery of 50 mg of T per day. If the desired clinical response is not achieved or serum levels are not sufficiently increased, the dose can be increased to 7.5 g or 10 g.[11,13] A concentration of T 2% is available. The minimum dose is 10 mg, the maximum dose is 70 mg. 70 mg of T 2% gel is delivered in only 3.5 g of gel while the minimum of T 1% gel is delivered in 5 g of gel.[31] The daily dose of T 1.62% can be titrated between 20.25 mg and 81 mg (maximum), but the starting dose is usually 40.5 mg. With dose increases, serum T levels should be monitored serially. The recommended period to apply T gel is in early morning on dry intact skin around the shoulders, upper arms, inner thighs (Fortesta™), axilla (Axiron™) and abdomen (AndroGel™).[11,13,14,31,33,38,44,80]

Transdermal T gel defeated the drawbacks of the other delivery systems because of ease of use, tolerability, dose flexibility and limited side effects even though inter-personal transfer is a concern if precautions are not taken.[11,13] T patches can lead to application site reactions, T pellets can lead to extrusion and infection, and injectable esters are more often associated with peaks and troughs of serum T levels beyond the physiological range.[11,13] Oral formulations have a half life of less than 24 hours often requiring frequent daily dosing.[39]

Transdermal patches usually deliver 5–6 mg of T daily and provide relatively steady state T levels at low to midnormal ranges.[13,15,16,31,40,60,61,88] Higher T level can be achieved by applying more than one transdermal patch. Long term use of patches for 3–10 years has been shown to be effective in maintaining SF, bone density and muscle mass in both young and elderly hypogonadal men.[15,25,31,41–43,76] The Androderm™ patch (Watson Laboratories Parisppany, NJ) is currently marketed in the US as 2 mg and 4 mg patches. The scrotal skin patch (Testoderm™, Alza Laboratories, Mountain View, CA) has the disadvantage of requiring adequate preparation of the scrotal skin to allow adherence of the patch.[13] The nonscrotal patch with a reservoir containing T in an alcoholic base (Androderm™) causes skin irritation in about one third of the subjects and leads to discontinuation in 10%–15% because of these side effects.[13]

Even though several publications have demonstrated the benefits of T gel in patients with underlying cardiovascular diseases there is concern regarding the safety especially when used at supra-therapeutic doses.[14]

Side Effects of Testosterone Replacement Therapy

Testosterone enanthate, testosterone patch and gels have the following side effects depending on the population of patients in which it is administered:

Dermatologic and endocrine side effects

When T replacements are administered to hypogonadal pubertal boys and teens within the first few months, signs of undesirable normal puberty (acne, gynecomastia) and verbal and physical aggressive behavior can occur.[24,30] Long time treatment in these age groups can lead to premature closure of the epiphysis

and permanent short stature. Acne is found in up to 8% while gynecomastia is found in up to 3%. Large doses of exogenous T can suppress spermatogenesis through feedback inhibition by the follicle stimulating hormone which could possibly affect the quality of the semen.

Benign prostatic hyperplasia (up to 2%)

Deficiency of androgen partly protects against prostate disease.[49] Prostate volumes and serum prostate specific antigen (PSA) increases have been reported in response to T replacement.[24,26,29,47–48] However, at least one study demonstrated that prostate size and PSA levels during treatment with a nonscrotal permeation-enhanced T transdermal system were in the normal range.[23]

PSA increases mildly in most hypogonadal men on TRT which is not clinically significant.[50] A retrospective clinical study evaluated 48 hypogonadal men on TRT (intramuscular T; n = 33 and T gel; n = 25) for 1 year. A prostate biopsy was negative in all patients prior to treatment. PSA was unchanged in 22%, decreased in 21%, and increased in about 57%. Only 24% of patients demonstrated an increase in PSA of ≥ of 0.5 ng/ml. There was no statistical difference in the change in PSA based on age of the patient, baseline T and PSA levels.[50]

