

## REVIEW

# Testosterone in men with hypogonadism and transgender males: a systematic review comparing three different preparations

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This paper forms part of a special series collated by the European Reference Network on Rare Endocrine Conditions, celebrating its fifth year. The guest editors for this section are Violeta Iotova, Jérôme Berherat, and George Mastorakos.

## Abstract

Testosterone therapy is the cornerstone in the care of men with hypogonadism and transgender males. Gel and intramuscular injections are most frequently used and are registered and included in the international guidelines. The specific preparation should be selected according to the patient's preference, cost, availability, and formulation-specific properties. As the majority of men with hypogonadism and transgender males require lifelong treatment with testosterone, it is important to utilize a regimen that is effective, safe, inexpensive, and convenient to use with optimal mimicking of the physiological situation. This systematic review reviews current literature on differences between the three most used testosterone preparations in adult men with hypogonadism and transgender males. Although it appeared hardly any comparative studies have been carried out, there are indications of differences between the preparations, for example, on the stability of testosterone levels, hematocrit, bone mineral density, and patient satisfaction. However, there are no studies on the effects of testosterone replacement on endpoints such as cardiovascular disease in relation to hematocrit or osteoporotic fractures in relation to bone mineral density. The effect of testosterone therapy on health-related quality of life is strongly underexposed in the reviewed studies, while this is a highly relevant outcome measure from a patient perspective. In conclusion, current recommendations on testosterone treatment appear to be based on data primarily from non-randomized clinical studies and observational studies. The availability of reliable comparative data between the different preparations will assist in the process of individual decision-making to choose the most suitable formula.

## Key Words

- ▶ testosterone therapy
- ▶ transgender males
- ▶ men with hypogonadism
- ▶ short-acting injections
- ▶ long-acting injections
- ▶ transdermal gel

*Endocrine Connections*  
(2022) **11**, e220112

## Introduction

Testosterone is the primary sex hormone and anabolic steroid in men. It is secreted primarily by the Leydig cells of the testicles and, to a much lesser extent, by the adrenal glands. Testes produce 3–10 mg of testosterone daily, corresponding roughly to serum concentrations of 10.4–34.7 nmol/L with a peak value in the morning. Testosterone

acts directly via androgen receptors and via its conversion into two active metabolites, dihydrotestosterone or estradiol (1).

Low testosterone concentrations in males can lead to a clinical syndrome known as male hypogonadism. This can be caused by testicular disease (primary hypogonadism)

or central, pituitary, or hypothalamic disease (secondary hypogonadism). Causes can be genetic, like in Klinefelter and Kallman disease, or acquired, for example mass related or iatrogenic (e.g. post orchiectomy and post treatment of pituitary tumors). The diagnosis of male hypogonadism is based on the assessment of signs and symptoms and on low testosterone concentrations in serum in the morning on at least two occasions ( $<10.4$  nmol/L) (2, 3). Low androgen levels cause morbidity and affect health-related quality of life (HR-QoL) due to infertility, decrease of sexual functions, muscle mass, strength and vitality, low mood and self-esteem, decrease of cognitive functions, osteoporosis, and a change of metabolism. Low testosterone is regarded as a marker for poor general health and as increased risk for cardiovascular disease and mortality.

Another increasing testosterone-dependent group are transgender people looking for masculinization. These people are birth-assigned female but identify as male or non-binary. To induce virilization, testosterone therapy is prescribed. This includes deepening of the voice, increase in body and facial hair, and psychological and sexual changes (4).

Several testosterone preparations are approved for treatment and should be selected according to the patient's preference, cost, availability, and formulation-specific properties. As the majority of men with hypogonadism and transgender males require lifelong treatment with testosterone, it is important to utilize a regimen that is effective, safe, inexpensive, and convenient to use with optimal mimicking of the physiological situation.

Gel is frequently prescribed due to its favorable pharmacokinetic profile, convenient use, and positive long-term clinical results. However, for stable testosterone levels, gels require daily administrations, including adequate drying time prior to getting dressed, which can be experienced as cumbersome and can reinforce the concept of having a chronic condition. Also, the transfer of testosterone to partners or children via direct skin contact is a risk (5).

Short-acting intramuscular injections, such as Sustanon<sup>®</sup>, are esters of testosterone (TE) that have been used for many years for the treatment of testosterone deficiency prior to the availability of transdermal testosterone preparations. However, they have to be administered two to three times weekly, and after injection, serum testosterone concentrations rise into the supraphysiologic range within 24–48 h and then gradually decline into the low-normal range over 2 weeks (6, 7), possibly leading to bothersome fluctuations in the patient's mood, sexual

desire, and energy level. Long-acting intramuscular testosterone undecanoate (TU) (e.g. Nebido<sup>®</sup>) by contrast has to be administered only four to five times annually and does rarely result in supraphysiologic testosterone levels but instead produces stable levels of testosterone. Nebido<sup>®</sup> has to be slowly injected deep into the gluteal muscle. Patients can experience pain following an injection due to the large volume, but in study context, very few patients reported injection-site irritation or pain, and no patients voluntarily discontinued therapy as a result of local discomfort. The convenient dosing schedule might lead to better compliance yielding better therapeutic effect compared to gel. Importantly, pharmacokinetic studies showed consistent maintenance of stable physiological levels of testosterone during the use of Nebido<sup>®</sup> (7, 8, 9). Other available testosterone administration types are: (i) oral testosterone, although easy in use and cheap, is hardly prescribed because of two to three times daily intake with unpredictable absorption and large fluctuations in serum testosterone levels (10), (ii) patches, associated with a high frequency of skin irritation, (iii) buccal tablets, with its twice-daily dosing, gum irritation, altered taste, and poor adhesion to buccal mucosa, and (iv) testosterone pellets, requiring surgical incision with the possibility of infection, risk of spontaneous pellet extrusion and fibrosis, are not recommended (2). Recent research has shown promising results for an oral TU formulation. However, due to the current limited amount of research, we did not include this in this review (11). All preparations are registered for the treatment of hypogonadal and transgender males and are included in the international guidelines (2, 3, 12, 13, 14, 15, 16).