Some men, especially those over the age of 50, experience an exacerbation of benign prostatic hyperplasia (BPH), a testosterone-dependent process.[27] There have been concerns that lower urinary tract symptoms (LUTS) due to urinary outflow obstruction may worsen. It is recommended that regular rectal exams and PSA levels are checked in men on TRT.[49]

Prostate cancer (up to 1.2%)

Several studies including placebo-control studies using different T formulations over periods of months to several years (15 years) have not shown any increased risk of prostate CA[16] following T replacement but there are suggestions that TRT in hypogonadal men with unrecognized prostate CA might lead to development of clinically overt disease.[16,24,49] As an example, a case of a 85 year old hypogonadal man with occult adenocarcinoma of the prostate showed a rapid rise of PSA after TRT.[24]

In a prospective study of 2200 men with hypogonadal symptoms over a period of 15 years, prostate cancer was detected in only 10 patients (0.48% cases/year).[16] In a 2010 meta-analysis of 51 randomized trials of T therapy in men with the primary endpoints mortality, cardiovascular events and risks, prostate outcomes and erythrocytosis, no significant effects were recorded with regard to an increased incidence of prostate cancer, need for prostate biopsies, increases in PSA, or change in lower urinary tract symptoms when compared to placebo groups.[28,48]

In a long term study of 200 hypogonadal men receiving TRT (T patch), 50 patients received TRT for a period of 5 years and there was no report of prostate cancer (CA).[51] Prostate CA incidence in hypogonadal men in TRT is lower than the incidence among eugonadal men without any treatment.[51] It was advocated that it might be beneficial to treat patients cured of prostate CA with T substitution under a rigorous surveillance monitoring regimen.[51]

It has not been conclusive that the levels of circulating T in patients developing prostate cancer are higher than in the control groups.[16] In fact, it has been suggested that men with low T might be at higher risk of developing more aggressive tumors.[16]

Other side effects that have been reported include cholestatic jaundice syndrome, edema, liver carcinoma, peliosis hepatis, headaches (up to 6%), sleep apnea, erythrocytosis, and local application-site reactions that occur in 4% with rash occurring in 1.9% of patients.[20]

Testosterone and its Effect on Sexual Dysfunction

Testosterone is the most effective treatment for sexual dysfunction in hypogonadal men.[52] It functions through restoring erectile function as often assessed by the international index of erectile function (IIEF) scores.[25] A double-blind, randomized, placebo-controlled study among 40 individuals using a critical review of the different sexual function domain scores of the IIEF-15 and the score of the IIEF-5, the sexual function (SF) of men in hypogonadal status before and after 3 months of T gel treatment were evaluated. Effect size was used to compare the drug effects for each SF domain and the results were confirmed by multivariate analysis. A total of 30 men remained at

the end of the study. After 3 months of T gel therapy, the most beneficial effects was seen on erectile function (EF), with sexual desire and orgasmic satisfaction insignificantly affected. It was concluded that transdermal T gel treatment for hypogonadal patients can improve SD through improving erectile function.[25] Another study evaluated the relationship between androgen deficiency and ED using 50 mg/day of 1% hydroalcoholic T gel applied to non-scrotal skin of hypogonadal men with SD. In a consecutive series 85 hypogonadal (total T $<$ 12 nmol/L) men (mean age 51.0 ± 14.0 years) were interviewed using the ANDROTEST structured interview. Subjects with ED at baseline (61.2%) showed a significant increase of IIEF score after 6 months of TRT (9.7 ± 7.7 vs. 14.6 ± 9.8, $P < 0.001$). Subjects with more severe hypogonadism at baseline (T in the lowest quartile) showed the highest increase in IIEF scores. The authors concluded that 1% hydroalcoholic T gel is an effective and safe treatment for men with ED,[53] since late onset hypogonadism may play a significant role as a contributing factor in the pathophysiology of ED. A threshold level of T may be necessary for normal EF. T replacement therapy is therefore useful and often clinically indicated in hypogonadal patients with ED. A number of studies demonstrated that a combination of T and other ED treatment options such as phosphodiesterase type 5 (PDE5) inhibitors appears to be beneficial in patients with ED and hypogonadism, especially in those who failed PDE-5 inhibitor therapy before, but also in diabetics who are at risk of developing hypogonadism. T replacement has potentially evolved from a monotherapy for ED in cases of low T, to a combination therapy with PDE-5 inhibitors in selected cases.[53] Studies in animals indicated that the nitric oxide erectile pathway is T-dependent. T replenishment reverses physiological, biochemical and structural changes in experimental models and in patients with ED. Several studies have demonstrated the benefits of a combination of T (T gel) and sildenafil in producing an erectile response in hypogonadal men who did not respond to sildenafil therapy alone.[51,52] Therefore, it appears logically to screen for hypogonadism in men who fail PDE-5 inhibitors, especially among diabetics.[54–56]

Two randomized, controlled studies demonstrated that T 1% gel (Testim™) significantly improved sexual function, desire, motivation, performance mood and body composition after 3 months of therapy compared to baseline.[9]

A randomized double blind placebo-control clinical trial on Taiwan men with hypogonadism showed T gel (AndroGel™) restored total and free T to physiological range and improved sexual function.[57]

Data from a retrospective study of 211 hypogonadal men treated with TRT suggested that hypogonadal sexual symptoms; erectile function and libido responded well to T therapy in men with low to normal total T levels.[58]

In a study of 163 hypogonadal men treated with 5, 7.5, or 10 g T 1% gel (AndroGel™) per a day over a 42 months period resulted in rapid improvement in sexual function and mood, increase in lean body mass ($P < 0.0001$), decrease in fat mass ($P < 0.0001$) and a gradual increase in bone density.[31]

A multicenter study of 409 hypogonadal men demonstrated significant improvements in sexual desire, motivation and spontaneous erections when treated with 100 mg/d Testim™ gel compared to controls.[42] Another randomized multinational study showed that Testim™ significantly improved spontaneous erection, sexual desire, motivation and performance.[59]

In the TIMES-2 study (TRT on hypogonadal men with type 2 DM and metabolic syndrome), topical T (2%) demonstrated beneficial effects on sexual function, libido, body composition, total and LDL-cholesterol, lipoprotein, and insulin resistance over a period of 6 months in hypogonadal men with type 2 diabetes mellitus and/or the metabolic syndrome.[86]

Continued application of AndroGel™ resulted in beneficial effects similar to those with injectables and other transdermal preparations. This study was neither placebo controlled nor powered to determine the effects of T treatment on prostate cancer risk. Thus, monitoring for prostatic disease and assessment for erythrocytosis are strongly advised to reduce the risk of adverse events with T treatment of hypogonadal men. Restoring T levels to normal in men with subnormal T levels improves libido (sexual desire) in most and erectile function (EF) in more than 50%. It may take 12–24 weeks before the effects of T become clinically manifest.[84]

Testosterone and its Effects on the Cardiovascular System

Even though some data support the concept of a possible protection of T on vascular function, epidemiological studies did not demonstrate a correlation between the occurrence of cardiovascular diseases (CVD) and hypogonadism.[43] Low T appears to be associated with the metabolic syndrome, hypertension, type 2 diabetes, obesity, elevated low density lipoprotein (LDL) levels, increased production of cytokines and thickening of vascular walls that might eventually lead to endothelial dysfunction.[63,82] Longitudinal studies indicate that male hypogonadism might be considered a surrogate of underlying cardiovascular disorders.[63] According to one study, resumption and maintenance of T levels within the normal range of young adults might represent a reduction in cardiovascular risk factors.[63] Among cross-sectional studies, patients with CVD have significantly lower T and higher 17-β estradiol levels (but no difference in DHEAS levels). The association between low T and high 17-β estradiol levels with CVD was confirmed in a logistic regression model after adjusting for patient age and body mass index (BMI) (hazard ratio = 0.763 (0.744–0.783) and hazard ratio = 1.015 (1.014–1.017), respectively, for each increment of total T and 17-β estradiol levels. Longitudinal studies showed that baseline T levels were significantly lower among patients with overall-and CV-related mortality compared to controls. TRT on the other hand, was positively associated with a significant increase in exercise stress test duration and the time to develop 1 mm ST segment depression.[64] Whether low T is associated or directly correlated to CVD and morbidity and mortality requires further investigation.[64] It appears that chronic heart failure patients may benefit from TRT with improved muscle; mass, physical conditioning and possible improved cardiac capacity, in both men and women.[65,92]