This systematic review aims to review current literature on the difference between the different treatment options in adult hypogonadal and transgender males, specifically aimed at the most used preparations, transdermal testosterone gel, and intramuscular testosterone injections, and to determine which knowledge gaps remain for further research.

## Methods

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (17) and has been developed in collaboration with an information specialist (CP).

The literature was systematically searched using international databases: PubMed (1995 to February 2021) and the Cochrane Library (including EMBASE (OVID

version) and Web of Science; 1995 to February 2021). We included studies on male hypogonadism, hypogonadal men, transgender, transsexual, transgender men, transmen, female-to-male, FtM, combined with several keywords related to treatment including transdermal testosterone gel, intramuscular testosterone injections, testosterone undecanoate, propionate, enanthate, cypionate, Nebido, and Sustanon.

Inclusion criteria were studies on adult humans; primary and secondary hypogonadism or transgender males using testosterone, randomized controlled trials, clinical trials and prospective trials; written in English or Dutch. Exclusion criteria were studies on late-onset hypogonadism, only reporting on patient groups with other symptoms or illnesses such as androgenic-anabolic steroid withdrawal syndrome, chronic opioid use, HIV, obesity, metabolic syndrome, type 2 diabetes mellitus, or end-stage renal disease.

Studies were selected independently by two different reviewers (M M, L B) and any disagreement in eligibility was resolved by discussion.

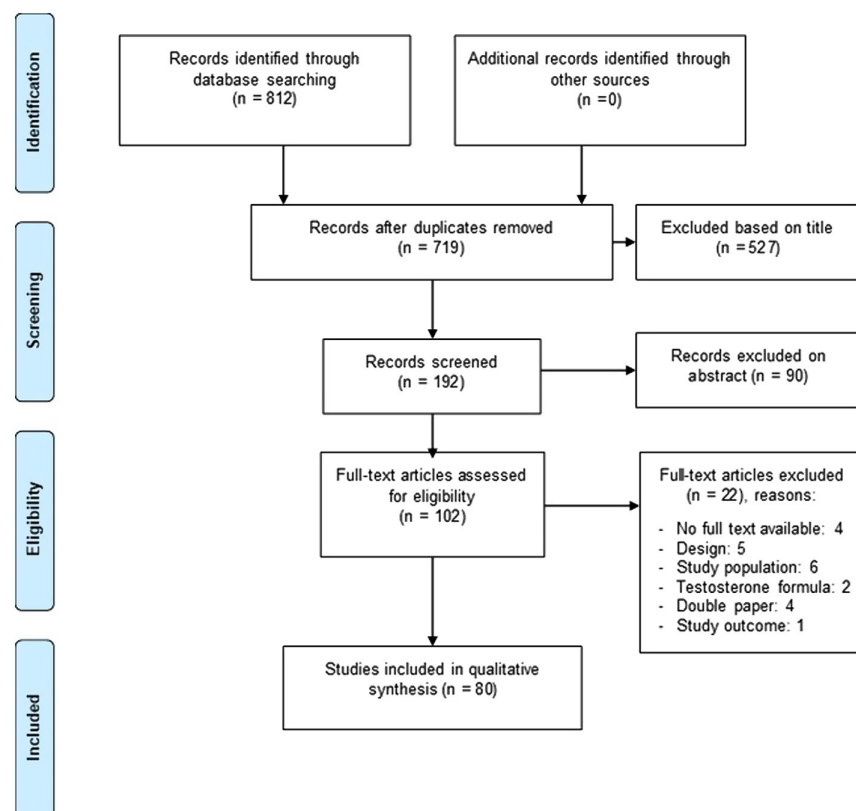
The selection of articles is depicted in Fig. 1. Search strategy can be found in the Supplementary information (see section on [supplementary materials](#) given at the end of this article).

Results from the selected studies on pharmacokinetics, hypogonadal symptoms, virilization, metabolic and anthropometric parameters, bone mineral density, HR-QoL, and side/adverse effects were extracted from the included articles and described in this review.

## Results

### Pharmacokinetics

The goal of testosterone therapy is to raise serum testosterone levels to the mid-normal (birth-assigned male) range, without significant side effects or safety concerns, and alleviating the hypogonadal symptoms or, in transgender males, inducing virilization. Hence, both too low trough levels and too high peak levels are unwanted. Based on several randomized (only men with hypogonadism) and non-randomized (both hypogonadal and transgender males) clinical trials, different testosterone formulations have been approved for androgen therapy and are included in (inter)national guidelines (2, 3, 12, 13, 14, 15, 16). Table 1 shows the pharmacokinetic properties of testosterone gel (2, 18, 19, 20, 21, 22, 23, 24, 25, 26), and short-acting (7, 27, 28, 29, 30, 31) and long-acting injections (7, 9, 32, 33, 34, 35, 36).