Of interest, in a study of 2,416 Swedish men between the ages of 69 and 81 total T and sex hormone-binding globulin (SHBG) levels were inversely related to the risk of cardiovascular events.[66] In this study baseline T and sex hormone-binding globulin (SHBG) were measured and patients were followed for a total duration of 5 years. A total of 485 cardiovascular events (CV) occurred mainly in men with low T levels (95% confidence interval = 0.56 to 0.88, hazard ratio = 0.70). Men with underlying CVD were excluded from this study.[66] In an analysis involving T and SHBG, high T but not SHBG predicted a reduced risk of CV events. The authors concluded that high levels of serum T are associated with reduced risks of CV events among elderly men.[66]

In aging men, serum T levels appear to be inversely related to carotid intima-media thickness (IMT) and directly to plasma lipids levels; however, the relationship to endothelial function is poorly characterized. Examination of the association between serum T and endothelium-dependent brachial artery flow-mediated dilation (FMD) in 83 men (mean age 55.9 ± 7.9 years) with andropausal symptoms demonstrated an inverse correlation between serum T and brachial FMD, suggesting that T levels might affect endothelial function.[67]

Another study showed that patients with androgen deprivation post radical prostatectomy had an increased incidence of MS and diabetes.[14,16]

T deficiency has also been associated with an increased incidence of atherosclerosis. In a cohort study of 90 men, 60 with coronary artery disease (CAD), 30 without CAD, men with CAD demonstrated significant lower levels of T compared to men without CAD.[63]

Of interest, the presence of androgen receptors in mammalian cardiomyocytes implies that T might play a role in cardiac function, myocardial injury and the regulatory mechanisms. In an experimental study the effects of T deficiency, physiological T therapy and androgen receptor on oxidative stress were studied in cardiomyocytes of testicular feminized and castrated male mice. The authors found that T deficiency induces oxidative stress in cardiomyocytes whereas physiologic T replacement is able to suppress oxidative stress via an androgen receptor-independent pathway.[68]

Hypogonadism indirectly appears to raise the risk of cardiovascular disease through various components of the metabolic syndrome.[59] TRT may have a positive effect on risk factors for vascular complications including fat reduction, normalization of blood pressure, and correction of dyslipidemia.[69] A study demonstrated that T-induced relaxation of the endothelium of the coronary arteries is partly mediated

Table 1. Study overview using testosterone gel applications.