**Figure 1**  
PRISMA flow chart of inclusion of studies.

Both gel and i.m. testosterone preparations are able to achieve physiological testosterone levels. With the exception of one small open-label randomized controlled trial (RCT) comparing i.m. TE and i.m. TU (7), no randomized studies comparing the above preparations on pharmacokinetics have been performed. Gel achieves relatively stable testosterone levels within a week with small peak to trough fluctuations, provided it is applied daily, that is with good compliance (20, 21, 22, 23, 24, 25). Testosterone levels return to baseline relatively quickly after termination (22). Use of gel is accompanied by several instructions to the patient in order to minimize the risks of transfer to other people (i.e. to wash hands after application and to wear a shirt covering the application sites before having physical contact) and to optimize bioavailability of testosterone (i.e. to wait at least 5–6 h after application before taking a bath or shower) (37, 38). The short-acting injections achieve on average physiological levels of testosterone. However, the pharmacokinetic profile is characterized by supraphysiological peaks shortly after each injection and levels below the lower limit of normal, prior to the next (7, 27, 28, 29). In addition, administration is given intramuscularly two to three times weekly by a healthcare provider (29). Long-acting injections maintain serum testosterone levels in the normal range with lower peak and less deep trough values in comparison to

short-acting injections and reach a steady state after three injections (7, 9, 32, 39, 40). An initial dose of i.m. TU 1000 mg/4 mL should be followed by a second injection 6 weeks later, after which injections may resume every 12 weeks. Hence, 4–5 i.m. injections annually have to be administered by a healthcare provider.

### Hypogonadal symptoms

Testosterone is prescribed to relieve hypogonadal complaints in men with hypogonadism. These complaints include less sexual desire and function, lower testicular volume, decreased body hair, gynecomastia, decreased lean body mass and muscle strength, and complaints of fatigue and depression. Sexual desire and function improve 3–6 weeks after initiation of testosterone therapy, and it can take 6 months until effect is seen on erections/ejaculations. Effects on depression and mood can be seen after 3–6 weeks but can take longer to fully stabilize (33). In transgender males, testosterone is prescribed to induce virilization. However, after ovariectomy, hypogonadal symptoms can also be a sign of inadequate testosterone therapy in transgender males. As shown in Table 2, there are a variety of studies that report the presence or absence of hypogonadal symptoms (26, 32, 39, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56). All types of testosterone

**Table 1** Testosterone preparations and pharmacokinetics.

Preparation	T max	Therapeutic range	Kinetics	Target value	Dose adjustment	References
Gel ( <i>Testogel 1%, Testim 1%, AndroGel 1%, Androgel 1.62%, Fortesta 2%, Tostran 2%, Testavan 2%</i> )	8 h	+24 h	Stable, depending on compliance	20–30 nmol/L	Multiple to get in target range	(Randomized controlled trials (RCTs): (18, 19, 20, 21, 22, 23, 122), observational studies: (24, 25, 26)).
Short-acting esters (e.g. <i>Testoviron® Depot 50: 20 mg testosterone propionate and 55 mg testosterone enanthate (TE); Testoviron® Depot 100: 25 mg testosterone propionate and 100 mg testosterone enanthate; Sustanon® 250: 30 mg testosterone propionate, 60 mg testosterone phenylpropionate, 60 mg testosterone isocaproate and 100 mg testosterone decanoate</i> )	24–48 h	2–4 weeks	High peaks shortly after each injection and low troughs prior to the next	10–15 nmol/L prior to injection	On the basis of concentrations prior to injection	(6, 7, 28, 29, 30, 31)
Long-acting undecanoate ( <i>Nebido® 1000 mg/4 mL TU (available in a.o. Europe (not US)) and Aveed® 750 mg/3 mL TU (available in US)</i> )	1 week	10–14 weeks, second booster injection after 6 weeks	Stable	20–30 nmol/L	Steady state after third injection	(7, 9, 32, 34, 35, 36, 40)

administration relieve hypogonadal symptoms. TU seems to give the most stability in the relief of hypogonadal symptoms, as well as an improvement in concentration (53). One comparative study did not show any difference in on-treatment testosterone and symptoms between gel and injections (49).

### Virilization

In transgender people wishing for masculinization, testosterone therapy induces virilization, and this includes increase in facial and body hair, deepening of the voice, and mental and sexual changes. These changes start 3 months after initiation of testosterone therapy, but it can take years until the maximum effect is seen. All testosterone administration types induce virilization. There does not seem to be a difference in testosterone administration type and the rapidness of changes (57, 58, 59).

### Metabolic and anthropometric parameters

It is known that testosterone has an effect on different metabolic and anthropometric parameters. In general, glucose sensitivity improves and also changes in BMI are generally seen. Changes in fat mass, lean body mass, and muscle strength occur within 12–16 weeks, stabilize at 6–12 months but can marginally continue over years (33). Conflicting results are available on the effect of testosterone on lipids, which mostly appear already after 4 weeks (33). Table 2 shows an overview of studies investigating metabolic and anthropometric parameters (32, 39, 41, 43, 45, 53, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80).

Comparing different administration types, one study did not find any difference between TU and TE in lipids and BMI (67). Comparing TU and TE in transgender males, a greater increase in BMI was seen with TE (67). Both resulted in an increase in cholesterol and lean body mass (LBM) (73). Also, a small increase in systolic blood pressure was frequently seen. Although often characterized as not significant by the authors, this could still be of influence on the cardiovascular risk, as seen previously in the Framingham Study (81).