Author	Year	Design	No of patients	Results
Muram D[38]	2012	Multinational open-label study	155	T 2% gel (Axiron™) demonstrated to be a safe treatment for male hypogonadism with mild or moderate skin reactions in a minority of patients, seldom led to discontinuation
Dobs A[44]	2012	Multicenter, open-label non-comparative trial	149	Once daily T gel restored levels of T in more than 75% of patients with low risk of supraphysiologic T levels
de Ronde W[74]	2011	Prospective 3-way crossover trial	10	Showering within 30 mins after T gel application 50 mg/day reduces absorption of T and results in unacceptably low plasma T levels
Khera M[35]	2011	Multicenter registry	271	12 months of treatment with T 1% gel in hypogonadal men resulted in increase in total and free T and improvement in sexual function, even in patients on prior TRT
Kaufman JM[36]	2011	Randomized, double-blind, placebo-controlled	274	T 1.62% gel was efficacious and safe treatment for male hypogonadism, resulting in increase in serum total and free T to eugonadal ranges
Rhoden EL[60]	2010	Chart review	127	Two thirds of hypogondal men on TRT will experience symptomatic benefit and complete at least 12 months of treatment. Benefit was noted in a majority by 3 months
Chiang HS[25]	2009	A double-blind randomized placebo-control trial	40	Transdermal T gel treatment for hypogonadal patients can improve erectile function
Corona G[53]	2008	ANDROTEST structured interview	85	Hypogonadal men with ED demonstrated significant increase of IIEF-6 score after 6 months of therapy with T 1% gel
Karazindiyanoğlu S[8]	2008	Prospective investigation	25	In addition to improvement in SF, TRT may also improve LUTS/bladder functions
Saad F[73]	2008	Cohort study	55	Hypogonadal men treated with TRT showed statistically significant improvements in sexual symptoms as well as symptoms of the MS starting from 3 months of therapy
Reyes-Vallejo L[58]	2006	Retrospective study	211	Hypogonadal men with sexual dysfunction responded well with TRT
Schrader S[75]	2005	Open-label study	48	Most HIV patients who failed prior treatment with AndroGel™ demonstrated improvements in sexual function and satisfaction after four[4] week of treatment with Testim™ 1% gel
Greenstein A[85]	2005	IIEF questionnaire and a global assessment question (GAQ)	49	Combined treatment with sildenafil and T-gel has a beneficial effect on ED in hypogonadal patients with failed TRT alone

(*Continued*)

Table 1. (*Continued*)

Author	Year	Design	No of patients	Results
Meikle AW[77]	2004	Three-way matrix-size crossover study	18	3 g/2% T dose daily applied to the skin resulted in serum T in the normal range in most men with hypogonadism
Wang C[31]	2004	Randomized multicenter parallel study	163	Long term treatment of hypogonadal men with T 1% gel resulted in rapid improvement in mood and sexual function, increase in lean body and decrease in fat mass as well gradual improvement of bone mineral density
Marbury T[78]	2003	Crossover study	29	Testim™ provided higher serum levels and greater bioavailability than AndroGel™
Steidle C[42]	2003	Randomized, multidose, multicenter, active, and placebo-controlled study	406	Hypogonadal men treated with 100 mg/d of AA2500 gel (Testim™) showed significant improvements in sexual desire, motivation and spontaneous erection
McNicholas TA[59]	2003	Randomized multinational clinical trial	208	Testim™ produced dose-dependent consistent improvements in sexual performance, desire, motivation, performance and spontaneous erections in most men with hypogonadism
Schultheiss D[79]	2000	Pilot study	46	Some hypogonadal men with ED showed improvement in erectile function after 6–8 weeks of treatment with transdermal T gel
Wang C[13]	2000	Crossover study	9	T gel application over multiple sites seems to be an effective and nonirritating delivery method for hypogonadal men with dosage flexibility

Abbreviations: SD, Sexual Dysfunction; SF, Sexual Function; MS, Metabolic syndrome; ED, Erectile Dysfunction; T, Testosterone; LUTS, Lower Urinary Tract System; IIEF, International Index of Erectile Function.

by enhanced nitric oxide production which leads to synthesis of cGMP and activation of protein kinase (PKG) that leads to opening of calcium-activated potassium channels. These results might explain why androgens might be able to relax coronary arterial smooth muscles and relieve angina.[70]

Experimental and case-control studies in men demonstrated that T may affect overall homeostasis in many ways and that TRT in physiologic doses may be beneficial on generation of tissue factor-induced thrombin and the prevention of development of cardiovascular disease.[71]

Testosterone Therapy and Effects in Women

Hypoactive sexual desire disorder (HSDD) is one of the most common sexual problems reported by women, but few studies have been conducted to evaluate treatment options.[87] Reduced levels of T in postmenopausal women are associated with loss of libido, decreased sexual activity, diminished feelings of physical well-being, and fatigue.[89] Menopause, whether surgically induced or naturally occurring, can lead to decreases in sexual desire in 50% of cases by removing ovarian contribution to circulating T levels. Testosterone is a potential therapeutic option to improve signs and symptoms related to hypoactive sexual desire but the use of T supplementation has not been approved in United States due to lack of data and possible side effects.[89,90] In a double-blind, parallel placebo-controlled 24-week study (SM 1 Study) in women aged 26–70 years, placebo (n = 279) or testosterone 300 μg/d (n = 283) was administered. Nineteen patients withdrew due to adverse events in

the placebo group and 24 in the T group. Testosterone (300 µ/d) or placebo patches were applied twice weekly. At 24 weeks, there was a change in the frequency of total satisfying sexual activity of 2.10 episode/4 weeks in the T group compared to 0.98 episodes/4 weeks in the placebo group ($P = 0.0003$). This study concluded that T improved sexual function and decreased stress in surgically menopausal women with HSSD and was well tolerated.[87] Transdermal patches and topical gels are the preferred formulations because they avoid the hepatic first—pass metabolism.[90] T therapy is usually administered concomitantly with estrogen therapy due to a lack of adequate safety and efficacy data on TRT in women.[90]

Results from both phase III and other clinical studies with T patches for symptom relief in menopausal women with or without concomitant estrogen or estrogen/progestin therapy reported increased hair growth and acne. Although not conclusive, data were reassuring with respect to a lack of development or progression of cardiovascular diseases, breast diseases, and endometrial diseases.[91]

A study of 36 female patients with chronic heart failure who were treated with external testosterone supplementation demonstrated improvements in muscle strength, exercise capacity and insulin resistance. TRT was well tolerated by these women.[92]

Clinical Study Data Review

A reference search of clinical studies on T gel use on male hypogonadism revealed 44 clinical studies. 20 clinical studies involving the use of testosterone gel on human patients with hypogonadism were analyzed (Table 1). The main findings are summarized in Table 1. Among those studies, T application appeared to normalize and maintain serum T levels at a steady state with significant improvements in mood, sexual motivation, desire, performance, spontaneous erection, lean body mass, fat distribution, and bone density.[9,60,72] TRT had beneficial effects on sexual dysfunction (SD) and the metabolic syndrome in elderly men.[73] These data suggest that T gel formulations are a safe and effective treatment for men with hypogonadism.[11,53]

Conclusions

Hypogonadal men appear to benefit from topical T gel application with improvements in sexual function, desire, motivation, performance, mood, muscle strength, lean body mass, fat distribution and body composition. Contraindications need to be considered prior to substitution therapy such as a baseline hematocrit $>$ 50%, a recent diagnosis of prostate cancer, breast cancer, or undiagnosed palpable prostate nodule, or if the PSA is greater than 4 ng/mL (without a urological evaluation) as well as lower urinary tract symptoms without a previous urological evaluation. T therapy should be administered carefully in men with benign prostatic hypertrophy and mild to moderate lower urinary tract symptoms. Men with moderate to severe obstructive sleep apnea should be evaluated before T administration.[11] Overall, T gel is well accepted by patients due to the ease of its application and appears to represent a valid alternative option for T replacement therapy with beneficial effects on symptoms of hypogonadism and sexual dysfunction with an acceptable side effect and risk spectrum, but adequate long-term follow up and head to head comparisons between gels and other application forms are lacking.[53,73,77,79]

Author Contributions

Conceived and designed the experiments: DU, ES. Analysed the data: DU, AP, PK, ES. Wrote the first draft of the manuscript: DU, ES. Contributed to the writing of the manuscript: RW, DU, AP, PK, ES. Agree with manuscript results and conclusions: DU, AP, PK, ES. Jointly developed the structure and arguments for the paper: DU, ES. Made critical revisions and approved final version: RW, AP, PK, ES. All authors reviewed and approved of the final manuscript.

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have read and confirmed their agreement with the ICMJE authorship and conflict of interest criteria. The authors have also confirmed that this article is unique and not under consideration or published in any other publication, and that they have permission from rights holders to reproduce any copyrighted material. Any disclosures are made in this section. The external blind peer reviewers report no conflicts of interest. Provenance: the authors were invited to submit this paper.

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