In conclusion, there are conflicting results on the effect on anthropometric parameters and lipids. In general, BMI increased, but this was mostly due to an increase in LBM and concomitant decrease in fat mass. Some studies showed an increase in lipid values and others, a decrease. Lipids, mainly LDL-cholesterol (LDL-C), are a well-known surrogate marker for cardiovascular disease with

an association between the height of LDL-C level and the occurrence of cardiovascular disease (82). This indicates that small unfavorable changes in LDL-C after testosterone therapy could have a high impact as testosterone is widely used among hypogonadal and transgender males. It is noteworthy that in all studies among transgender males on testosterone treatment demonstrated an unfavorable effect on lipids, whereas in men with hypogonadism divergent results were observed on lipid changes with both favorable and unfavorable effects after testosterone initiation. The observation that in men with hypogonadism, lipid changes were observed in all directions in contrast to the studies performed in transgender males showing only detrimental effects on lipids may be explained by the fact that transgender people are mostly eugonadal before initiation of testosterone treatment. Male hypogonadism on itself is still under debate as risk factor for cardiovascular disease, and it could be hypothesized that the favorable changes in lipids that were observed in some studies in men with hypogonadism may be the result of the treatment of their hypogonadism (83).

### Bone mineral density

Table 2 shows studies that researched the effect of testosterone on bone mineral density (BMD) (31, 45, 51, 58, 59, 61, 71, 78, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95). Several small randomized and observational trials have shown that testosterone treatment, both gel and i.m. preparations, improves BMD. Effects on BMD have been shown in studies of 6 months duration and longer, both on spinal and hip BMD and on trabecular and cortical BMD (51, 90, 96). Several observational studies showed a gradual and progressive increase during treatment up to at least 3 years (52, 84, 87, 91, 97, 98). The effect on BMD appears to be preceded by a change in bone turnover markers. In a RCT by Wang *et al.* (51), testosterone gel replacement in 227 men with hypogonadism during 6 months resulted in a decrease in osteoclastic activity and an early but transient stimulation of osteoblastic activity in the first 90 days of treatment, with maintenance of lower bone resorption and return to baseline of bone osteoblastic activity at 180 days.

In transgender people looking for masculinization, the effect of testosterone treatment on bone is different, as there is also an effect on estrogen (in non-ovariectomized transgender males). Based on several studies (see Table 2), testosterone treatment in transgender males has at least no negative effect on bone, and possibly a small positive effect (58, 59, 61, 71, 86, 92, 94).

**Table 2** Studies on the influence of testosterone therapy on hypogonadal symptoms, BMD, and metabolic and anthropometric parameters. First table shows results for hypogonadal men, and second table shows results for transgender men.

Author, year, (ref), study design	Intervention/comparator	Study population	Follow-up	Hypogonadal symptoms	Bone mineral density (BMD)	Metabolic and anthropometric parameters
<b>Studies on men with hypogonadism</b>						
Aydogan 2012 (41), Prospective non-randomized study	Testosterone esters (TE) (Sustanon 250 mg every 3 weeks)/none	39 men with congenital hypogonadotropic age-matched eugonadal men	6 months	Improvement of sexual function		Significant increase in BMI
Benito 2005 (84), Prospective study	Gel/none	10 untreated men with hypogonadism vs 10 eugonadal men	2 years		Increase in BMD	
Bolu 2012 (60), Prospective study	TE/gel	70 men with hypogonadism vs 70 controls	6 months			After treatment, lower total cholesterol and lower high-density lipoprotein (HDL) cholesterol observed. BMI increased.
Cherrier 2003 (54), Prospective study	Gel (2 dosages)/patch	12 men with hypogonadism		Improvement in verbal memory after testosterone therapy (TT)		
Chiang 2007 (42), Double-blind, randomized, placebo-controlled study	Gel/placebo	40 men with hypogonadism	3 months	Improvement of sexual function		
Cunningham 2017 (26), Phase 3 open-label non-comparator study	Gel/none	160 men with hypogonadism	4 months	Improvement of sexual function, less fatigue		
De Rosa 2001 (85), Cross-sectional study	TE/none	12 men with hypogonadism			Still decreased BMD after testosterone therapy	
Efros 2016 (43), Phase II, open-label, sequential dose escalation studies	Gel, three different concentrations	38 men with hypogonadism	1 week	Improvement of sexual function. Less fatigue and distress		

(Continued)

**Table 2** Continued.

<b>Author, year, (ref), study design</b>	<b>Intervention/comparator</b>	<b>Study population</b>	<b>Follow-up</b>	<b>Hypogonadal symptoms</b>	<b>Bone mineral density (BMD)</b>	<b>Metabolic and anthropometric parameters</b>
Kaufman 2011 (65), Multicenter, randomized, double-blind, placebo-controlled study	Gel/placebo	Men with hypogonadism gel were 214 and placebo 37	6 months			Increased BMI with TT
Khera 2011 (55), Prospective multicenter registry study	Gel/none	271 men with hypogonadism	1 year	Improvement of sexual function		
Lasaita 2016 (44), Prospective study	TU/none	19 men with hypogonadism		Improvement in cognitive tests (trail making test, digit span test)	Increase in BMD	Testosterone treatment gave reduction of total cholesterol and serum triglycerides
Leifke 1998 (87), Prospective study	TE/none	32 men with hypogonadism	3.2 ± 1.7 years			
Malik 2004 (66), Randomized, single-blind, placebo-controlled, crossover trial	TE/placebo	29 men with hypogonadism	1 month			
McNicholas 2003 (45), Randomized, multidose, multicenter, active-controlled study	Gel/patch	208 men with hypogonadism (68 Testim 50, 72 Testim 100, 68 Andropatch)	3 months	Improvement of sexual function	No changes in BMD	Increase in BMI, total cholesterol, decrease in HDL
Medras 2001 (89), Prospective, controlled study	TE/none	26 men with hypogonadism			No improvement in BMD	
Miner 2013 (46), Registry study	Gel/ none	849 men with hypogonadism	1 year	Improvement of mood and depression		
Minneman 2008 (67), Open-label, randomized, prospective clinical trial	TE/TU	40 men with hypogonadism	2.1 years			No difference in BMI. TU HDL lower compared to low density lipoprotein (LDL).
Mulhall 2004 (47), Prospective, observational study	Gel → patch → TE adjusted for testosterone levels	32 men with hypogonadism	1 year	Improvement of sexual function		

(Continued)

**Table 2** Continued.

Author, year, (ref), study design	Intervention/comparator	Study population	Follow-up	Hypogonadal symptoms	Bone mineral density (BMD)	Metabolic and anthropometric parameters
Nieschlag 1999 (32), Open-label, clinical, non-randomized study	TU/none	13 men with hypogonadism	24 weeks	Improvement of sexual function compared to previous treatment (TE/gel)		Decrease in HDL, Stable BMI other lipids, glucose and HbA1c
O'Connor 2001 (48), Single-blind placebo-controlled study	TE/placebo	30 eugonadal and 7 men with hypogonadism		No improvement of cognitive tests in hypogonadal group (compared to eugonadal)		
Ramasamy 2015 (49), Prospective, observational study	Gel/injections	42 men with hypogonadism	Median 3.8 years	No difference between gel and injections in hypogonadal symptoms		
Schubert 2003 (90), Prospective, open-label randomized, trial	Mesterolone 100 mg/day/oral testosterone undecanoate 160 mg/day/ testosterone enanthate depot 250 mg i.m./21 days, or testosterone pellets	53 men with hypogonadism	6 months		Increase in BMD in all groups	
Seftel 2004 (56), Randomized, multidose, multicenter, active, placebo-controlled study	Gel (two different dosages)/patch/placebo	406 men with hypogonadism	2 years	Improvement in sexual desire and function		
Sonnez 2015 (72), Prospective, controlled study	TE/Gel	60 men with hypogonadism vs 70 age-matched controls	6 months			Increase in systolic blood pressure, BMI and decrease in HDL cholesterol
Tahani 2018 (91), Prospective study	Gel/TU	15 men with hypogonadism with Klinefelter syndrome, 26 controls	3 years		Increase in BMD after testosterone treatment	
Van den Berg 2001 (93), Cross-sectional study	TU/TE/oral	52 men with hypogonadism (Klinefelter)	1 year		44–48% had osteopenia, 6–14% osteoporosis. No fractures reported.	

(Continued)





**Table 2** Continued.

<b>Author, year, (ref), study design</b>	<b>Intervention/comparator</b>	<b>Study population</b>	<b>Follow-up</b>	<b>Hypogonadal symptoms</b>	<b>Bone mineral density (BMD)</b>	<b>Metabolic and anthropometric parameters</b>
Von Eckardstein 2002 (39), Phase 2 study	TU/none	7 men with hypogonadism	2.8 years	Improvement of sexual function		Increase in BMI (due to increase in LBM), decrease in HDL, and total cholesterol
Wang 1996 (50), Prospective study	TE/sublingual	Men with hypogonadism 18 testosterone esters, 35 sublingual	2 months	Improvement in mood, decreased anger, and irritability sadness and tiredness	Increase in BMD	
Wang 2001 (51), Prospective, randomized, multi-center, parallel clinical trial	Gel 50 or 100 mg	227 men with hypogonadism	6 months			
Wang 2004 (78), Long-term, open-label efficacy study	Gel 50, 75, 100 mg	169 men with hypogonadism	3 years	Improvement of sexual function	Increase in BMD	BMI rose mostly due to an increase in lean body mass
Wolf 2017 (76), Observational post-marketing study	TU/none	867 men with hypogonadism 3 transgender males	1 year			Stable BMI. Men with low blood pressure had an increase in blood pressure, men with high blood pressure had a decrease in blood pressure.
Wu 2009 (75), Prospective controlled study	3 months TU oral, after this monthly injections TU 250 mg	26 men with hypogonadism vs 26 healthy controls	9 months			Total cholesterol, LDL-C, HDL-C, and triglyceride were all decreased. No changes in body fat
Yassin 2013 (79), Cumulative registry study	TU/none	261 men with hypogonadism	5 years			Decrease in waist circumference and BMI after TT
Zitzmann 2013 (53), International, multicenter, one-arm, prospective, observational study in 23 countries	TU/none	1438 men with hypogonadism	5 injections (1 year)	Improvement of concentration and sleep quality. Stability in mood, less hot flushes, and sweating.		Lower blood pressure and better lipid profile

(Continued)



**Table 2** Continued.

Author, year, (ref), study design	Intervention/comparator	Study population	Follow-up	Hypogonadal symptoms	Bone mineral density (BMD)	Metabolic and anthropometric parameters
<b>Studies on transgender males</b> Elbers 2003 (43), Prospective study	TE/none	17 transgender males	1 year			Decrease in HDL cholesterol, increase in cholesterol, increase in BMI 1 year after TT
Emri 2008 (80), Prospective study	TE/ no treatment	63 untreated and 48 treated transgender males	-			Treated individuals had higher blood pressure, increased cholesterol, and decreased HDL cholesterol.
Gava 2021 (61), Randomized, double-blind PL-controlled pilot trial	Testosterone undecanoate (TU) + placebo/ TU + 5 $\alpha$ -reductase inhibitor	14 ovariectomized transgender males	1 year		No difference in BMD	Stable BMI, HDL decreased, fat% lower
Goh 1995 (62), Prospective study	TE/none	85 transgender males	33 months			Higher levels of triglyceride, total cholesterol, LDL and Apo-B, lower HDL
Haraldsen 2007 (95), Prospective study	TE/none	12 transgender males	1 year		No difference in BMD	
Jacobeit 2007 (64), Prospective study	TU/none	12 transgender males	1 year			Stable BMI and lipid profile
Jacobeit 2009 (63), Prospective study	TU/none	17 transgender males	1.5 year			Stable lipid profile and BMI
Lips 1996 (88), Prospective study	TE (12)/oral (3)	15 transgender males	39 months		Normal BMD	
Mueller 2007 (58), Prospective, observational study	TU/none	35 transgender males	1 year		No changes in BMD	Increased BMI, decreased HDL, other lipid parameters stable. Increase in systolic and diastolic blood pressure

(Continued)

**Table 2** Continued.

<b>Author, year, (ref), study design</b>	<b>Intervention/comparator</b>	<b>Study population</b>	<b>Follow-up</b>	<b>Hypogonadal symptoms</b>	<b>Bone mineral density (BMD)</b>	<b>Metabolic and anthropometric parameters</b>
Mueller 2010 (71), Prospective, observational study	TU/none	45 transgender males	2 years		No changes in BMD	Stable BMI but lean body mass (LBM) increased, decreased HDL, other lipid parameters stable
Pelusi 2014 (59), Observational study	Gel/Testoviron/TU	45 transgender males	1 year		No difference in BMD	BMI increased after starting testosterone therapy, independent of formulation. HDL decreased, LDL increased in all groups.
Turner 2004 (31), Prospective case series	TE/None	15 transgender males	2 years		Increase in BMD	
Van Caenegem 2015 (92), Prospective, controlled study	TU/none	26 transgender males, 23 age-matched cis women	1 year		Small increase BMD	
Van Velzen 2019 (74), Prospective, controlled study	TE or TU or Gel	188 transgender males 47 gel, 63 TE 79 TU	1 year			No differences in lipids, BMI, systolic and diastolic blood pressure, cholesterol HDL, LDL, and triglycerides for different formulations. Although BMI was higher in the group using TE. Stable BMI but increase in LBM
Van Velzen 2020 (73), Prospective, controlled study	TE or TU or Gel	323 transgender males	2 years		Increase in BMD in younger transgender males, decrease in older transgender males	
Vlot 2019 (94), Prospective, controlled study	TE or TU or Gel	132 transgender males	1 year			
Wierckx 2014 (77), Prospective study	TE/TU	53 transgender males				Total body weight increased due to an increase in LBM. Systolic blood pressure increased

**Table 3** Quality of life.

Author, year, (ref), study design	Intervention/comparator	Study population	Follow-up	Health-related quality of life
Aydogan 2012 (41), <i>Prospective, non-randomized study</i>	TE/none in age-matched controls	Men with hypogonadism (Sustanon 39, age-matched controls 40)	6 months	SF-36: statistically significant difference was found in physical role difficulty, pain, general health, emotional role difficulty, and mental health parameters
Belkoff 2018 (24), <i>Phase 3 open-labeled prospective study</i>	Gel/none	180 men with hypogonadism	9 months	SF-12: significant improvements in QoL for all four domains, physical and mental component summaries, and the mean total score were observed on 3 months, which sustained till 9 months
Cunningham 2017 (26), <i>Phase 3 open-label, non-comparator study</i>	Gel/none	160 men with hypogonadism	4 months	SF-12: improvement of physical component summary, also improvement of mental component summary
Shiraishi 2014 (99), <i>Prospective study</i>	hCG + rhFSH/TE	Men with hypogonadism (hCG+rhFSH 31, TE 6)	24 months	SF-36: no improvements with TE

### Health-related quality of life

Limited studies are available assessing the effect of testosterone therapy on HR-QoL. Moreover, the impact of testosterone therapy on HR-QoL in men with hypogonadism is difficult to quantify due to significant heterogeneity in study population, study duration, and QoL measures. Based on these data, testosterone treatment in men with hypogonadism seems to improve QoL (Table 3) (24, 26, 41, 99). Given the limited amount of data, it is certainly not possible to draw any conclusion on the different formulations. In addition, we did not find randomized or non-randomized clinical trials on QoL measures in adult transgender males.

### Side effects/adverse events

In general, testosterone therapy is not known to have many side effects. In transgender males, the most important side effect is acne, and this was reported in up to 44.6% (57, 77, 100, 101, 102, 103). Fortunately, this acne was mostly mild and did not lead to discontinuation of testosterone therapy. Acne was, to a lesser extent, also reported in the treatment of men with hypogonadism (9, 32, 39, 52). In transgender males, anger was also reported as a side effect (104). Other general side effects were skin reactions with the use of gel (20, 25, 45, 46, 78, 105) and pain at the injection site with the use of injections (67). This was more frequently reported with the use of TU (9, 77, 100). One study reported dizziness as a side effect of TE (106). In general, snoring and insomnia were also reported in some studies (107).

In conclusion, there are, besides acne and local reactions on the application site, no major side effects of testosterone therapy. Comparing the different administration types, skin reactions are more frequently seen with the use of testosterone gel and pain at the injection site with the use of testosterone injections.

### Hematocrit

Testosterone is known to stimulate erythropoiesis. Erythrocytosis is the most frequent adverse event related to testosterone therapy, with a reported prevalence varying between 5 and 66% (108). Effects on hematocrit levels are apparent approximately 3 months after initiation of testosterone therapy, peaking at 9–12 months. Table 4 shows the included studies reporting hematocrit levels after initiation of testosterone therapy (45, 53, 67, 78, 80, 109, 110). The increase in hematocrit level is larger in transgender than in men with hypogonadism due to a lower (female) baseline level but reaches the same range during treatment in both groups (between 0.47 and 0.52). Injections seem to give the highest prevalence of hematocrit levels above 0.50 L/L (111).

### Other adverse events

Studies in men with hypogonadism report a low frequency of serious adverse events with replacement doses of testosterone. Long-term safety of testosterone therapy in relation to cardiovascular diseases remains uncertain

**Table 4** Hematocrit.

Author, year, (ref), study design	Intervention/comparator	Study population	Follow-up	Hematocrit
Defreyne 2018 (111), <i>Prospective study</i>	TU/TE/Gel	192 transgender males	1 year	TU: 40.9%→ 45.1% (levels above 0.50: 2.2%) TE: 41.0%→ 46.0% (levels above 0.50: 13.4%) Gel: 40.0%→ 46.5% (levels above 0.50: 9.9%)
Emi 2008 (80), <i>Prospective study</i>	TE/no treatment	63 untreated and 48 treated transgender males	-	Untreated: 38.8% Treated: 44.9%
Levcikova 2017 (110), <i>Prospective study</i>	TU/none	69 men with hypogonadism		Increase in hematocrit in 30%
McNicholas 2003 (45), <i>Randomized, multidose, multicenter, active-controlled study</i>	Gel/patch	208 men with hypogonadism 68 testim 50, 71 testim 100, 68 andropatch.	90 days	Higher dosage of gel showed higher hematocrit
Minnemann 2008 (67), <i>Open-label, randomized, prospective clinical trial</i>	TE/TU	40 men with hypogonadism	30 weeks	TE: 44.4%→ 47.8% TU 43.3%→ 46.8%
Wang 2004 (78), <i>Long-term, open-label efficacy study</i>	Gel/patch	163 men with hypogonadism	3 years	9% hematocrit >0.56
Zitzmann 2013 (53), <i>International, multicenter, one-arm, prospective, observational study in 23 countries</i>	TU/none	1438 men with hypogonadism	1 year	No cases of >0.52

because no adequately powered trials with a sufficiently long follow-up have investigated the effects of testosterone on cardiovascular events. A comprehensive and detailed meta-analysis of available randomized placebo-controlled trials concluded that the data did not support a causal role between testosterone therapy and cardiovascular adverse events (112). On the other hand, low testosterone is regarded as a marker for poor general health and as increased risk for cardiovascular disease and mortality. Observational studies have indeed reported that testosterone treatment improves survival when compared to men who were not treated (113). Furthermore, a multinational, longitudinal disease registry of men diagnosed with hypogonadism showed not testosterone therapy but age and prior cardiovascular disease history as risk factors for cardiovascular events (114). Another registry study with adjudicated major adverse cardiovascular events (MACE) found no difference between treated or untreated men and did not report any testosterone treatment related event during a 3 year follow-up (12). The European Medicine Agency (EMA) has stated in a consensus that there is no consistent evidence of an increased risk for cardiovascular adverse events from testosterone therapy in men with hypogonadism. To minimize cardiovascular events, it is important to keep testosterone values in the mid-normal physiological range and prevent hematocrit levels of >0.54 L/L. Furthermore, in men with an increased risk of cardiovascular disease,

it is important to start with replacement therapy only after consulting a cardiologist.

In men with hypogonadism treated with testosterone, levels of prostate-specific antigen (PSA) and prostate volume rise, marginally, plateauing at 12 months. Observational studies indicate that testosterone replacement therapy does not increase the risk of developing prostate cancer or result in more aggressive prostate tumors.

## Discussion

Testosterone treatment is shown to achieve physiological male testosterone levels leading to positive effects on hypogonadal symptoms (men with hypogonadism) or virilization (transgender males), well-being, metabolic parameters, body composition, BMD, with relatively few side effects and good safety. The time course of these effects is variable ranging from several weeks for sexual desire, from 6 to 12 months for body composition, and up to 3 years for maximum effects on bone (33, 115). Several preparations differing in the route of administration and pharmacokinetics have been approved for androgen therapy and are included in (inter)national guidelines (2, 3, 12, 13, 14, 15, 16). It should be selected according to the patient's preference, cost, availability, and formulation-specific properties. Worldwide, the most commonly

used preparations are transdermal testosterone gel and i.m. injections. However, with the exception of only one small open-label RCT comparing i.m. TE and i.m. TU on pharmacokinetics, clinical efficacy and safety (7, 67, 106) (same RCT, but results published in three articles), no randomized studies comparing these preparations have been performed. The (inter)national guidelines do not recommend one preparation specifically, advising that the choice should be a joint decision by both the patient and the physician (2, 3, 12, 13, 14, 15, 16), although some suggest to start first with gel to evaluate the treatment effect before switching to the longer-acting injections (3, 12). In addition, some guidelines for transgender care (14) have a preference for gel or long-acting injections since short-acting injections in transgender males are frequently associated with aggressive behavior due to the large fluctuations in testosterone concentrations with supraphysiological levels. An additional problem in several countries is that, for unclear reasons, long-acting injections have a limited reimbursement, which limits the patient's freedom of choice and possibilities for optimal personalized medicine.

Although hardly any comparative studies have been carried out, there are indications of differences between gel and i.m. preparations. Gel, with good compliance, and long-acting injections achieve more stable testosterone levels than short-acting injections. The large fluctuations in serum testosterone with supraphysiological levels and low trough values can lead to bothersome fluctuations in the patient's mood, sexual desire, and energy level. Based on a survey in the Netherlands in 2019 (116), Sustanon-users experienced much more mood swings than Nebido- and gel-users (25.3% vs 7.6% of gel-users and 5.9% of Nebido-users), increased aggression and anger (14.4% vs 5.5% and 4.3%), and excessive sexual desire (17.1% vs 4.7 and 5.9%). Concerning hematocrit, injections seem to increase hematocrit more than gel, and this could be explained by several reasons. Injections give higher peaks in testosterone. Moreover, compliance is often higher with injections due to the longer intervals between administrations. In a recent retrospective study in transgender males, the largest increase in hematocrit levels was seen within the first year (for both injections and gel), and also after this first year, a slight increase was seen (117). Studies on a possible different effect on hematocrit between short- and long-acting injections have given mixed results. There are no data on cardiovascular events related to this testosterone-induced increase in hematocrit. In a systematic review on cardiovascular disease in transgender persons treated with cross-sex hormones, exposure to testosterone was not

associated with a strong increase in cardiovascular events in transgender males; however, more studies are necessary with longer follow-up as cohorts of transgender males were relatively small to draw firm conclusions on (118). The beneficial effect on bone on the other hand may be greater for injections compared to gel, although no comparative studies between the different preparations have been performed. A meta-analysis from Tracz *et al.*, showed that i.m. but not transdermal testosterone increased lumbar spine BMD, but effects on femoral neck were inconclusive (119). Importantly, no trial has assessed the effect of testosterone therapy on the risk of incident fractures.

With regard to most clinical parameters, side effects, and safety, testosterone treatment appears to be roughly similar in hypogonadal and transgender males. Remarkably, the impact of testosterone treatment on HR-QoL is strongly underexposed in the reviewed studies, while this has a highly relevant outcome measure from a patient perspective. Available studies show an improvement in HR-QoL with testosterone treatment, which is confirmed by two meta-analyses (119, 120). In the meta-analysis by Elliot *et al.*, 23 RCTs, representing 14 treatments in addition to placebo, were included. When compared as a class against placebo, testosterone treatment improved QoL with substantial heterogeneity. Intramuscular TU significantly improved QoL relative to placebo and to oral TU, with no other significant differences among the other treatments (120). The authors do not report on the methods used to measure QoL in the included RCTs. Most RCTs involved men with late-onset hypogonadism, which were excluded from our search. In these studies, the Aging Males' Symptom (AMS) scale, a self-administered 17-item questionnaire, was often used to measure HR-QoL and symptoms in aging men (e.g. somato-vegetative, psychological, and sexual symptoms). Improvements on scores on the AMS have been noted within 3–4 weeks, but maximum benefits take longer time period. Regarding prostate cancer risk, a meta-analysis did not show a rise in International Prostate Symptom Score, and no detection of abnormal PSA values and no increase in prostate cancer were observed (121).

## Conclusions

In conclusion, both gel and i.m. testosterone replacement therapy appear to be effective preparations for the treatment of hypogonadal and transgender males. However, recommendations on testosterone treatment are based on data primarily from non-randomized clinical studies and observational studies and virtually no RCTs,

and there are no studies on the effects of testosterone replacement on endpoints such as cardiovascular disease in relation to hematocrit or osteoporotic fractures in relation to BMD. Additionally, the impact of testosterone treatment on HR-QoL is strongly underexposed in the reviewed studies. Although hardly any comparative studies have been carried out, there are indications of differences between the preparations, for example, on stability of testosterone levels, hematocrit, and BMD. Furthermore, patient satisfaction seems to be in favor of long-acting i.m. injections due to the low injection frequency with stable testosterone levels and no daily confrontation with treatment/disease. Patient satisfaction is lower with the use of gel, which is easy in use, but daily application is needed with daily confrontation with treatment and the risk of less compliance, possibly resulting in less stable values, and the least with short-acting injections due to the high injection frequency but especially due to the large fluctuations with concomitant swings in mood, sexual desire, and energy level (116). Given the increasing importance of personalized medicine, new randomized comparative studies are needed that also look into the effect on patient-reported outcome measures. This might also aid in obtaining full reimbursement for long-acting i.m. injections in various countries, increasing the patient's freedom of choice and possibilities for optimal personalized medicine.

#### Supplementary materials

This is linked to the online version of the paper at <https://doi.org/10.1530/EC-22-0112>.

#### Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

#### Funding

This publication has been supported by the European Reference Network on Rare Endocrine Conditions (Endo-ERN), which is co-funded by the European Union's 3rd Health Program (CHAFAE Framework Partnership Agreement No. 739527).

#### Author contribution statement

M M, L B, M H, C P, and N B made substantial contributions to design and conception of this review. All authors gave final approval of the version to be submitted. M M and L B participated in drafting the article. C P contributed to the search strategy. L B, M H, and N B participated in revising the manuscript critically for important intellectual content.

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Received in final form 30 May 2022

Accepted 27 June 2022

Accepted Manuscript published online 28 June 2022